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Pharmacokinetic characteristics of antiepileptic drugs (AEDs)

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Abstract

Antiepileptic drugs (AEDs) are routinely prescribed for the management of a variety of neurologic and psychiatric conditions, including epilepsy and epilepsy syndromes. Physiologic changes due to aging, pregnancy, nutritional status, drug interactions, and diseases (ie, those involving liver and kidney function) can affect pharmacokinetics of AEDs. This review discusses foundational pharmacokinetic characteristics of AEDs currently available in the United States, including clobazam but excluding the other benzodiazepines. Commonalities of pharmacokinetic properties of AEDs are discussed in detail. Important differences among AEDs and clinically relevant pharmacokinetic interactions in absorption, distribution, metabolism, and/or elimination associated with AEDs are highlighted. In general, newer AEDs have more predictable kinetics and lower risks for drug interactions. This is because many are minimally or not bound to serum proteins, are primarily renally cleared or metabolized by non–cytochrome P450 isoenzymes, and/or have lower potential to induce/inhibit various hepatic enzyme systems. A clear understanding of the pharmacokinetic properties of individual AEDs is essential in creating a safe and effective treatment plan for a patient.

Keywords: antiepileptic drugs, pharmacokinetic interactions, CYP450, UGT, hepatic metabolism, protein binding

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Introduction

Antiepileptic drugs (AEDs) decrease seizure frequency and severity in patients with seizure disorders, epilepsy, and epilepsy syndromes.[1-28] These AEDs can be divided into older medications (ie, first generation)—carbamazepine, ethosuximide, methsuximide, phenobarbital, phenytoin, primidone, and valproic acid/divalproex sodium/valproate sodium—and newer medications (ie, second or third generation) (Table 1). Over the past 3 decades, AEDs (eg, carbamazepine, gabapentin, lamotrigine, oxcarbazepine, pregabalin, topiramate, valproic acid/divalproex sodium/valproate sodium, and zonisamide)[3,15,17,23,24,28-31] were also used for management of non-epileptic neurologic conditions and psychiatric disorders (Table 1).[32]

This article reviews foundational pharmacokinetic characteristics of AEDs currently available in the United States.

including clobazam but excluding the other benzodiazepines. Pharmacokinetic properties of AEDs will be discussed in detail. Important differences among AEDs as well as clinically significant pharmacokinetic interactions are highlighted so health care professionals can provide safe and effective patient-centered care for neurologic and psychiatric disorders. Select pharmacokinetic characteristics of AEDs are summarized in Tables 2 and 3 and discussed in the text.

Absorption

All AEDs except fosphenytoin are available in oral formulation(s) with various dosing frequencies.[33] Only a few AEDs (eg, phenytoin, fosphenytoin, phenobarbital, lacosamide, levetiracetam, and valproic acid) are available in intravenous (IV) formulation(s)[33]; however, IV administration is typically reserved for use during medical emergencies (eg, status epilepticus) when oral dosing is inappropriate or impossible or when the drug therapeutic level needs to be achieved quickly using an IV loading dose. In addition, fosphenytoin and phenobarbital are the

only AEDs that may be administered intramuscularly, usually when IV access cannot be established and immediate action of medication is needed.[33]

Immediate-release (IR) oral formulations of AEDs with short half-lives (eg, carbamazepine, phenytoin, valproic acid/divalproex sodium/valproate sodium) are typically administered 3 or 4 times a day. Typically, AEDs with long half-lives (eg, eslicarbazepine acetate, lamotrigine, oxcarbazepine, perampanel, topiramate, and zonisamide) are administered once or twice a day. Prolonged-release oral formulations, such as extended-release (ER) or delayed-release tablets or capsules (Table 1), were designed to prolong absorption of AEDs with short half-lives (ie, carbamazepine, valproic acid/divalproex sodium/valproate sodium, phenytoin, and levetiracetam). The ER and delayed-release formulations allow for less frequent administration while minimizing fluctuations of drug serum concentration over the course of the day.[34] Improved outcomes associated with use of ER formulations of AEDs have, however, been only clearly documented for carbamazepine. Compared with carbamazepine IR, the carbamazepine ER oral formulation, typically given twice a day, was shown to provide more consistent drug delivery with less variable absorption while minimizing transient adverse effects associated with peak dose.[3,23,35] It has been suggested that fluctuations in the levels of select AEDs in cerebrospinal fluid may be less evident than in serum. This calls into question the additional benefits of ER formulations of other AEDs above and beyond benefits of increasing dosing interval for adherence.[34]

Current AEDs have different oral bioavailabilities (Table 2). Most AEDs are absorbed by passive diffusion in the gastrointestinal (GI) tract.[1-16,18-29,31] Gabapentin absorption is dependent on a saturable low-capacity L-amino acid transporter in the proximal portion of the small bowel.[2,17,36] Bioavailability of gabapentin IR decreases from 60% of a 300-mg dose to 35% of a 1600-mg dose given in 3 divided doses.[17,37] Strategies to improve or optimize gabapentin bioavailability involve administration of smaller doses at more frequent intervals. Gabapentin enacarbil,[30] a recently develop prodrug of gabapentin, is transported via high-capacity nutrient transport systems found along the length of the GI tract and has improved bioavailability compared with gabapentin (74.5% versus 36.6%) in the fed state.[30,38]

For most AEDs, coadministration with food can slow the absorption rate, but this does not have a clinically relevant effect on the extent of absorption (area under the curve [AUC]).[1,3-29,31] Therefore, most AEDs can be administered with or without food. Coadministration with food can be a helpful strategy to reduce GI irritation and dose-dependent adverse effects associated with excessive drug peak blood levels, and thus can improve drug tolerability of such AEDs as tiagabine.[12] Conversely, intake of rufinamide with food increases peak exposure (C_{max}) by >50% and AUC by 30%–40%; therefore, administration of rufinamide with food is recommended.[2,39] Gabapentin enacarbil should also be taken with food as the rate and extent of absorption increases when administered with a high-fat meal.[30] When phenytoin is administered via enteral tube feeding, its bioavailability is reduced due to adhesion of phenytoin to the plastic tubing and drug-nutrition interactions.[40] It is recommended that administration of phenytoin be separated from feeding by 1–2 hours (before or after) and to ensure adequate tube flush after each dose.[10,40,41] In general, to achieve a therapeutic serum concentration of phenytoin, the daily maintenance dose of phenytoin should be increased by 50% when phenytoin is changed from oral administration to enteral tube feeding.[42] It is imperative that phenytoin serum concentration be closely monitored and the phenytoin dose adjusted as needed.

Administration of phenytoin suspension[10] or gabapentin[17] with antacids containing aluminum, magnesium, and calcium has been associated with reduced bioavailability. In an open-label study by Yagi et al,[43] 13 healthy volunteers received gabapentin IR 200 mg orally, either alone or with 1 g magnesium oxide. The study found that the AUC of gabapentin when coadministered with magnesium oxide was decreased by 43% compared with gabapentin alone. The authors suggest that this is due to a reduction in the extent and rate of gabapentin intestinal absorption.[43] It is recommended that gabapentin, as well as phenytoin, should be taken at least 2 hours apart from any antacid.[10,17] This will ensure adequate absorption and minimize serum concentration fluctuation. Phenytoin ER capsules should also be administered at least 2 hours before or after any antacids containing calcium.[9]

Distribution

Distribution of AEDs in the body varies due to individual volume of distribution (Vd) (Table 2), which is influenced by drug plasma-protein binding and drug lipophilicity.[44] The Vd information is useful for loading dose (LD) calculation: LD = (concentration desired − concentration at baseline) $\times$ weight (kg) $\times$ Vd (L/kg).[45]

Gabapentin, vigabatrin, and pregabalin are not serum protein bound, whereas other AEDs are bound to serum proteins, mainly albumin, to varying degrees (Table 2).[1-28] For most AEDs, protein binding is linear, and the percent free fraction is a constant within serum concentration. Valproic acid is the single exception. Its free fraction is concentration dependent as protein binding is decreased markedly at high serum concentration due to protein-

TABLE 1: Antiepileptic drugs (AEDs) and their most common clinical use in the United States[1-33]

AED	Brand Name	Administration	Indication
Carbamazepine	Tegretol (Novartis Pharmaceuticals Corporation)[23] Tegretol XR (Novartis Pharmaceuticals Corporation)[33] Carbatrol (Shire US Inc) Equetro (Validus Pharmaceuticals LLC)[29]	PO	Partial seizures Tonic-clonic seizures Mania Bipolar I disorder Trigeminal neuralgia Neuropathic pain Phantom limb pain[a] Diabetic neuropathy[a] Postherpetic neuralgia[a] Singultus[a] Agitation[a]
Clobazam	Onfi (Lundbeck Inc)[18]	PO	Lennox-Gastaut syndrome Partial seizures[a]
Eslicarbazepine acetate	Aptiom (Sunovion Pharmaceuticals Inc)[1]	PO	Partial seizures
Ethosuximide	Zarontin (Pfizer US Pharmaceuticals)[27]	PO	Absence seizures
Ezogabine	Potiga (GlaxoSmithKline)[21]	PO	Partial seizures
Felbamate	Felbatol (MedPointe Pharmaceuticals)[11]	PO	Partial seizures Lennox-Gastaut syndrome
Fosphenytoin	Cerebyx (Pfizer Injectables)[4]	IV, IM	Partial seizures Tonic-clonic seizures Status epilepticus Seizure prophylaxis
Gapabentin	Neurontin (Pfizer Inc)[17] Gralise (Depomed Inc)[33]	PO	Partial seizures Postherpetic neuralgia Phantom limb pain[a] Restless leg syndrome[a] Diabetic neuropathic pain[a] Fibromyalgia[a] Anxiety disorders[a] Migraine prophylaxis[a]
Gabapentin enacarbil	Horizant (XenoPort, Inc)[30]	PO	Restless leg syndrome Postherpetic neuralgia
Lacosamide	Vimpat (UCB, Inc)[26]	PO, IV	Partial seizures
Lamotrigine	Lamictal (GlaxoSmithKline)[14] Lamictal XR (GlaxoSmithKline)[33] Lamictal ODT (GlaxoSmithKline)[33] Lamictal CD (GlaxoSmithKline)[33]	PO	Partial seizures Tonic-clonic seizures Lennox-Gastaut syndrome Juvenile myoclonic epilepsy[a] Bipolar I disorder Bipolar depression[a] Absence seizures[a]
Levetiracetam	Keppra (UCB, Inc)[13] Keppra XR (UCB, Inc)[33]	PO, IV	Partial seizures Tonic-clonic seizures Myoclonic seizures Seizure prophylaxis[a] Juvenile myoclonic epilepsy[a] Status epilepticus[a]
Methsuximide	Celontin (Pfizer US Pharmaceuticals)[33]	PO	Absence of seizures
Oxcarbazepine	Trileptal (Novartis Pharmaceuticals Corporation)[25] Oxtellar XR (Supernus Pharmaceuticals, Inc)[33]	PO	Partial seizures Mania[a] Bipolar disorder[a] Trigeminal neuralgia[a]
Perampanel	Fycompa (Eisai Inc)[19]	PO	Partial seizures
Phenobarbital	Luminal (Hospira Worlwide Inc)[33]	PO, IV, IM	Myoclonic seizures Partial seizures Status epilepticus Sedation induction Sedation maintenance

AED	Brand Name	Administration	Indication
Phenytoin	Dilantin (Parke-Davis Division of Pfizer Inc)[10] Dilantin ER (Parke-Davis Division of Pfizer Inc)[9] Phenytek (Mylan Pharmaceuticals)[33]	PO, IV	Partial seizures Tonic-clonic seizures Seizure prophylaxis Status epilepticus Neuropathic pain[a] Paroxysmal atrial tachycardia[a] Ventricular tachycardia[a]
Pregabalin	Lyrica (Parke-Davis Division of Pfizer Inc)[15]	PO	Partial seizures Neuropathic pain Fibromyalgia Postherpetic neuralgia Spinal cord injury Phantom limb pain[a] Generalized anxiety disorders[a] Social phobia[a]
Primidone	Mysoline (Valeant Pharmaceuticals N.A.)[16]	PO	Partial seizures Tonic-clonic seizures Benign familial tremor[a]
Rufinamide	Banzel (Eisai Co, Ltd)[2]	PO	Lennox-Gastaut syndrome Partial seizures[a]
Tiagabine	Gabitril (Cephalon, Inc)[12]	PO	Partial seizures
Topiramate	Topamax (Janssen Pharmaceuticals, Inc)[24] Topamax Sprinkle (Jansen Pharmaceuticals, Inc)[33] Trokendi XR (Supernus Pharmaceuticals, Inc)[33] Qudexy XR (Upsher-Smith Laboratories, Inc)[33]	PO	Lennox-Gastaut syndrome Partial seizures Tonic-clonic seizures Migraine prophylaxis Juvenile myoclonic epilepsy[a] Bulimia nervosa[a] Alcohol dependence[a] Binge-eating disorder[a]
Valproic acid Divalproex sodium Valproate sodium	Depakene (AbbVie Inc)[6] Depakote (AbbVie Inc)[7] Depakote Sprinkle Depakote ER (AbbVie Inc)[8] Depakote DR (AbbVie Inc)[33] Stavzor (Noven Therapeutics, LLC)[31] Depacon (AbbVie Inc)[5]	PO, IV	Partial seizures Tonic-clonic seizures Absence seizures Myoclonic seizures Mania Bipolar disorder Migraine prophylaxis Agitation[a] Singultus[a] Status epilepticus[a]
Vigabatrin	Sabril (Lundbeck, Inc)[22]	PO	Partial seizures Infantile spasms
Zonisamide	Zonegran (Elan Biopharmaceuticals)[29]	PO	Partial seizures Juvenile myoclonic epilepsy[a] Lennox-Gastaut syndrome[a] Binge-eating disorder[a]

DR = delayed-release; ER = extended-release; IM = intramuscular; IV = intravenous; PO = by mouth; XR = extended-release.

[a]This indication is not approved by the US Food and Drug Administration.

binding site saturation.[5-7] For adults on monotherapy, the average of free fraction of valproic acid is between 10% at 40 µg/mL and 18.5% at 130 µg/mL.[5-7]

In general, only AEDs with a high protein binding, that is, ≥90%, are associated with clinically relevant protein-binding interactions that result in clinically significant changes in drug effect due to an increased or decreased drug-free fraction. Phenytoin, valproic acid, tiagabine, and perampanel have the greatest plasma protein binding (Table 2). Phenytoin has the highest risk for protein-binding interactions among all AEDs as it is a narrow therapeutic index agent with nonlinear pharmacokinetics that is extensively bound to serum albumin.[9,10] Despite being highly protein bound, perampanel and tiagabine do not seem to have high risk for protein-binding interac-

TABLE 2: Pharmacokinetic profiles of select antiepileptic drugs (AEDs)[1-31,46,56,58]

AED Serum Concentration	Oral Absorption (%)	Vd (L/kg)	T1/2 (h)	Proteing Bind (%)	Elimination	Active Metabolite
Carbamazepine[a,b] 4–12 μg/mL (CMZ), <0.2–2.0 μg/mL (epoxide)	85	0.8–2	12–17	76	H (100%): *CYP3A4* (major), *CYP1A2, CYP2C8*	CMZ-10,11-epoxide
Clobazam 100–300 μg/mL	100	0.9–1.4	18 (CBZ) 42 (N-DMC)	85 (CBZ) 70 (N-DMC)	H (98%): *CYP3A4* (major), *CYP2C19, CYP2B6*	N-DMC
Eslicarbazepine acetate NE	>90 prodrug	2.7	20–24	<40	R (66%): unchanged NH: hydrolysis by esterases to eslicarbazepine (91%) H: UGT isoenzymes (33%) of eslicarbazepine	ELC OXC
Ethosuximide 40–100 μg/mL	100	0.6–0.7	25–60	0	R (20%): unchanged H: *CYP3A4* (major), *CYP2E1*	No
Ezogabine NE	60	2–3	8–10	80	R (20%–30%): unchanged H (50%–65%): *UGT1A4*, NAT	No
Felbamate 30–140 μg/mL	<90	0.7–1.0	22–25	25	R (50%): unchanged H (50%): *CYP3A4* (20%), *CYP2E1* (major), UGT (20%)	No
Fosphenytoin[b,c] 10–20 μg/mL	N/A	0.04–0.13	15 min	95–99	M: *CYP2C9, CYP2C19*	PHT
Gabapentin[b,d] 4–16 μg/mL	35–60	0.85	5–7	0	R (>90%): unchanged	No
Gabapentin enacarbil NE	75%	0.85	5–7	0	R (>90%): gabapentin NH: gabapentin enacarbil undergoes extensive first-pass hydrolysis to gabapentin by carboxylesterases in enterocytes	Gabapentin
Lacosamide < 15 μg/mL	100	0.5–0.8	13	<30	R (40%): unchanged H: demethylation, *CYP2C19* (30%)	No
Llamotrigine 4–18 μg/mL	≥95	0.9–1.3	15–35	55	H (76%): *UGT1A4*	No
Levetiracetam 5–40 μg/mL	≥95	0.5–0.7	6-8	<10	R (66%): unchanged NH (30%): hydrolysis by type B esterase in white blood cells	No
Oxcarbazepine 10–35 μg/mL (MHD metabolites)	>90 prodrug	0.75 (MHD)	8–15 (MHD)	40 (MHD) 60 (OXC)	R (20%): unchanged H (80%): cytosolic arylketone reductase (OXC), UGT (MHD metabolites)	S-licarbazepine and R-licarbazepine
Perampanel NE	100	1.1	52–129	95	H (98%): *CYP3A4* (major), *CYP3A5*	No
Phenobarbital 15-40 μg/mL	70–90	0.5–1.0	36–118	55	R (20%): unchanged H: glucosidase, *CYP2C9, CYP2C19, CYP2E1*	No
Phenytoin[b,c] 10–20 μg/mL (total), 1–2 μg/mL (free)	90–100	0.5–1.0	7–42	90	H (98%): *CYP2C9* (major), *CYP2C19* (minor)	No
Pregabalin NE	≥90	0.57	5–7	0	R (>95%): unchanged	No

TABLE 2: Pharmacokinetic profiles of select antiepileptic drugs (AEDs)[1-31,46,56,58] (continued)

AED Serum Concentration	Oral Absorption (%)	Vd (L/kg)	T1/2 (h)	Proteing Bind (%)	Elimination	Active Metabolite
Primidone 5–12 μg/mL (PRM), 15–40 μg/mL (PHB)	60–80	0.64–0.72	10–12 (PEMA) 29–36 (PHB)	20–45 (PHB) <10 (PEMA, PRM)	R (40%–60%): unchanged and smaller amount of PEMA and PHB inactive metabolites H: *CYP2C9/19*, alcohol dehydrogenase PHB (15%–25%) and amide hydrolysis PEMA (~75%)	PHB PEMA
Rufinamide (NE)	≥85[e]	0.71–1.14	6–10	35	H (100%): Non-CYP450 enzymatic hydrolysis by carboxylesterases	No
Tiagabine (NE)	≥90	1.0	5–9	96	H (98%): *CYP3A4* metabolism to an inactive metabolites	No
Topiramate 2–25 μg/mL	≥80	0.6–0.8	20–30	15	R (70%): unchanged H (30%): *CYP2C19* metabolism and glucuronidation	No
Vigabatrin (NE)	60–80	0.8	5–8	0	R (95%): unchanged	No
Valproic acid/divalproex sodium/valproate sodium[b,f] 50-100 (125)[g] μg/mL (total VPA), 5–12.5 μg/mL (free VPA)	100	0.1–0.2	6–17	90[h]	H (95%): beta oxidation, *UGT1A6*, *UGT1A9*, *UGT2B7*, *CYP2C9*, *CYP2C19*	VPA
Zonisamide[b,i] 10–40 μg/mL	≥90	1.0–1.9	27–70	40	R (30%): unchanged H (70%): *CYP3A4* (major), NATs (15%), *CYP2C19*	No

CMZ = carbamazepine; CYP = cytochrome P450 enzyme; ELC = eslicarbazepine; H = hepatic elimination; M = metabolized by; MHD = monohydroxy derivate (10,11-dihydro-10-hydroxy-5H-dibenzo[b,f]azepine-5-carboxamide also known as 10-hydroxycarbazepine); NAT = N-acetyltransferase; N-DMC = N-desmethylclobazam (also known as norclobazam); N/A= not applicable; NE = not established; NH = nonhepatic elimination; OXC = oxcarbazepine; PEMA = phenylethylmalonamide; PHB = phenobarbital; PHT = phenytoin; PRM = primidone; R = renal elimination; T1/2 = half-life; UGT = uridine glucuronate-glucuronosyltransferase; Vd = volume of distribution; VPA = valproic acid; T1/2= half life.

[a]Autoinduction.

[b]Nonlinear kinetic.

[c]Saturable *CYP2C9* biotransformation (zero-order kinetics)

[d]Saturation of gastrointestinal absorption as extent of absorption decreases with increasing dose

[e]Underfed state.

[f]Saturation of plasma protein binding.

[g]Plasma concentrations of total valproic acid up to 125 μg/mL may be necessary for stabilization of some patients with acute mania.[31]

[h]Concentration-dependent protein binding.

[i]Saturable binding to red blood cells.

tions, though the relationships between tiagabine and perampanel plasma concentrations and clinical response are not currently understood.[12,19]

Protein binding of valproic acid and phenytoin can be reduced in the presence of decreased serum albumin levels or hypoalbuminemia associated with pregnancy (especially during the second and third trimesters), malnutrition, nephrotic/uremic states, or liver disease or when antiepileptic medication is coadministered with other highly protein-bound medications.[46-48] This leads to a disproportionate increase in free fraction of phenytoin or valproic acid and increased risk for dose-dependent adverse effects and toxicity.[5-10] Salicylates and certain nonsteroidal anti-inflammatory drugs (ie, naproxen) can significantly displace valproic acid from albumin-binding sites and thus increase free fraction of valproic acid.[5-8] Phenytoin has a complex interaction with warfarin. This interaction results from changes in protein binding and increased metabolic clearance. In a patient taking warfarin, phenytoin can immediately displace warfarin from its protein binding sites, thereby causing a rapid increase in the international normalized ratio (INR). After prolonged administration, phenytoin may actually reduce the effectiveness of warfarin by inducing cytoprotein (CYP) 450–dependent metabolism of warfarin.[9,10] Admin-

TABLE 3: Antiepileptic drugs (AEDs) with enzyme inducing/inhibiting properties and select clinically relevant drug interactions associated with their enzyme inducing/inhibiting properties[1-11,16,18-20,23-33,48]

AED	Induction	Interaction With AEDs	Inhibition	Interactions With Other Therapeutic Classes

Carbamazepine[a,b]	*CYP3A4*
	CYP1A2
	CYP2B6
	CYP2C9
	CYP2C19
	P-glycoprotein
	UGT
		Decreased level of
		  clobazam
		  clonazepam
		  CMZ (autoinduction)
		  felbamate
		  felbamate
		  lamotrigine
		  oxcarbazepine
		  perampanel
		  phenobarbital
		  phenytoin
		  primidone
		  rufinamide
		  tiagabine
		  topiramate
		  valproic acid
		  zonisamide
		Increased level of
		  phenobarbital from
		  primidone
		  phenytoin
				Decreased level of
				  CCBs
				  hormonal
				  contraceptives
				  lapatinib
				  maraviroc
				  methadone
				  nefazodone
				  non-nucleoside reverse
				  transcriptase inhibitors
				  phenothiazines
				  PPIs
				  statins: lovastatin,
				  simvastatin,
				  cerivastatin and
				  atorvastatin
				  tricyclic
				  antidepressants
				  telapravir
				  theophylline
				  vitamin D
				  warfarin

Clobazam	*CYP3A4* (weak)	Increased level of
		  CYP2D6 substrates (eg,
		  fluoxetine,
		  dextromethorphan)
			CYP2D6 (weak)	Decreased level of
				  hormonal
				  contraceptives

Eslicarbazepine	*CYP3A4* (weak)	Increased level of
		  clobazam
		  phenytoin
			CYP2C19 (moderate)	Decreased level of
				  hormonal
				  contraceptives
				  simvastatin
				  rosuvastatin

Felbamate	*CYP3A4* (weak)	Decreased level of
		  CMZ
		Increased level of
		  CMZ-10,11-epoxide
		  phenobarbital
		  phenytoin
		  valproic acid
			CYP2C19
			Beta oxidation
			  (moderate)
				Decreased level of
				  hormonal
				  contraceptives

Lamotrigine	UGT (weak)	Decreased level of
		  lamotrigine
		  valproic acid
				Decreased level of
				  levonorgestrel

Oxcarbazepine	*CYP3A4/5* (dose-
	dependent: moderate
	at doses > 1200 mg/
	day)
		Decreased level of
		  perampanel
		Increased level of
		  CMZ-10,11-epoxide
		  phenobarbital
		  phenytoin
			CYP2C19 (dose-
			dependent: moderate
			at doses > 1200 mg/
			day)
				Decreased level of
				  CCBs
				  cyclosporine
				  hormonal
				  contraceptives[c]

Perampanel	*CYP3A4* (weak)		N/A	Decreased level of levonorgestrel[d]

istration of valproic acid/divalproex sodium/valproate sodium was shown to increase the unbound fraction of warfarin by 33%. The therapeutic relevance of this interaction is unclear; however, monitoring INR more closely during concomitant therapy of warfarin with valproic acid/divalproex sodium/valproate sodium is advised.[5-8] Perampanel and tiagabine have not been associated with significant interaction with warfarin or other highly protein-bound medications.[12,19] In people with renal impairment, including those requiring hemodialysis, total and unbound tiagabine levels were unaffected.[12]

TABLE 3: Antiepileptic drugs (AEDs) with enzyme inducing/inhibiting properties and select clinically relevant drug interactions associated with their enzyme inducing/inhibiting properties[1-11,16,18-20,23-33,48] (continued)

AED	Induction	Interaction With AEDs	Inhibition	Interactions With Other Therapeutic Classes
Phenobarbital[a] Primidone[a]	*CYP2C9* *CYP2C19* *CYP2E1* *CYP1A2* *CYP3A4* UGTs	Decreased level of CMZ and MHD clonazepam felbamate lamotrigine oxcarbazepine perampanel phenytoin rufinamide zonisamide tiagabine		Decreased level of beta-blockers CCB digoxin hormonal contraceptives statins: lovastatin, simvastatin, cerivastatin, and atorvastatin vitamin D
Phenytoin[a]	*CYP3A4* *CYP2C9* *CYP2C19* *CYP1A2* UGT	Decreased level of CMZ and MHD metabolites clonazepam felbamate lamotrigine oxcarbazepine perampanel phenobarbital primidone rufinamide topiramate valproic acid zonisamide phenobarbital tiagabine	N/A	Decreased level of CCB digoxin hormonal contraceptives ibrutinib nilotinib PPIs quinidine sirolimus statins: lovastatin, simvastatin, cerivastatin, and atorvastatin tacrolimus telaprevir vitamins: vitamin D and folic acid warfarin (with prolong phenytoin administration)
Rufinamide	*CYP3A4* (weak)	Increased level of phenytoin	*CYP2E1* (weak)	Decreased level of hormonal contraceptives triazolam
Topiramate	*CYP3A4* Beta oxidation (mild)	Increased level of phenytoin[e]	*CYP2C19* (mild)	Decreased level of hormonal contraceptives[f]
Valproic acid/divalproex Sodium/valproate sodium[a]	N/A	Increased level of CMZ 10,11-epoxide ethosuximide lamotrigine phenytoin free level rufinamide	*CYP2C9* UGTs Epoxide hydrolase	Decreased level of N/A

CCB = calcium-channel blocker; CMZ = carbamazepine; CYP = cytochrome P$_{450}$ enzyme; MHD = monohydroxy derivate (10, 11-dihydro-10-hydroxy-5H-dibenzo[b,f]azepine-5-carboxamide also known as 10-hydroxycarbazepine); N/A = not applicable; PPI = proton-pump inhibitor; UGT = uridine glucuronate-glucuronosyltransferase

[a]Strong enzyme induction or inhibition

[b]Induction of its own metabolism via *CYP3A4* (autoinduction).

[c]Oxcarbazepine doses > 1200 mg/day.

[d]Perampanel 12 mg/day.

[e]Plasma concentration increased 25% in some patients, generally those on a twice-a-day dosing regimen of phenytoin.[24]

[f]Topiramate ≥ 200 mg/day.

To decrease the risk for adverse effects and complications resulting from the aforementioned physiologic changes and drug interactions, clinicians should closely monitor for dose-dependent adverse effects and toxicities, adjusting the medication dose for altered or unpredictable protein-binding capacity of AEDs. Free fraction and total serum concentrations of phenytoin or valproic acid should be monitored closely when decreased protein binding may be indicated.[5-10,49] When warfarin is coadministered with valproic acid/divalproex/valproate sodium sodium or phenytoin, INR should also be monitored closely, especially during antiepileptic drug initiation, dose increase, and discontinuation.[5-10]

Metabolism and Elimination/Excretion

Most AEDs undergo metabolic conversion to active or inactive metabolites in the liver. This is primarily through hydroxylation via the CYP450 enzyme system and/or conjugation with glucuronide metabolites by uridine glucuronate-glucuronyltranferase (UGT) (Table 2).[3-12,14,16,18-21,23-29,31] A large proportion of AEDs are substrates for major CYP450 isoenzymes (including *CYP1A2*, *CYP3A4*, *CYP2C9*, and *CYP2C19*) and UGT isoenzymes. This makes them more susceptible to drug interaction with agents with induction (eg, rifampin, phenytoin, carbamazepine, phenobarbital, primidone, and St John's wort) or inhibition (eg, cimetidine, azole antifungals, macrolide antibiotics, nondihydropyridine calcium channel blockers, and grapefruit juice) properties of CYP450 and UGT isoenzymes (eg, valproic acid/divalproex sodium/valproate sodium).[3-12,14,16,18-21,23-29,31] In order to predict or identify drug-drug interactions, understanding of CYP450 isoenzymes and other major enzyme systems involved in metabolism of individual AEDs is important.

Carbamazepine,[23] oxcarbazepine,[25] and eslicarbazepine acetate[1] are structurally related medications. They do, however, differ significantly in terms of metabolism. Carbamazepine is chiefly converted to carbamazepine-10,11-epoxide (an active metabolite with anticonvulsant activity) by *CYP3A4* in the liver and is later metabolized by epoxide hydrolase to inactive carbamazepine-10,11-trans-diol derivative metabolite.[23] It is believed that carbamazepine-10,11-epoxide is responsible for increased risks for hepatotoxicity, congenital abnormalities observed during pregnancy (pregnancy class D), and autoinduction properties. Increased epoxide levels can be especially problematic for children, causing vomiting, tiredness, and increased seizure frequency.[50] Carbamazepine autoinduction is usually initiated on day 3 and is fully completed within a month.[23,51] Oxcarbazepine is a prodrug that is rapidly reduced in the liver to its 2 enantiomeric monohydroxy derivatives, namely (R)-licarbazepine

(20%) and (S)-licarbazepine (80%), also known as eslicarbazepine.[52,53] Eslicarbazepine is believed to be a significant active metabolite with anticonvulsant activity, and oxcarbazepine and (R)-licarbazepine are believed to be responsible for additional adverse effects.[25,54] In addition, oxcarbazepine and monohydroxy derivative metabolites create dose-related inhibition of *CYP2C19* and induction of *CYP3A4/5*.[25] Eslicarbazepine acetate, a prodrug, is almost completely metabolized to eslicarbazepine (95%) by hydrolytic first-pass metabolism. It is an active metabolite with anticonvulsant activity and minor metabolites, including (R)-licarbazepine (4.5%) and oxcarbazepine (0.5%) formed by non-CYP450-mediated metabolism.[1,52] Eslicarbazepine acetate has a lower risk for drug interactions due to lack of CYP450-dependent metabolism. It is also thought to have more favorable tolerability than carbamazepine and oxcarbazepine due to lack of epoxide formation and only minor presence of metabolites, oxcarbazepine, and (R)-licarbazepine.[1,55]

Gabapentin,[17] pregabalin,[15] and vigabatrin[22] are completely renally excreted in unchanged form. Levetiracetam (66%)[13] and topiramate (70%)[24] are renally eliminated, predominantly in unchanged form (Table 2). Clinically significant interactions with other drugs through UGT or CYP450 hepatic enzyme systems are unlikely for all of the aforementioned medications except for topiramate (Table 3).[56-59] Pharmacokinetic variability of these medications is less pronounced and more predictable under various physiologic conditions (eg, pregnancy and kidney impairment/disease) as renal function can be predicted by measuring creatinine clearance, which allows for adjustment in medication dose or frequency.[13,15,17,22,24]

The AEDs have varying half-lives (Table 2). In general, the half-life of a medication can be used to determine the time needed for a medication to reach steady-state plasma concentration (almost complete after 5 half-lives when it is ~97%). It is also used to determine dosing frequency required to maintain steady-state plasma concentration. The AEDs with the strongest evidence/justification for drug serum-level monitoring are carbamazepine, valproic acid, lamotrigine, oxcarbazepine, phenobarbital, and zonisamide, especially in patients with epilepsy.[60] Available serum-level monitoring of AEDs can be particularly important (1) when changes in a patient occur that can significantly alter AED pharmacokinetics (eg, pregnancy, impaired kidney or liver function, concomitant therapy with enzyme inducer or enzyme inhibitor, and displacement from protein binding sites), (2) in assessing medication adherence, (3) in managing breakthrough seizures and status epilepticus, (4) for considering generic substitution, or (5) for changng dosage form.[61]

Most AEDs display first-order kinetics (drug serum concentration increases linearly with the total daily dose). This leads to a predictable increase or decrease in plasma drug concentration in response to a change in daily dose. Carbamazepine (autoinduction), gabapentin (saturable GI tract transport), valproic acid/divalproex sodium/valproate sodium (saturable albumin binding), zonisamide (saturable erythrocyte binding), and phenytoin (saturable *CYP2C9* biotransformation) exhibit nonlinear kinetics, as shown in Table 2.[62] Zonisamide is extensively bound to erythrocytes, and dose-proportional pharmacokinetics is reported at 200–400 mg/day. An increased AUC and a nonlinear relationship between zonisamide serum level and dose were reported at doses ≥800 mg/day, possibly due to saturable erythrocyte binding.[28] Phenytoin dosing can be complicated because it exhibits zero-order kinetics due to metabolism saturation.[10] Small changes in phenytoin dose can lead to disproportionate changes in phenytoin serum concentration.[63] Careful phenytoin dose adjustment and close serum concentration monitoring are warranted to decrease patients' risk for toxicity from excessive dosing or risk for therapeutic ineffectiveness.[9-10,63]

Select AEDs carry risks for hepatic enzyme induction and/or inhibition, which can result in altered serum drug concentrations of concomitant medication(s).[57,64] Table 3 lists AEDs and their effects on various hepatic metabolic enzyme systems and provides examples of outcomes of such interactions. Overall, first-generation AEDs have the greatest risk for drug interactions (Table 3).[57,59] Phenytoin,[10] carbamazepine,[23] phenobarbital,[20] and primidone[16] are potent, broad-spectrum inducers of CYP450 and UGT isoenzymes, whereas valproic acid/divalproex sodium/valproate sodium[5-8] strongly inhibit UGT isoenzymes, *CYP2C19*, and epoxide hydrolase. Coadministration of any of them can lead to altered metabolism of concomitant medications (Table 3). There is a complex interaction between carbamazepine and valproic acid when administered together. Carbamazepine induces hepatic clearance of valproic acid and decreases valproic acid serum concentration. Valproic acid decreases clearance of carbamazepine-10,11-epoxide by inhibiting epoxide hydrolase, leading to up to a 45% increase in the level of carbamazepine-10,11-epoxide and increased toxicity even at normal carbamazepine serum concentrations.[6,23] When these 2 drugs are administered together, careful monitoring of free and total serum levels of valproic acid and carbamazepine as well as carbamazepine-10,11-epoxide serum concentrations is warranted.[6,23]

Newer AEDs, topiramate[24] and oxcarbazepine,[25] are dose-dependent inhibitors of *CYP2C19*, and topiramate,[24] oxcarbazepine,[25] perampanel,[19] eslicarbazepine acetate,[1] rufinamide,[2] and felbamate[11] are dose-dependent inducers of *CYP3A4*, usually causing drug interactions with select medications at high doses.

Lamotrigine is devoid of any significant enzyme-inducing or enzyme-inhibiting properties. However, its metabolism is dependent on extensive glucuronidation, primarily via *UGT1A4*, making it prone to several clinically significant interactions with some AEDs (Table 3).[14,46,65] Coadministration of lamotrigine with valproic acid/divalproex sodium/valproate sodium leads to decreased elimination of lamotrigine, increased half-life from 30 to 60 hours, and increased lamotrigine serum concentration by >200%.[6,14] Concurrent administration of lamotrigine with medications inducing UGT leads, in general, to decreased plasma concentration and shortened half-life from 30 to 15 hours.[14] Lamotrigine steady-state serum concentrations have been reported to decrease by as much as 70% after the addition of methsuximide; 50% by phenytoin; 40% by carbamazepine, phenobarbital, and primidone; and 25% by oxcarbazepine.[14,58] In addition, non-epileptic medications (ie, rifampin) inducing UGT can also decrease the effectiveness of lamotrigine.[14]

One of the important drug interactions for AEDs is with hormonal contraception (Table 3). They can stimulate *CYP3A4*-dependent metabolism of estrogen and/or progesterone components. Women of reproductive age should be counseled on possible hormonal contraceptive failure while on these medications.[48] Clinicians should monitor for breakthrough bleeding, and alternative or supplemental forms of contraception should be considered while a patient is on an AED inducer.[1-4,9-11,16,18-20,23-33,48] Conversely, estrogen-containing hormonal contraceptives and hormonal replacement therapies may increase lamotrigine clearance and reduce its serum concentration by 50%.[14,67] Lamotrigine clearance is also increased during pregnancy and increases progressively until the 32nd gestational week with a mean increase from baseline to 365% during the third trimester. The return to pre-pregnancy clearance has been observed as early as 2 weeks after delivery.[68] Clinicians should consider more frequent monitoring of lamotrigine serum concentration during pregnancy, initiation or discontinuation of estrogen-containing medications, and coadministration of medications with the potential to inhibit or increase hepatic glucuronidation.

Summary

A variety of pharmacokinetic interactions are associated with AEDs in absorption, distribution, metabolism, and elimination. Compared with older AEDs, newer AEDs have more predictable kinetics and fewer risks for drug interactions. This is because many are minimally or not bound to serum proteins, are primarily renally cleared or metabolized by non-CYP450 isoenzymes, and/or have less potential to induce/inhibit various hepatic enzyme systems. As all AEDs are frequently used for management of

neurologic and psychiatric conditions, it is important to understand the pharmacokinetic characteristics of individual AEDs in order to create safe, effective, and patient-specific pharmacotherapeutic plans.

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