Anticonvulsants, Oral

Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Seizure Disorders				Neuropathic Pain	Lennox-Gastaut Syndrome	Migraine Prophylaxis	Bipolar Disorder
		Absence	Myoclonic	Partial	Tonic-Clonic				
Barbiturates									
mephobarbital[1]	generic	X			X				
primidone (Mysoline®)[2]	generic			X	X				
phenobarbital[3]	generic		X	X	X				
Hydantoins									
ethotoin (Peganone®)[4]	Ovation			X	X				
phenytoin ER (Dilantin®)[5]	generic, Pfizer			X	X				
phenytoin ER (Phenytek®)[6]	Mylan								
Succinimides									
ethosuximide (Zarontin®)[7]	generic	X							
methsuximide (Celontin®)[8]	Pfizer	X							
Benzodiazepines									
clonazepam (Klonopin®)[9]	generic	X	X				X		
diazepam rectal gel (Diastat®)[10]	generic								

Other Indications:

Mephobarbital and phenobarbital are indicated as a sedative for the relief of anxiety, tension, and apprehension.

Phenobarbital is indicated for insomnia, although the barbiturates are no longer used for this indication.

Phenobarbital is also indicated for treatment of status epilepticus; however, its full antiepileptic effect is not immediate. Intravenous benzodiazepines should be given initially for status epilepticus.

Phenytoin (Dilantin, Phenytek) is indicated for prevention and treatment of seizures occurring during or following neurosurgery.

Clonazepam (Klonopin) is indicated for panic disorder.

Diazepam rectal gel (Diastat) is indicated for the management of selected, refractory patients on stable regimens of anti-epileptic agents who require intermittent use of diazepam to control bouts of increased seizure activity.

Note: Mephobarbital and phenobarbital have not been found by the FDA to be safe and effective.[11]

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FDA-Approved Indications (continued)

* indicates approval for adjuvant therapy only

Drug	Manufacturer	Seizure Disorders				Neuropathic Pain	Lennox-Gastaut Syndrome	Migraine Prophylaxis	Bipolar Disorder
		Absence	Myoclonic	Partial	Tonic-Clonic				
Carbamazepine Derivatives									
carbamazepine (Tegretol®)[12]	generic			X	X	X (associated with trigeminal neuralgia)			
carbamazepine extended-release (Tegretol® XR)[13]	generic								
carbamazepine extended-release (Carbatrol®)[14]	Shire, generic								
carbamazepine (Epitol®)[15]	Teva			X	X	X (associated with trigeminal neuralgia)			
carbamazepine (Equetro™)[16]	Validus Pharm								X
oxcarbazepine (Trileptal®)[17]	generic			X					
Valproic Acid and Derivatives									
valproic acid (Depakene®)[18]	generic	X	X	X	X				
valproic acid delayed-release (Stavzor™)[19]	Noven Therapeutics	X		X	X			X	X
divalproex delayed-release (Depakote®)[20]	generic	X	X	X	X			X	X
divalproex sodium extended-release (Depakote ER®)[21]	generic	X		X				X	X

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FDA-Approved Indications (continued)

* indicates approval for adjuvant therapy only

Drug	Manufacturer	Seizure Disorders				Neuropathic Pain	Lennox-Gastaut Syndrome	Migraine Prophylaxis	Bipolar Disorder
		Absence	Myoclonic	Partial	Tonic-Clonic				
Other Anticonvulsants									
felbamate (Felbatol®)[22]	Meda			X[a]			X*		
gabapentin (Fanatrex™, Gralise™,Neurontin®)[23 24]	Fusion, generic			X*		X			
lacosamide (Vimpat®)[25]	UCB Pharma			X*					
lamotrigine (Lamictal®, ODT)[26]	generic, GSK			X	X*		X*		X
lamotrigine (Lamictal® XR)[27]	GSK			X*	X				
levetiracetam (Keppra™)[28]	generic		X*	X*	X*				
levetiracetam XR (Keppra XR™)[29]	UCB Pharma			X*					
pregabalin (Lyrica®)[30]	Pfizer			X*		X (associated with diabetic peripheral neuropathy or post herpetic neuralgia)			
rufinamide (Banzel™)[31]	Eisai						X*		
tiagabine (Gabitril®)[32]	Cephalon			X*					
topiramate (Topamax®)[33]	generic			X	X		X*	X	
vigabatrin (Sabril®)[34]	Lundbeck			X*					
zonisamide (Zonegran®)[35]	generic			X*					

[a] Felbamate (Felbatol) is not indicated as first line antiepileptic treatment and is recommended for use only in patients who respond inadequately to alternative treatments and whose epilepsy is so severe that a substantial risk of aplastic anemia and/or liver failure is deemed acceptable in relation to benefits.

Other Indications:

Pregabalin (Lyrica) is also indicated for treatment of fibromyalgia.

Vigabatrin (Sabril) is also indicated for the treatment of infantile spasms.

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OVERVIEW

Epilepsy/Seizure Disorders

Epilepsy is one of the most common disorders of the central nervous system (CNS). It affects approximately three million Americans, with 200,000 new cases diagnosed each year.[36] When a person has two or more seizures, they are considered to have epilepsy. Although epilepsy can develop at any age, the risk is estimated to be one percent from birth to age 20 years and three percent at age 75 years. Isolated seizures may also occur during a febrile illness, after head trauma, or as a result of withdrawal from alcohol or sedative/hypnotics.

A seizure is traceable to an unstable cell membrane or cluster of cells. Excessive excitability spreads either locally (partial seizure) or more widely (generalized seizure). Partial seizures begin in one hemisphere of the brain, and unless they become secondarily generalized, they can cause alterations in motor functioning, sensory symptoms, or automatisms. If there is no loss of consciousness, they are called simple partial. If there is loss or impairment of consciousness, they are called complex partial.

Both tonic-clonic and absence seizures are considered generalized seizures. Tonic-clonic seizures are characterized by body stiffness (tonic phase) followed by jerking movements as the muscles alternate between relaxation and rigidity (clonic phase). A tonic-clonic seizure preceded by an aura is likely a partial seizure that has secondarily generalized.

Absence seizures or petit mal seizures are more common in young children and adolescents.[37] Symptoms include staring, eye fluttering, and automatisms such as lip smacking, picking at clothes, and fumbling, if prolonged. Patients exhibit a sudden onset of lapses of awareness that begin and end abruptly, lasting only a few seconds.

Lennox-Gastaut syndrome is one of the most severe forms of childhood epilepsy and is one of the hardest forms to treat. It is characterized by mental retardation and multiple seizure types. Patients have seizures daily, sometimes experiencing several seizures within a day. Patients may also experience “drop attacks”, which is defined as a loss of muscle control causing the patient to fall abruptly to the floor.

Infantile spasm is a type of seizure seen in West Syndrome.[38] West Syndrome is characterized by infantile spasms, developmental regression, and a specific pattern on electroencephalography (EEG) testing called hypsarrhythmia (chaotic brain waves). The onset of infantile spasms is usually in the first year of life, typically between four and eight months. Infantile spasms usually stop by age five, but may be replaced by other seizure types. Many underlying disorders can cause spasms, making it important to identify the underlying cause.

Goals of treating epilepsy are to reduce the frequency of seizure occurrence along with providing the best possible quality of life for the patient. Ideally, this would be achieved using a medication with minimal adverse effects and drug interactions. Treatment will depend on the type of seizure. Many different classes of drugs are available to treat the different forms of seizures.[39] Some patients will require more than one drug to control their seizures.

Standard guidelines have not been created to help differentiate the superiority of one agent over another agent. The reason for this is that there is a lack of comparative data on which to base such a guide. This was the recurring theme in an attempt by the International League Against Epilepsy (ILAE)

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to develop treatment guidelines in 2006.[40] In 2007, the American Epilepsy Society (AES) and the American Academy of Neurology (AAN) developed a set of evidence-based guidelines to help healthcare professionals better understand the published research on the newer anticonvulsant agents.[41,42,43] The guidelines summarize the use of the newer agents in patients newly diagnosed with seizures, patients with refractory seizures, and patients with refractory epilepsy. The guidelines suggest that gabapentin (Fanatrex, Neurontin), lamotrigine (Lamictal), topiramate (Topamax), and oxcarbazepine (Trileptal) have enough supporting evidence to use as monotherapy in adolescents and adult patients newly diagnosed with partial or mixed seizures. They may also prove beneficial as adjunctive therapy in adult patients with partial seizures. Lamotrigine may be useful as monotherapy in children newly diagnosed with absence seizures. For adults and children with Lennox-Gastaut syndrome, the guidelines recommend that lamotrigine and topiramate may be used to control the "drop attacks". The guidelines mention the option of using of felbamate (Felbatol) in Lennox-Gastaut and partial seizures, but the guidelines suggest its use only when all other options have been exhausted due to the risks involved.

Fibromyalgia[44,45,46,47,48]

Fibromyalgia is a chronic disorder characterized by pain, fatigue, and sleep disturbances. It predominantly affects women and is difficult to treat. A multidisciplinary approach should be utilized. Diagnostic criteria for fibromyalgia are based on the American College of Rheumatology (ACR) criteria, characterized by widespread musculoskeletal pain and excess tenderness in at least 11 of 18 predefined anatomic sites, referred to as trigger points. Pain is considered widespread when all of the following are present: pain in the left and right side of the body, pain above and below the waist, and axial skeletal pain (cervical spine, anterior chest, thoracic spine, or low back). Digital palpation should be performed with an approximate force of four kg. For a tender point to be considered "positive" the subject must state that the palpation was painful. "Tender" is not to be considered "painful." For classification purposes, patients will be said to have fibromyalgia if both criteria are satisfied. Widespread pain must have been present for at least three months. The presence of a second clinical disorder does not exclude the diagnosis of fibromyalgia. Lab tests for thyroid stimulating hormone (TSH) and erythrocyte sedimentation rate (ESR) are recommended to rule out hypothyroidism and polymyalgia rheumatica, respectively, as they have similar symptomatology.

Tricyclic antidepressants (TCAs), an unapproved class of drugs for the treatment of fibromyalgia, have been found to be effective in a couple of trials of short duration.[49,50] These drugs are associated with a number of adverse effects including anticholinergic effects (e.g., dry mouth and urinary retention), orthostatic hypotension, and cardiac dysfunction. Gabapentin, also unapproved for the treatment of fibromyalgia, has low bioavailability and is not rapidly absorbed; therefore, it requires a dosage regimen of three to four times daily. Data exist to support the effectiveness of gabapentin in the treatment of fibromyalgia.[51] FDA-approved drugs for the treatment of fibromyalgia include duloxetine (Cymbalta®), milnacipran (Savella®), and pregabalin (Lyrica). The American Pain Society (APS) last produced guidelines for fibromyalgia pain treatment in 2005, prior to any product receiving FDA approval for treatment of this condition.[52] The APS guidelines recommend amitriptyline (and other TCAs) or cyclobenzaprine as the initial pharmacologic option, with selective serotonin reuptake inhibitors (SSRIs), tramadol, and opioids also listed as subsequent options. Amitriptyline and cyclobenzaprine received the highest ranking regarding strength and consistency of evidence at the time. There is no comparative evidence to support the superiority of any of these products in fibromyalgia.

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Diabetic Peripheral Neuropathic Pain and Neuropathic Pain[53,54,55,56,57]

Anticonvulsant medications have long been used in the management of pain. The clinical impression is that they are useful for chronic neuropathic pain, especially when the pain is lancinating or burning.[58] Several of the anticonvulsants have unlabeled uses for the treatment of various types of neuropathic pain. Carbamazepine (Tegretol, Tegretol XR, Epitol, and Carbatrol), one of the carbamazepine derivatives reviewed in this document, is indicated for treatment of trigeminal neuralgia.[59]

Diabetic peripheral neuropathic pain (DPNP) is a common complication of diabetes mellitus. The etiology, though not completely understood, is thought to be multifactorial. The most common symptoms associated with DPNP are pain or loss of feeling in the toes, feet, legs, and arms. DPNP can affect many aspects of life and severely limit the patient's daily functions. Loss of sensation in the periphery may lead to muscle weakness and loss of reflexes, especially in the ankles, which can lead to gait disturbances. Patients with DPNP may be unaware of pressure or injury, leading to blisters or sores appearing on numb areas of the foot or leg. These areas may go unnoticed for extended periods of time, increasing the risk for infection and possibly amputation.

Diagnosis of DPNP is based on the presence of symptoms and a physical exam. A comprehensive foot exam is performed to assess skin appearance and integrity, muscles, bones, circulation, and sensation of the feet. Pin prick sensation, vibration perception, 10-g monofilament pressure sensation, and assessment of ankle reflexes are commonly performed tests used to screen, diagnose, and assess DPNP. General treatment measures include glycemic control, foot care, and the treatment of pain.

Consensus guidelines (2006) from the Mayo Clinic recommend duloxetine (Cymbalta), as well as oxycodone CR (Oxycontin®), pregabalin (Lyrica) and tricyclic antidepressants as first-tier agents for the treatment of DPNP.[60] Duloxetine is not recommended for patients with hepatic insufficiency or where drug interactions are a factor. Venlafaxine ER (Effexor XR, Venlafaxine Extended-Release Tablets), along with tramadol (Ultram) and the antiepileptic drugs carbamazepine, gabapentin, and lamotrigine, are identified as second-tier agents. These guidelines were supported by a grant from the manufacturer of duloxetine.

For the management of neuropathic pain, first-line treatments include nortriptyline, desipramine, duloxetine, venlafaxine, gabapentin, pregabalin, or topical lidocaine according to the 2007 Neuropathic Pain treatment guidelines.[61] Efficacy of the recommended medications was supported by at least one methodologically sound, randomized clinical trial demonstrating superiority to placebo or a relevant comparison treatment. Recommendations were based on the amount and consistency of evidence, degree of efficacy, safety, and clinical experience of the authors. Second line agents include opioid analgesics and tramadol. Medication selection should be individualized, considering adverse effects, potential beneficial or deleterious effects on comorbidities, and whether prompt onset of pain relief is necessary.

Bipolar Disorder

With bipolar disorder, a person can experience recurrent attacks cycling between periods of depression and mania. Therefore, two different sets of DSM-IV criteria exist to diagnosis bipolar disorder and treat from the perspective of whether the person is experiencing a manic/hypomanic episode or a depressive episode.[62] Criteria used to diagnose the manic/hypomanic episode for bipolar disorder consist of the patient experiencing persistent elevated, expansive, or irritable mood for at least four days and three or more characteristic symptoms. These symptoms include inflated self-

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esteem or grandiosity, decreased need for sleep, more talkative than usual or pressured speech, flight of ideas or feelings of racing thoughts, distractibility, increase in goal-directed activity or psychomotor agitation, and excessive involvement in risky pleasurable activities. Criteria used to diagnose a depressive bipolar episode include first determining if the person has experienced at least one manic/hypomanic episode in the past in addition to the depressed mood, which has been present during a two-week period at minimum. In addition, five or more depression symptoms must be present, which include a depressed mood most of the day every day, diminished interest in activities and hobbies, significant weight change, insomnia or hypersomnia, psychomotor agitation or retardation nearly every day, fatigue, feeling of guilt or worthlessness, indecisiveness or inability to concentrate, and recurrent thoughts of death or suicide. Two primary types of bipolar disorder exist and are designated based on the severity of the disease and the manic episodes. People with bipolar disorder I (formerly manic depression) have had at least one fully manic episode with periods of major depression. In contrast, patients with bipolar disorder II seldom experience full-fledged mania. Rather, they experience periods of hypomania with elevated levels of energy and impulsiveness that are not as extreme as the symptoms of mania.

There is no cure for bipolar disorder, but the appropriate pharmacological treatment can decrease morbidity and mortality associated with the disorder. Per the 2002 American Psychiatric Association (APA) guidelines, first-line pharmacological treatment for more severe manic or mixed episodes requires the initiation of lithium or valproate plus an antipsychotic agent. Second generation antipsychotics are preferred over the first generation antipsychotic agents due to their more tolerable short-term adverse effect profile.[63] For a bipolar manic episode with less severity, monotherapy with lithium, valproate, or an antipsychotic may be sufficient. Use of standard antidepressants as monotherapy can precipitate a manic episode in bipolar patients. Use of antidepressants in bipolar patients, misdiagnosed as having non-bipolar depression, precipitates the first manic episode. During maintenance treatment, recommendations suggest to first optimize the medication dose in bipolar patients, especially in patients experiencing a breakthrough manic episode, and then consider adding another first-line agent if dose optimization of the initial agent doesn't lead to a satisfactory response. Another option is to change antipsychotic agents and monitor the patient for response. In contrast to first-line treatment for a bipolar manic episode, first-line treatment for a bipolar depressive episode is the initiation of lithium or lamotrigine; antidepressant monotherapy is not recommended. An alternative treatment option for more severe depressive episodes is the initiation of lithium with an antidepressant. Finally, if an acute depressive episode doesn't respond to the optimal dose of first-line medication treatment, then the addition of lamotrigine, bupropion (Wellbutrin), or paroxetine (Paxil) is recommended. Patients with bipolar depression experiencing psychotic features usually require adjunctive treatment with an antipsychotic.

Some of the anticonvulsants have been used for the treatment of bipolar disorder; a few have been approved for the treatment of bipolar disorder. Carbamazepine (Equetro), an extended-release formulation, is indicated for treatment of acute manic and mixed episodes associated with bipolar I disorder. Lamotrigine (Lamictal) is also approved for bipolar disorder. Several valproic acid derivatives are approved for management of bipolar disorder including valproic acid ER (Stavzor), divalproex (Depakote), and divalproex ER (Depakote ER).

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Prevention of Migraine

Migraine headache prophylaxis has been suggested for patients whose headaches occur in a predictable pattern (menstrual migraine), occur more than two to three times per month, produce profound impairment, where symptomatic therapies have failed or produced serious adverse effects, and/or headaches that can not be tolerated by the patient.[64] An evidence-based practice guideline recommended that preventive therapy goals include: reduction of migraine frequency, severity, and duration, improved responsiveness to treatment of acute attacks, improve function, and reduce disability.[65] Agents that are FDA-approved for the prevention of migraine include the beta-blockers – timolol and propranolol (Inderal®, Inderal® LA); topiramate (Topamax), divalproex sodium (Depakote), divalproex sodium ER (Depakote ER), and valproic acid ER (Stavzor).

Pharmacology[66]

Drug	Mechanism Of Action
Barbiturates	
mephobarbital	Barbiturates depress CNS activity by binding to the barbiturate site at the gamma-aminobutyric acid (GABA) receptor complex, enhancing GABA activity. Barbiturates reduce monosynaptic and polysynaptic transmission resulting in decreased excitability of the entire nerve cell. They also increase the threshold for electrical stimulation of the motor cortex.
Primidone (Mysoline)	
phenobarbital	
Hydantoins	
ethotoin (Peganone)	The hydantoins appear to stabilize rather than raise the seizure threshold and to prevent the spread of seizure activity rather than abolish the primary focus of discharge. The primary site of action appears to be the motor cortex. Possibly by promoting sodium efflux from neurons, hydantoins tend to stabilize the threshold against hyperexcitability caused by excessive stimulation or environmental changes capable of reducing membrane sodium gradient.
Phenytoin (Dilantin, Phenytek)	
Succinimides	
ethosuximide (Zarontin)	Succinimides suppress the paroxysmal three-cycles-per-second spike and wave activity associated with lapses of consciousness common in absence seizures. The frequency of epileptiform attacks is reduced, apparently by motor cortex depression and elevation of the threshold of the CNS to convulsive stimuli.
Methsuximide (Celontin)	
Benzodiazepines	
clonazepam (Klonopin)	Benzodiazepines potentiate the effects of GABA. Benzodiazepines suppress the spike and wave discharge associated with absence seizures.
Diazepam rectal gel (Diastat)	
Carbamazepine Derivatives	
carbamazepine (Tegretol, Tegretol XR, Carbatrol, Epitol, Equetro)	Carbamazepine reduces polysynaptic responses and blocks the post-tetanic potentiation. The mechanism of action of carbamazepine in bipolar disorder and treatment of pain in trigeminal neuralgia is unknown.
Oxcarbazepine (Trileptal)	*In vitro* electrophysiological studies indicate that oxcarbazepine produces blockade of voltage-sensitive sodium channels, resulting in stabilization of hyperexcited neural membranes, inhibition of repetitive neuronal firing, and diminution of propagation of synaptic impulses.

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Pharmacology (continued)

Drug	Mechanism Of Action
Valproic Acid And Derivatives	
valproic acid (Depakene) valproic acid ER (Stavzor) divalproex (Depakote, Depakote ER, Depakote Sprinkle)	Valproic acid and derivatives increase brain concentration of GABA.
Other Anticonvulsants	
felbamate (Felbatol)	*In vitro* studies indicate felbamate has weak inhibitory effects on GABA-receptor binding and benzodiazepine receptor binding.
Gabapentin (Fanatrex, Gralise, Neurontin)	Gabapentin binds to the presynaptic α_2-delta subunit of voltage sensitive calcium channels.
Lacosamide (Vimpat)	Lacosamide selectively enhances slow inactivation of voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes and inhibition of repetitive neuronal firing.
Lamotrigine (Lamictal, Lamictal XR)	Lamotrigine inhibits voltage-sensitive sodium channels, thereby stabilizing neuronal membranes which modulate presynaptic transmitter release of excitatory amino acids.
Levetiracetam (Keppra, Keppra XR)	Levetiracetam inhibits burst firing without affecting normal neuronal excitability. It may also prevent propagation of seizure activity.
Pregabalin (Lyrica)	Pregabalin binds to presynaptic α_2-delta subunit of voltage sensitive calcium channels, inhibiting release of pro-nociceptive neurotransmitters in the spinal cord
rufinamide (Banzel)	*In vitro* studies indicate rufinamide modulates the activity of the sodium channels by prolonging the inactivity of the channel.
Tiagabine (Gabitril)	Tiagabine enhances the activity of GABA.
Topiramate (Topamax)	Topiramate exhibits sodium channel blocking action; potentiates activity of GABA; antagonizes the glutamate (excitatory amino acid) receptor; and inhibits carbonic anhydrase.
Vigabatrin (Sabril)	Vigabatrin is believed to be the result of its action as an irreversible inhibitor of γ-aminobutyric acid transaminase (GABA-T), the enzyme responsible for the metabolism of the inhibitory neurotransmitter GABA. This action results in increased levels of GABA in the CNS.
Zonisamide (Zonegran)	Zonisamide blocks sodium channels and reduces voltage-dependent, transient, inward currents, consequently stabilizing neuronal membranes and suppressing neuronal hypersynchronization. It also facilitates both dopaminergic and serotonergic transmission and is a weak carbonic anhydrase inhibitor.

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PHARMACOKINETICS

Drug	Half-Life (Hr)	Active Metabolites	Excretion (%)	Therapeutic Serum Levels (μG/mL)
Barbiturates				
mephobarbital[67]	--	75 percent of dose is converted to phenobarbital	--	--
primidone (Mysoline)[68]	10-12	PEMA (half-life 29-36 hours) phenobarbital (half-life 53-140 hours)	Renal: 40-60	5-12 15-40
phenobarbital[69]	53-140	--	Urine: 25	15-40
Hydantoins				
ethotoin (Peganone)[70]	3-9	3	Urine	15-50
phenytoin (Dilantin, Phenytek)[71,72]	7-42	No	Urine	10-20
Succinimides				
ethosuximide (Zarontin)[73]	60 (adults) 30 (children)	No	Renal	40-100
methsuximide (Celontin)[74]	2.6-4	N-desmethyl-methsuximide (NDM)	--	--
Benzodiazepines				
clonazepam (Klonopin)[75]	30-40	No	Urine	20-80 ng/mL
diazepam rectal gel (Diastat)[76]	46	desmethyldiazepam (half-life 71 hours) 3-hydroxydiazepam 3-hydroxy-N-diazepam	Urine	--
Carbamazepine Derivatives				
carbamazepine (Tegretol, Tegretol XR, Carbatrol, Epitol, Equetro)[77,78,7980]	25-65 initially then 12-17 after repeated doses	10,11-epoxide	Urine: 72 Feces: 28	4-12
oxcarbazepine (Trileptal)[81]	2	10-mono-hydroxy (MHD, half-life 9 hours)	Urine: 95 Feces: <4	--
Vaproic Acid And Derivataives				
valproic acid (Depakene)[82], valproic acid ER (Stavzor)[83], divalproex sodium (Depakote, Depakote ER, Depakote Sprinkle)[84,85]	9-16	Yes	Renal	50-100

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Pharmacokinetics (continued)

Drug	Half-Life (Hr)	Active Metabolites	Excretion (%)	Therapeutic Serum Levels (mcg/mL)
Other Anticonvulsants				
felbamate (Felbatol)[86]	20-23	No	Urine: >90	--
gabapentin (Fanatrex,Gralise, Neurontin)[87 88]	5-7	No	Renal	--
lacosamide (Vimpat)[89]	13	No	Urine: 95	--
lamotrigine (Lamictal)[90]	25	No	Urine: 94 Feces: 2	--
lamotrigine (Lamictal XR)[91]	33	No	Urine: 94 Feces: 2	--
levetiracetam (Keppra, Keppra XR)[92,93]	6-8	No	Urine: 66	--
pregabalin (Lyrica)[94]	6	No	Urine: 90-98	--
rufinamide (Banzel)[95]	6-10	No	Urine: 85	--
tiagabine (Gabitril)[96]	7-9	No	Urine: 25 Feces: 63	--
topiramate (Topamax)[97]	21	6 metabolites	Renal	--
vigabatrin (Sabril)[98]	7.5	No	Renal	--
zonisamide (Zonegran)[99]	63	N-acetyl zonisamide SMAP	Urine: 62 Feces: 3	--

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CONTRAINDICATIONS/WARNINGS

Drug	Selected Warnings	Monitoring
barbiturates[100]	habit forming, additive CNS depression when used with other CNS depressants, contraindicated in patients with porphyria, marked impairment of liver function, or respiratory disease in which dyspnea or obstruction is evident.	periodic lab evaluation of hematopoietic, hepatic, and renal systems
benzodiazepines[101,102]	interference with cognitive and motor functioning	periodic blood counts and liver function tests (LFTs)
carbamazepines[103,104,105]	serious dermatologic reactions, bone marrow suppression	testing for HLA-B*1502 in patients with Asian ancestry, pretreatment blood count
hydantoins[106,107,108]	lymphadenopathy, alcohol intake, exacerbation of porphyria, hepatic abnormalities and hematologic disorders	serum concentrations, complete blood count (CBC), LFTs, urinalysis
succinimides[109,110]	blood dyscrasias, functional liver and renal changes, systemic lupus erythematosus (SLE)	periodic blood counts, liver function testing, urinalysis

In 2008, the Food and Drug Administration (FDA) informed healthcare professionals that the Agency has analyzed reports of suicidality (suicidal behavior or ideation) from placebo-controlled clinical studies of eleven drugs used to treat epilepsy, as well as psychiatric disorders and other conditions.[111] In the FDA's analysis, patients receiving antiepileptic drugs had approximately twice the risk of suicidal behavior or ideation (0.43 percent) compared to patients receiving placebo (0.22 percent). The increased risk of suicidal behavior and suicidal ideation was observed as early as one week after starting the antiepileptic drug and continued through 24 weeks. The results were generally consistent among the eleven drugs. The relative risk for suicidality was higher in patients with epilepsy compared to patients who were given one of the drugs in the class for psychiatric or other conditions.

Healthcare professionals should closely monitor all patients currently taking or starting any antiepileptic drug for notable changes in behavior that could indicate the emergence or worsening of suicidal thoughts, behavior, or depression. The 11 drugs included in the analysis were carbamazepine (Carbatrol, Equetro, Tegretol, Tegretol XR), felbamate (Felbatol), gabapentin (Fanatrex, Neurontin), lamotrigine (Lamictal), levetiracetam (Keppra), oxcarbazepine (Trileptal), pregabalin (Lyrica), tiagabine (Gabitril), topiramate (Topamax), valproate (Depakote, Depakote ER, Depakene, Stavzor), and zonisamide (Zonegran). Even though other products were not included in the analysis, the risk of suicidal behavior and suicidal ideation is still possible and should be monitored in patients receiving treatment. All antiepileptic drugs contain this warning.

All antiepileptic drugs should be gradually withdrawn to minimize the potential of increased seizure frequency.

A population-based study showed that congenital malformations were significantly more common among offspring of women using antiepileptic drugs (4.6 percent) than among offspring of women with epilepsy who were not treated throughout pregnancy (2.8 percent).[112] This study did not show an increased risk in children of mothers using carbamazepine, oxcarbazepine, or phenytoin (Dilantin, Phenytek) for epilepsy. Pregnant women taking valproate products during the first trimester had three-

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to four-times higher risk for congenital malformations than mothers with epilepsy who were untreated during pregnancy. Doses of valproate greater than 1.5 gm/day increased the risk ten-fold.

Benzodiazepines should not be used in patients with clinical or biochemical evidence of significant liver disease. They may be used in patients with open angle glaucoma who are receiving appropriate therapy but is contraindicated in acute narrow angle glaucoma.

carbamazepine (Carbatrol, Equetro, Tegretol/XR, Epitol)[113,114,115,116]

For carbamazepine products, serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson Syndrome (SJS), have been reported during treatment with carbamazepine. These reactions are estimated to occur in one to six per 10,000 new users in countries with mainly Caucasian populations, but the risk in some Asian countries is estimated to be about ten times higher. Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS or TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. HLA-B*1502 is found almost exclusively in patients with ancestry across broad areas of Asia. Patients with ancestry in genetically at-risk populations should be screened for the presence of HLA-B*1502 prior to initiating treatment with carbamazepine. Patients testing positive for the allele should not be treated with carbamazepine unless the benefit clearly outweighs the risk.

Aplastic anemia and agranulocytosis have been reported in association with the use of carbamazepine. Data from a population-based, case-control study indicates the risk of developing these reactions is five to eight times greater than in the general population; however, the overall risk of developing these reactions in the untreated general population is low. Furthermore, these reactions occur in approximately six patients per one million population per year for agranulocytosis, and two patients per one million population per year for aplastic anemia. Even though reports of transient or persistent decreased platelet or white blood cell counts are associated with the use of carbamazepine, data are not available to accurately estimate their incidence or outcome. The majority of the reported cases of leukopenia have not progressed to the more serious conditions of aplastic anemia or agranulocytosis. Due to the very low incidence of agranulocytosis and aplastic anemia, the majority of minor hematologic changes observed while monitoring patients on carbamazepine are unlikely to signal the occurrence of either abnormality. Nonetheless, complete pretreatment hematological testing at baseline should be obtained, and monitoring should occur if the patient exhibits low or decreased white blood cell or platelet counts during treatment. Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.

Carbamazepine should not be used in patients with a history of previous bone marrow depression, hypersensitivity to the drug, or known sensitivity to any of the tricyclic compounds, such as amitriptyline, desipramine, imipramine, protriptyline, and nortriptyline. Theoretically, the use of carbamazepine with monoamine oxidase (MAO) inhibitors is not recommended. Before administration of carbamazepine, MAO inhibitors should be discontinued for a minimum of 14 days or longer if the clinical situation permits. Carbamazepine should be avoided in patients with a history of hepatic porphyria (e.g., acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda). Acute attacks have been reported in such patients receiving carbamazepine therapy.

felbamate (Felbatol)[117]

Felbamate is not indicated as a first line antiepileptic therapy. It is recommended for use only in those patients who respond inadequately to alternative treatments and whose epilepsy is so severe that the

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benefits of its use outweighs the substantial risk of aplastic anemia and/or liver failure conferred by its use. Among felbamate-treated patients, aplastic anemia occurs at an incidence of more than 100-fold greater than that seen in the untreated population. The clinical manifestation of aplastic anemia may not be seen until after a patient has been on felbamate for several months; however, the injury to the bone marrow stem cells that is ultimately responsible for the anemia may occur weeks to months earlier. Patients who discontinue felbamate remain at risk for developing anemia for a variable and unknown period afterwards. Felbamate should be discontinued if bone marrow suppression develops. Routine blood testing cannot be reliably used to reduce the incidence of aplastic anemia, but in some cases, it will allow for the detection of hematologic changes before the syndrome presents clinically.

Postmarketing data suggests that acute liver failure is associated with the use of felbamate. Of the reported cases, two-thirds resulted in death or liver transplantation, usually within five weeks of the onset of signs and symptoms of liver failure. Felbamate should be initiated only in patients without active liver disease and with normal baseline serum transaminases. Periodic serum transaminase testing may detect early drug-induced hepatic injury, but it has not been proven to prevent serious injury. Immediate withdrawal of felbamate is warranted with evidence of hepatic injury (≥ two times upper limit of normal for aspartate aminotransferase [AST] or alanine aminotransferase [ALT] or if clinical signs and symptoms develop). Baseline and periodic monitoring of serum transaminases (AST and ALT) are recommended. Patients are considered at an increased risk of liver injury if felbamate is reintroduced after the development of hepatocellular injury during felbamate treatment and who are withdrawn from the drug for any reason. These patients should not return to felbamate treatment. Treatment with felbamate should occur only if the criteria for normal liver function are met, the patient has been fully advised of the risk, and has provided written, informed consent. After meeting these recommendations, it can be considered for either monotherapy or adjunctive therapy in adults.

lacosamide (Vimpat)[118]

Dose-dependent PR interval prolongation and atrioventricular block have been observed in clinical trials. Lacosamide should be used with caution in patients with known cardiac conduction problems or with severe cardiac disease such as myocardial ischemia or heart failure. Atrial fibrillation and flutter have also been reported.

lamotrigine (Lamictal, Lamictal XR)[119,120]

Serious rashes requiring hospitalization and discontinuation of treatment have been reported in association with the use of lamotrigine. The incidence of these rashes, which have included SJS, is approximately 0.8 percent in pediatric patients (age <16 years) and 0.3 percent in adults receiving lamotrigine as adjunctive therapy for epilepsy. In clinical trials of bipolar and other mood disorders, the rate of serious rash was 0.08 percent in adult patients receiving lamotrigine as initial monotherapy and 0.13 percent receiving as adjunctive therapy. Rare cases of TEN and/or rash-related death have been reported in adult and pediatric patients. Although uncertain, the coadministration of lamotrigine with valproate, exceeding the recommended initial dose of lamotrigine, or exceeding the recommended dose escalation for lamotrigine may increase the risk of rash; however, case reports have occurred in the absence of these factors. Nearly all cases of life-threatening rashes associated with lamotrigine have occurred within two to eight weeks after treatment initiation. Benign rashes also occur with lamotrigine; however, it is difficult to determine which rashes will prove serious or life-threatening.

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Recommendations are to discontinue lamotrigine at the first sign of rash unless the rash is clearly not drug-related.

Aseptic meningitis has been reported in both children and adults receiving lamotrigine. The FDA identified 40 cases of aseptic meningitis in patients receiving lamotrigine from December 1994 to November 2009. Post-marketing reports indicate that symptoms may include headache, fever, nausea, vomiting, and nuchal rigidity, as well as rash, photophobia, myalgia, chills, altered consciousness, and somnolence. Cerebrospinal fluid analysis has shown mild to moderate pleocytosis, normal glucose concentrations, and mild to moderate increases in protein. Some patients have had an underlying autoimmune disease such as systemic lupus erythematosus (SLE). New onset hepatic and renal involvement have occurred in some instances, which may suggest these cases were part of a hypersensitivity reaction. Aseptic meningitis associated with lamotrigine has historically developed between one day and 1.5 months after treatment initiation, and resolution usually occurs upon discontinuation of the drug. Re-exposure to lamotrigine can result in a rapid return of the condition (i.e., 30 minutes to one day) with more severe symptoms. If aseptic meningitis is suspected during the use of lamotrigine, the patient should be promptly evaluated and the underlying cause diagnosed so that the appropriate treatment can be initiated. Discontinuation of lamotrigine should be considered if no other cause can be identified. Patients receiving lamotrigine should be advised to report signs and symptoms of meningitis to their healthcare professional.[121]

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), a multi-organ hypersensitivity reaction, has occurred with lamotrigine. Manifestations of DRESS typically include fever, rash, and/or lymphadenopathy in conjunction with other organ system abnormalities including hepatitis, nephritis, hematologic abnormalities, myocarditis, or myositis. Eosinophilia is often present. Early manifestations such as fever and lymphadenopathy may be present without evidence of a rash. Cases of isolated hepatic failure without rash or other organ involvement have also been reported. Three cases of multiorgan dysfunction and disseminated intravascular coagulation (DIC) occurred within 14 days of adding lamotrigine to an existing antiepileptic drug regimen, with subsequent resolution of symptoms following discontinuation of the drug. Fatalities associated with hepatic failure or multiorgan failure occurred in two of 3,796 adults and four of 2,435 pediatric patients during clinical trials. Fatalities have also been reported rarely during post-marketing use. Pruritus was reported in two percent of pediatric patients and five percent or more of adult patients during clinical trials. Maculopapular rash and urticaria were reported infrequently (0.1-one percent). Angioedema, erythema, and eosinophilia occurred rarely (< 0.1 percent).[122]

levetiracetam (Keppra, Keppra XR)[123,124]

In adults experiencing partial onset seizures, levetiracetam is associated with the occurrence of CNS adverse events that can be classified into the categories of somnolence and fatigue, coordination difficulties, and behavioral abnormalities. Somnolence, asthenia, and coordination difficulties occur most frequently within the first four weeks of treatment. Also, levetiracetam is associated with somnolence, fatigue, and behavioral abnormalities in pediatric patients experiencing partial onset seizures.

oxcarbazepine (Trileptal)[125]

Clinically significant hyponatremia, defined by serum sodium level less than 125 mmol/L, can develop during oxcarbazepine use and has generally occurred during the first three months of treatment. Some

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patients first developed hyponatremia more than one year after initiation of therapy, which highlights the importance of monitoring serum sodium levels during maintenance treatment with oxcarbazepine. Monitoring should occur, especially if the patient is receiving other medications known to decrease serum sodium levels, such as those associated with inappropriate antidiuretic hormone secretion or if symptoms develop that possibly indicate hyponatremia, such as lethargy, confusion, obtundation, or increase in seizure frequency or severity.

Rare cases of anaphylaxis and angioedema involving the larynx, glottis, lips, and eyelids in patients after taking the first or subsequent doses of oxcarbazepine have been reported. Angioedema associated with laryngeal edema can be fatal. If a patient develops any of these reactions after treatment with oxcarbazepine, the drug should be discontinued and an alternative treatment started. These patients should not be rechallenged with the drug.

Patients who have had hypersensitivity reactions to carbamazepine should be informed that approximately 25 to 30 percent of them will experience hypersensitivity reactions with oxcarbazepine. For this reason, a thorough history of hypersensitivity reactions with carbamazepine should be obtained prior to treatment, and patients with a positive history should receive it only if the potential benefit justifies the potential risk.

Serious dermatological reactions, including SJS and TEN, have been reported in both children and adults in association with oxcarbazepine use. The median time of onset for reported cases was 19 days.

phenytoin (Dilantin, Phenytek)[126]

There have been a number of reports suggesting a relationship between phenytoin and the development of lymphadenopathy (local or generalized) including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs resembling serum sickness (e.g., fever, rash, and liver involvement). In all cases of lymphadenopathy, follow-up observation for an extended period is indicated, and every effort should be made to achieve seizure control using alternative antiepileptic drugs. Acute alcoholic intake may increase phenytoin serum levels, while chronic alcohol use may decrease serum levels. Phenytoin is contraindicated in those patients with a history of hypersensitivity to phenytoin or other hydantoins.

primidone (Mysoline)[127]

Primidone is contraindicated in patients with porphyria and patients who are hypersensitive to phenobarbital.

rufinamide (Banzel)[128]

Rufinamide demonstrated a decrease in the QT interval and is contraindicated in patients with familial short QT syndrome. Patients with this syndrome have an increased risk of sudden death and ventricular arrhythmias. It should also be used with caution in patients already receiving drugs that shorten the QT interval.

During clinical trials, patients less than 12 years of age receiving rufinamide for at least four weeks experienced multi-organ hypersensitivity syndrome. The patients presented with a rash and at least one of the following symptoms: fever, elevated liver function tests, hematuria, and lymphadenopathy;

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however, due to the variability in the syndrome's expression, abnormalities in other organ systems may indicate the presence of this syndrome. If this syndrome is suspected, rufinamide should be discontinued, and an alternative therapy started. Also, patients who develop a rash without any other symptoms during treatment should be closely monitored.

To prevent the precipitation of seizures, seizure exacerbation, or status epilepticus during discontinuation, the dose of rufinamide should be gradually withdrawn by 25 percent every two days. Patients who require abrupt discontinuation due to medical necessity should be closely monitored while being transitioned over to another agent.

topiramate (Topamax)[129 130]

Hyperchloremic, non-anion gap, metabolic acidosis (e.g., decreased serum bicarbonate below the normal reference range in the absence of chronic respiratory alkalosis) is associated with topiramate treatment. Metabolic acidosis is caused by renal bicarbonate loss due to the inhibitory effect of topiramate on carbonic anhydrase. Conditions or therapies that predispose to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhea, surgery, ketogenic diet, or drugs) may add to the bicarbonate lowering effects of topiramate.

A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has been reported in patients receiving topiramate. Symptoms include acute onset of decreased visual acuity and/or ocular pain. Ophthalmologic findings can include myopia, anterior chamber shallowing, ocular hyperemia (redness), and increased intraocular pressure. Mydriasis may or may not be present. This syndrome may be associated with supraciliary effusion resulting in anterior displacement of the lens and iris, with secondary angle closure glaucoma. Symptoms typically occur within one month of initiating topiramate. Topiramate should be discontinued.

Topiramate can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries indicate that infants exposed to topiramate in utero have an increased risk for cleft lip and/or cleft palate (oral clefts). When multiple species of pregnant animals received topiramate at clinically relevant doses, structural malformations, including craniofacial defects, and reduced fetal weights occurred in offspring.

valproate/divalproex (Depakene, Depakote/ER, Stavzor)[131,132,133,134]

Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid and its derivatives. Children under the age of two years are at increased risk of developing fatal hepatotoxicity, especially those on multiple anticonvulsants, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease. When valproic acid/divalproex is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. These incidents usually have occurred during the first six months of treatment. Serious or fatal hepatotoxicity may be preceded by nonspecific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and vomiting. In patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for appearance of these symptoms. Liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first six months.

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Valproate derivatives can produce teratogenic effects such as neural tube defects (e.g., spina bifida). Accordingly, the use of valproic acid/divalproex in women of childbearing potential requires that the benefits of its use be weighed against the risk of injury to the fetus.

Cases of life-threatening pancreatitis have been reported in both children and adults receiving valproate and its derivatives. Some of the cases have been described as hemorrhagic with a rapid progression from initial symptoms to death. Cases have been reported shortly after initial use as well as after several years of use. Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation. If pancreatitis is diagnosed, valproate should be discontinued.

Valproate/divalproex products are contraindicated in patients with hepatic disease or significant hepatic dysfunction, known hypersensitivity to the drug, or urea cycle disorders.

vigabatrin (Sabril)[135]

Vigabatrin can cause irreversible vision loss. Because of this, if clinical improvement is not seen within two to four weeks of treatment, vigabatrin should be discontinued. Vision testing should be administered at baseline and at least every three months while on therapy.

Abnormal MRI signal changes and vacuolization have also been reported with vigabatrin use.

zonisamide (Zonegran)[136]

Zonisamide is contraindicated in patients with hypersensitivity to sulfonamides. Zonisamide may cause a severe rash, including Stevens-Johnson syndrome, and toxic epidermal necrolysis. Patients who develop a rash should stop taking zonisamide. Hepatic necrosis, agranulocytosis, and aplastic anemia have also resulted from hypersensitivity. Oligohidrosis, hyperthermia, and heat stroke are also reported in patients on zonisamide. Pediatric patients appear to be at a greater risk.

Risk Mitigation Evaluation Strategy (REMS)

These products must be dispensed with a Medication Guide: carbamazepine (Equetro), clonazepam (Klonopin), ethotoin (Peganone), ethosuximide (Zarontin), gabapentin (Neurontin), lacosamide, lamotrigine (Lamictal, Lamictal ODT, Lamictal XR), levetiracetam (Keppra, Keppra XR), methsuximide (Celontin), pregabalin, rufinamide, tiagabine, topiramate, and zonisamide.

In addition to a Medication Guide, vigabatrin is associated with a Communication Plan that will send Dear Healthcare Professional Letters to all registered ophthalmologists annually. An Implementation System requires that the manufacturer maintains a database of certified pharmacies and prescribers and enrolled patients. The manufacturer must also ensure proper training of all parties involved with the proper dispensing of vigabatrin. Elements To Assure Safe Use mandate that healthcare providers and dispensing pharmacies issuing vigabatrin prescriptions be certified and that vigabatrin is dispensed to recipients who meet treatment criteria and are registered properly.

DRUG INTERACTIONS

There are many different drug interactions associated with each anticonvulsant agent. Phenobarbital, phenytoin (Dilantin, Phenytek), primidone (Mysoline), and carbamazepine (Tegretol, Tegretol XR, Carbatrol, Equetro, Epitol) are potent inducers of CYP 450 and other enzyme systems.

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Barbiturates can induce hepatic microsomal enzymes resulting in increased metabolism and decreased anticoagulant response in oral anticoagulants (e.g., warfarin, acenocoumarol, dicoumarol and phenprocoumon). Phenobarbital has been shown to shorten the half-life of doxycycline for as long as 2 weeks after barbiturate therapy is discontinued. MAO inhibitors prolong the effects of barbiturates probably because metabolism of the barbiturate is inhibited.

Ethosuximide (Zarontin) is metabolized mainly by CYP 3A4 enzyme via hydroxylation to inactive metabolites.[137] Drugs that inhibit, induce, or are metabolized by this enzyme can change the therapeutic levels of the active drug. Depending on the type of drug interaction, dosages of ethosuximide or the interacting drug may need to be adjusted and monitored. Ethosuximide does not inhibit or induce CYP 450 isozymes. Lacosamide (Vimpat) is a CYP 2C19 substrate, but it does not induce or inhibit CYP enzymes. Vigabatrin (Sabril) may induce CYP 2C enzymes in some patients. Methsuximide may increase the plasma concentrations of phenytoin and phenobarbital.

The CNS-depressant action of the benzodiazepine class of drugs may be potentiated by alcohol, narcotics, barbiturates, nonbarbiturate hypnotics, antianxiety agents, the phenothiazines, thioxanthene and butyrophenone classes of antipsychotic agents, monoamine oxidase inhibitors and the tricyclic antidepressants, and by other anticonvulsant drugs.

Coadministration of carbamazepine and nefazodone may result in insufficient plasma concentrations of nefazodone and its active metabolite to achieve therapeutic effect. Coadministration of carbamazepine with nefazodone is contraindicated. Concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects. Concomitant use of carbamazepine and isoniazid has been reported to increase isoniazid-induced hepatotoxicity. Concomitant medication with carbamazepine and some diuretics (hydrochlorothiazide, furosemide) may lead to symptomatic hyponatremia. Carbamazepine may antagonize the effects of nondepolarizing muscle relaxants (e.g., pancuronium). Alterations of thyroid function have been reported in combination therapy with other anticonvulsant medications.[138,139,140,141]

Rufinamide (Banzel) is a weak inducer of the CYP 3A4 enzyme and has been shown to cause a decrease concentration of drugs that are substrates of the CYP 3A4 enzyme. [142] It is also a weak inhibitor of CYP 2E1. Drugs that induce carboxylesterases, such as carbamazepine and phenobarbital, may decrease the concentration of rufinamide; while drugs that inhibit the carboxylesterase enzymes may increase the concentration of rufinamide. Rufinamide has been shown to increase the plasma concentration of phenytoin by 21 percent or more, and valproic acid (Depakene) has been shown to increase the concentration of rufinamide up to 70 percent.

The concomitant use of valproic acid and topiramate (Topamax) has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either agent individually.[143] Symptoms associated with the occurrence of hyperammonemia include acute alteration in level of consciousness, decrease in cognitive function, lethargy, or vomiting. This adverse event is not due to any pharmacokinetic drug interaction, but it has been theorized to occur in patients who have deficiencies in hepatic mitochondrial activity. The administration of these two drugs together uncovers this metabolic defect.

The concomitant use of topiramate (Topamax) with any other drug producing metabolic acidosis (e.g., zonisamide, acetazolamide, or dichlorphenamide), or potentially in patients on a ketogenic diet, may create a physiological environment that increases the risk of kidney stone formation, and should therefore be avoided. The use of metformin is contraindicated in metabolic acidosis conditions.

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Zonisamide (Zonegran) is principally inactivated by CYP 3A4-dependent reduction; therefore, when used in combination with these drugs, its clearance is increased resulting in the possible necessity of a dosage increase.[144] Valproate derivatives (Depakene, Depakote/ER, Stavzor) inhibit many hepatic enzyme systems and can displace drugs from albumin.

Carbamazepine (40 to 90 percent), phenytoin (90 percent), primidone (80 percent), tiagabine (Gabitril) (95 percent), and valproic acid (80 to 95 percent) are highly bound to protein. Tiagabine is displaced from protein by naproxen, salicylates, and valproic acid. Valproic acid displaces diazepam, phenytoin, tolbutamide, and warfarin.

There is concern related to increased risk of failure of oral contraceptives with use of cytochrome P450 3A4 enzyme-inducing AEDs, such as phenobarbital, carbamazepine, phenytoin, felbamate (Felbatol), topiramate, oxcarbazepine (Trileptal), and rufinamide. Since a particular antiepileptic drug may induce metabolism of the estrogen or the progestin and it is unclear which component is clinically more important in pregnancy prevention, it is recommended that women taking enzyme-inducing antiepileptic drugs should receive an oral contraceptive containing at least 50 mcg of ethinyl estradiol and that low-dose formulations should generally be avoided. Patients taking an oral contraceptive and rufinamide are recommended to use secondary non-hormonal form of contraception. Antiepileptic drugs that do not induce cytochrome P450 3A4 enzymes, including valproic acid, gabapentin (Fanatrex, Gralise, Neurontin), levetiracetam (Keppra, Keppra XR), tiagabine, zonisamide, vigabatrin, and pregabalin (Lyrica), do not interact with oral contraceptives. Lamotrigine (Lamictal, Lamictal XR) levels are reduced by 50 percent with use of oral contraceptives. Therefore, dose adjustment of lamotrigine may be required when oral contraceptives are initiated or discontinued, and it should be noted that clinical toxicity could occur during the placebo or pill-free week of the oral contraceptive regimen.[145]

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Drug Interactions Table

Drug	Substrate	Inhibitor	Inducer
barbiturates[146]	--	--	CYP 1A2, 2B6, 2C8, 2C9, 2C18, 2C19, 3A4, 3A5-7
hydantoins[147,148,149]	CYP 2C9, 2C19	--	CYP 1A2, 2B6, 2C8, 2C9, 2C18, 2C19, 3A4, 3A5-7
succinimides[150]	CYP 3A4	--	CYP 3A4 (methsuximide only)
benzodiazepines[151,152]	CYP 3A4 (clonazepam) CYP 2B6, 2C8, 2C9, 2C19, 3A4, 3A5-7 (diazepam)	CYP 2C19, 3A4 (diazepam)	--
Carbamazepine Derivatives			
carbamazepine (Tegretol, Tegretol XR, Carbatrol, Equetro, Epitol)[153,154,155,156]	CYP 3A4	--	CYP 1A2, 3A4
oxcarbazepine (Trileptal)[157]	--	CYP 2C19	CYP 3A4/5
Valproic Acid Derivatives			
valproic acid, divalproex sodium, valproic acid ER (Depakene, Depakote, Depakote ER, Stavzor)[158,159,160,161]	CYP 2C19	CYP 2C9, 2D6, 3A4	--
Other Anticonvulsants			
felbamate (Felbatol)[162]	--	CYP 2C19	--
gabapentin (Fanatrex, Gralise, Neurontin)[163 164]	Not metabolized		
lacosamide (Vimpat)[165]	2C19	--	--
lamotrigine (Lamictal, Lamictal XR)[166,167]	Greater than 75 percent metabolized in the liver by glucuronic acid conjugation; autoinduction may occur		
levetiracetam (Keppra, Keppra XR)[168]	Not extensively metabolized and not dependant on the CYP 450 isoenzymes		
pregabalin (Lyrica)[169]	Not metabolized		
rufinamide (Banzel)[170]	--	CYP 2E1	CYP 3A4
tiagabine (Gabitril)[171]	CYP 3A4 possibly: 1A2, 2D6, 2C19	--	--
topiramate (Topamax)[172]	CYP 2C19	CYP 2C19	--
vigabatrin (Sabril)[173]	Not extensively metabolized, but may induce CYP 2C enzymes in some patients		
zonisamide (Zonegran)[174]	CYP 3A4	--	--

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ADVERSE EFFECTS

Drug	Nausea	Diarrhea	Weight Change	Tremor	Somnolence	Dizziness
Carbamazepine Derivatives						
carbamazepine (Tegretol/XR, Carbatrol)[175,176]	reported	reported	nr	nr	reported	reported
carbamazepine (Equetro)[177]	29	10	nr	nr	32	44
oxcarbazepine (Trileptal)[178]	16	7	+ 2	4	28	22
Valproic Acid Derivatives						
valproic acid (Depakene)[179] divalproex sodium (Depakote/ER)[180,181] valproic acid ER (Stavzor)[182]	34	23	+ 9	57	30	18
Other Anticonvulsants						
felbamate (Felbatol)[183]	reported	5.2	weight loss 3.4	reported	reported	reported
gabapentin (Fanatrex, Gralise, Neurontin)[184 185]	reported	reported	+ 2.9	6.8	19.3	17.1
lacosamide (Vimpat)[186]	7-17 (4)	3-5 (3)	nr	4-12 (4)	5-8 (5)	16-53 (8)
lamotrigine (Lamictal) [187]	7	5	- 5	nr	nr	7
lamotrigine (Lamictal XR) [188]	7 (8)	2 (5)	+ 2 (+ 1)	7 (2)	7 (2)	19 (5)
levetiracetam (Keppra)[189]	5	8	+ >1	>1	15	9
levetiracetam XR (Keppra XR)[190]	5 (3)	nr	nr	nr	8 (3)	5 (3)
pregabalin (Lyrica)[191]	nr	nr	+ 4	8	7-20	10-39
rufinamide (Banzel)[192]	7-12	nr	nr	6	11-17	8-19
tiagabine (Gabitril)[193]	11	2-10	nr	9-21	18-21	27-31
topiramate (Topamax)[194]	10-12	5-6	weight loss 9-13	9	9-15	13-14
vigabatrin (Sabril)[195]	2-10 (8)	10-16 (7)	+6 - +14 (+3)	15-16 (8)	22-26 (13)	24-26 (17)
zonisamide (Zonegran)[196]	9	5	weight loss 3	nr	17	13

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported.

The adverse events reporting for barbiturates, hydantoins, succinimides, and benzodiazepines is not quantified in the majority of the package inserts but rather listed as occurring or not in a review of systems.

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Carbamazepine (Tegretol, Tegretol XR, Carbatrol, and Equetro) may induce hyponatremia similar to the Syndrome of Inappropriate Antidiuretic Hormone release (SIADH). Rashes are frequent, occurring in up to 9.9 percent of patients. Hematological adverse effects have also been reported. Agranulocytosis and aplastic anemia are rare. Thrombocytopenia and anemia have an incidence of less than five percent and usually respond to a cessation of therapy. Leukopenia is the most common hematological side effect with a ten percent incidence. It is usually transient, persisting in about two percent of patients.[197]

Similar to carbamazepine, oxcarbazepine (Trileptal) is associated with hyponatremia (25 percent); this incidence does increase with age. Thirty percent of patients that have experienced a skin rash with carbamazepine will react similarly to oxcarbazepine.[198]

Felbamate (Felbatol) is associated with a marked increase in the incidence of aplastic anemia (one in 3,000 patients) and hepatitis (one in 10,000 patients).[199] Accordingly, use only in patients whose epilepsy is so severe that the risk of aplastic anemia is deemed acceptable in light of the benefits conferred by its use.

Gabapentin (Fanatrex, Gralise, Neurontin) has an 8.3 percent incidence of nystagmus.[200]

Diplopia may occur in six to 16 percent of patients taking lacosamide (Vimpat).[201]

Lamotrigine (Lamictal, Lamictal XR) therapy is associated with rashes; serious rashes requiring hospitalization and discontinuation of treatment have been reported in association with the use of lamotrigine.[202] Pediatric patients on adjunctive therapy appear to have a higher risk of serious rash (eight in 1,000 patients) versus adult patients on adjunctive therapy (three in 1,000 patients). Rashes are usually mild to moderate and associated with high initial doses, rapid titration, and concomitant valproate use (including valproic acid and divalproex sodium). SJS and TEN have also occurred with rare deaths reported. Although benign rashes also occur with lamotrigine, it is not possible to reliably predict which rashes will prove to be serious or life-threatening. Accordingly, lamotrigine should ordinarily be discontinued at the first sign of rash, unless the rash is clearly not drug-related.

Levetiracetam (Keppra) is associated with a slight decrease in red and white blood cells, but levetiracetam XR (Keppra XR) has not demonstrated this in clinical studies; however, the manufacturer recommends monitoring the cell counts due to the results from the immediate release form.[203,204]

Post-marketing reports have shown that tiagabine (Gabitril) is associated with seizures and status epilepticus in patients without epilepsy based on experience from off-label use.[205] In most cases, patients were also taking medications known to lower the seizure threshold. Seizures and status epilepticus are known to occur with overdose. Also, tiagabine is associated with cognitive/neuropsychiatric adverse events such as impaired concentration, speech or language problems, confusion, somnolence and fatigue. These adverse events have led to six percent of patients receiving tiagabine versus two percent of patient receiving placebo to discontinue treatment during controlled clinical trials.

There have been post-marketing reports of angioedema in patients during initial and chronic treatment with pregabalin (Lyrica). Specific symptoms included swelling of the face, mouth (tongue, lips, and gums), and neck (throat and larynx). There were reports of life-threatening angioedema with respiratory compromise requiring emergency treatment. Pregabalin should be discontinued immediately in patients with these symptoms. Exercise caution when prescribing pregabalin to

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patients with a history of angioedema or who are already taking medications associated with angioedema such as angiotensin-converting enzyme (ACE) inhibitors.

Topiramate (Topamax) is a carbonic anhydrase inhibitor. There is an increased rate of kidney stone formation (reduced urinary citrate excretion and increased urinary pH) with nephrolithiasis occurring in 1.5 percent of patients.[206] Metabolic acidosis (due to renal loss of bicarbonate) may also develop because of carbonic anhydrase inhibition. Oligohidrosis, hyperthermia, and heat stroke have been reported, usually following exposure to elevated environmental temperatures. Finally, there are patients who have developed acute myopia and secondary angle-closure glaucoma. These symptoms seem to occur within the first month of therapy.

Zonisamide (Zonegran) is also a carbonic anhydrase inhibitor and a sulfonamide derivative.[207] It is contraindicated in patients with sulfonamide allergy. Zonisamide causes hyperchloremic, non-anion gap, metabolic acidosis caused by renal bicarbonate loss resulting from its effect on carbonic anhydrase. Kidney stones are reported in approximately four percent of epilepsy patients on zonisamide.

Thrombocytopenia is common in patients on valproic acid (Depakene, Stavzor) and divalproex (Depakote, Depakote ER).[208,209,210,211] It occurs in about 27 percent of patients and responds to a decrease in dose. Bone marrow changes also occur, as do leukopenia, transient neutropenia, and erythroblastopenia. There are at least ten known metabolites; one may account for the reported fatal hepatotoxicities and is increased during dosing with enzyme-inducing drugs. This risk is higher in children and decreases in older age groups. Life-threatening pancreatitis has also been reported. Hyperammonemia may also occur, especially in patients with underlying urea cycle disorders.

SPECIAL POPULATIONS[212]

Pediatrics

Barbiturates are used for treatment of epilepsy in children. Mephobarbital is not recommended in infants, although dosage recommendations exist for children less than five years of age and for older children. Dosage recommendations for primidone (Mysoline) exist for neonates, infants, and older children. There are dosage recommendations for phenobarbital for adolescents and older; dosage for infants and children should be individualized.

Dosage of the hydantoins in pediatric patients should be individualized and usually requires serum blood level determinations. Dosage of ethotoin (Peganone) in pediatric patients depends on the age and weight of the patient. Pediatric dosage of phenytoin (Dilantin, Phenytek) is based on weight; children over six years of age and adolescents may require the minimum adult dosage.

Ethosuximide (Zarontin) may be used in children three years of age and older. The initial dose for patients three to six years is 250 mg per day and for patients six years of age and older is 500 mg per day; thereafter, the dose should be individualized based on patient response and plasma level determinations. A smaller capsule providing a lower drug dosage of methsuximide (Celontin) is available for small children; optimal dosage must be determined by trial and should be kept at the lowest dose to control seizures so as to minimize adverse effects.

Specific dosage recommendations for clonazepam (Klonopin) exist for children ten years of age and younger or less than 30 kg body weight. Recommended doses are meant to minimize drowsiness and

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provide seizure control. Clinical studies have not been conducted to establish the efficacy and safety of diazepam rectal gel (Diastat) in children less than two years of age.

Carbamazepine (Tegretol, Tegretol XR, Carbatrol, Epitol) can be used in pediatric patients with specific dosage recommendations for children younger than six years of age, children six to twelve years of age, and children older than twelve years of age. Dosage is ultimately determined by monitoring of blood levels and optimal clinical response. The therapeutic range is the same for both children and adults (4-12 mcg/mL). Carbamazepine ER (Equetro) has not been proven to be safe or effective in children or adolescents.[213]

Felbamate (Felbatol) is indicated in children only as adjunctive therapy for treatment of Lennox-Gastaut syndrome in patients two to 14 years of age and older.

Gabapentin (Fanatrex, Neurontin) is indicated for treatment of partial seizures in children 12 years of age and older with epilepsy and as adjunctive therapy for treatment of partial seizures in children three to 12 years of age with epilepsy. The safety and effectiveness of gabapentin (Fanatrex, Gralise, Neurontin) in the management of postherpetic neuralgia in patients less than 18 years of age has not been studied.

Lacosamide (Vimpat) has not been studied in patients 17 years of age and younger.

Lamotrigine (Lamictal) is indicated for treatment of children two years of age and older for approved indications (partial seizures, the generalized seizures of Lennox-Gastaut syndrome, and PGTC seizures). Safety and effectiveness in patients less than 18 years of age with bipolar disorder have not been established.

Lamotrigine (Lamictal XR) is not approved for patients younger than 13 years of age.

Levetiracetam (Keppra) is indicated as adjunctive therapy for treatment of myoclonic seizures in adolescents 12 years of age and older with juvenile myoclonic epilepsy.[214] Levetiracetam is also used in the management of partial onset seizures in children four years of age and older with epilepsy and of primary generalized tonic-clonic seizures in children six years of age and older with idiopathic generalized epilepsy. Levetiracetam XR (Keppra XR) is indicated as adjunctive therapy in the treatment of partial seizures in patients 16 years of age and older with epilepsy.[215]

Oxcarbazepine (Trileptal) is indicated as monotherapy for treatment of partial seizures in children four years of age and older and as adjunctive therapy in children two years of age and older with epilepsy.

The pharmacokinetics of pregabalin (Lyrica) have not been adequately studied in children. Tiagabine (Gabitril) is indicated as adjunctive therapy for treatment of partial seizures in children at least 12 years of age with epilepsy.

Rufinamide (Banzel) is indicated for adjunctive treatment for seizures associated with Lennox-Gastaut syndrome in patient four years of age and older.[216] Studies indicate that the pharmacokinetics of rufinamide in pediatric patients and adolescents are similar to adults, but drug interactions tend to be more pronounced in pediatric patients.

Topiramate (Topamax) is indicated as initial monotherapy for treatment of partial onset and primary generalized tonic-clonic seizures in children ten years of age and older. Topiramate is also indicated as adjunctive therapy for treatment of partial onset and primary generalized tonic-clonic seizures in children two to 16 years of age and as adjunctive therapy in patients two years of age and older with seizures associated with Lennox-Gastaut syndrome. Pediatric patients have a 50 percent higher

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clearance of topiramate and consequently shorter elimination half-life than adults. Consequently, the plasma concentration for the same mg/kg dose may be lower in pediatric patients compared to adults. Topiramate is not approved for migraine prophylaxis in children at this time.

Valproate has not been established to be safe and effective for the treatment of partial seizures in children under the age of 10 years. Safety and efficacy of valproic acid for epilepsy and migraine prophylaxis has not been established in children less than 10 and 16 years of age.

Vigabatrin (Sabril) is approved for use in infants as young as one month to two years for treatment of infantile spasms. The safety and efficacy for treatment of complex partial seizures with vigabatrin in patients younger than 16 years of age have not been established.

Although off-label use has been reported, safe and effective use of zonisamide (Zonegran) in children less than 16 years of age has not been established. All patients, especially children, should be told to limit exposure to ambient temperature increase or other extremes that might aggravate temperature regulation. Concurrent use of medications that might predispose a patient to heat intolerance (anticholinergics) should be used cautiously with zonisamide (Zonegran).

Pregnancy

Freedom from seizures is the ultimate goal of treatment of patients with epilepsy; however, adverse effects of the antiepileptic drugs should not outweigh the benefits, particularly in women with epilepsy who wish to become pregnant. These women and their partners need to understand the risks associated with uncontrolled seizures as well as the teratogenicity some of the antiepileptic drugs.[217]

Barbiturates and hydantpoins are all classified as Pregnancy Category D.

Clonazepam, diazepam, carbamazepine, and valproic acid, divalproex, topiramate, and valproic acid ER are also classified as Pregnancy Category D. Recent studies have indicated a higher risk of birth defects and possibly adverse cognitive effects with exposure to valproate compared to carbamazepine. Further studies are needed; however, it appears to be reasonable to use valproate with caution in epileptic women who desire to become pregnant with consideration given to possible alternative antiepileptic drugs that may be equally effective and safer. With appropriate counseling, women who need valproate for seizure control should continue the drug and not be discouraged from pregnancy.[218]

All of the drugs in this review of anticonvulsants, other than those named above, are classified as Pregnancy Category C. Although classified as Pregnancy Category C, gabapentin has not been evaluated for use during pregnancy.

A potentially life-threatening bleeding disorder related to decreased levels of vitamin K-dependent clotting factors may occur in newborns exposed to phenytoin *in utero*.[219] This drug-induced condition can be prevented with vitamin K administration to the mother before delivery and to the neonate after birth.

Oxcarbazepine is classified as Pregnancy Category C. It should be noted that there are no well-controlled clinical studies of oxcarbazepine in pregnant women; however, oxcarbazepine is structurally closely related to carbamazepine, which is considered to be teratogenic in humans. Given this fact and the results of animal studies, it is likely that oxcarbazepine is a human teratogen. It should be used during pregnancy only if the potential benefit justifies the potential risk.

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Renal Impairment

Dosage of mephobarbital and phenobarbital should be reduced in patients with impaired renal function.

Ethosuximide and methsuximide should be administered with extreme caution to patients with known renal disease. Periodic urinalysis tests should be performed for patients on these drugs. Ethosuximide and methsuximide do not have guidelines available for dose adjustment in patients with renal dysfunction.

Metabolites of clonazepam and diazepam are excreted by the kidneys; therefore, caution should be exercised in treating patients with impaired renal function.

Felbamate should be used with caution in patients with renal dysfunction.

Dosage adjustments are recommended for gabapentin in patients with compromised renal function. Gabapentin has not been studied in pediatric patients with renal insufficiency.

The maximum dose of lacosamide (Vimpat) in patients with severe renal impairment is 300 mg/day.

Lamotrigine has not been extensively evaluated in patients with severe renal function impairment; therefore, this medication should be used cautiously in these patients.

Dosing of levetiracetam must be individualized based on a patient's renal function.

In patients with impaired renal function (creatinine clearance less than 30 mL/min), oxcarbazepine therapy should be initiated at 50 percent of the usual starting dose and titrated slowly to achieve the desired clinical response.

Adverse reactions to pregabalin are dose-dependent, and it is excreted primarily by renal excretion; therefore, dosage should be adjusted based on renal function as determined by creatinine clearance.

No dosage adjustment is necessary in patients taking rufinamide with impaired renal function (creatinine clearance less than 30 mL/min), but hemodialysis has reduced the rufinamide exposure by about 30 percent. Adjustment of the dose during dialysis may be considered.

In patients with impaired renal function, 50 percent of the topiramate dose is recommended. Renally impaired patients will require a longer time to reach steady state at each dose.

Information about how to adjust the vigabatrin dose in pediatric patients with renal impairment is unavailable. In adults, dose adjustment is necessary in patients with mild, moderate, and severe renal impairment.

Since zonisamide is excreted by the kidneys, patients with renal disease should be treated with caution; titration may need to be slower and monitoring more frequent.

Hepatic Impairment

Dosage of mephobarbital and phenobarbital should be reduced in patients with impaired hepatic function.

Liver function tests should be performed if clinical evidence of liver dysfunction exists during therapy with ethotoin. Signs of liver damage are justification for discontinuation of therapy.

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The liver is the primary site of phenytoin biotransformation; therefore, patients with impaired hepatic function may show early signs of toxicity. As with all patients, phenytoin serum level concentrations should be monitored for optimal clinical effect and safe use of the medication.

Ethosuximide and methsuximide should be administered with extreme caution to patients with impaired hepatic function. Periodic liver function tests should be performed for patients on these drugs.

Clonazepam undergoes hepatic metabolism; therefore, it should not be used in treating patients with impaired hepatic function.

Felbamate should not be prescribed for anyone with a history of hepatic dysfunction as it carries a boxed warning related to hepatic failure.

The maximum dose of lacosamide (Vimpat) in patients with mild to moderate hepatic impairment is 300 mg/day.

Initial, escalation, and maintenance doses of lamotrigine should be reduced by 25 percent in patients with moderate and severe hepatic function impairment without ascites and by 50 percent in patients with severe hepatic function impairment with ascites.

The effects of hepatic impairment on the pharmacokinetics of rufinamide have not been studied, therefore, use in patients with severe hepatic impairment is not recommended. Caution should be exercised in treating patients with mild to moderate hepatic impairment.

Patients with impaired hepatic function may require reduced initial and maintenance doses of tiagabine and/or longer dosing intervals.

Liver disease impairs the capacity to eliminate valproate. Liver impairment is also associated with decreased albumin concentrations and larger unbound fractions (2 to 2.6 fold increase) of valproate. Therefore, monitoring of total concentrations may be misleading because free concentrations may be significantly increased in patients with hepatic disease whereas total concentrations may appear to be normal. Liver function tests should be performed prior to therapy with valproate and at frequent intervals thereafter, especially during the first six months of therapy.

Since zonisamide is metabolized by the liver, patients with hepatic disease should be treated with caution. Titration may need to be slower and monitoring more frequent.

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DOSAGES

Drug	Initial Dose	Maximum Daily Dose	Pediatric Dose	Availability
Barbiturates				
mephobarbital[220]	400 mg/day	600 mg/day (three or four times daily)	16-64 mg/day (three or four times daily)	32, 50, 100 mg tablets
primidone (Mysoline)[221]	100-125 mg	2,000 mg/day (three times daily)	Under 8 years of age: 10-25 mg/kg/day	50, 250 mg tablets
phenobarbital[222]	10-20 mg/kg (load), then 1-3 mg/kg/day	180-300 mg/day (one to two times daily)	1-8 mg/kg/day	20 mg/5 mL elixir 15, 16, 30, 32, 60, 65, 97 100 mg tablets
Hydantoins				
ethotoin (Peganone)[223]	250 mg four times a day	3 grams daily in four to six divided doses	500-1,000 mg daily	250 mg tablets
phenytoin (Dilantin)[224,225,226]	100 mg three times a day	600 mg/day (three to four times daily; convert to once daily with Kapseal)	4-8 mg/kg/day	30, 100 mg ER Kapseals 50 mg chewable tablets 125 mg/5 mL suspension
phenytoin (Phenytek)[227]	100 mg three times a day	600 mg/day (three to four times a day and then convert to once daily)	4-8 mg/kg/day	200 mg, 300 mg ER capsules
Succinimides				
ethosuximide (Zarontin)[228]	250-500 mg/day	1.5 gm/day or until control is achieved with minimal side effects (two times a day)	20 mg/kg/day	250 mg capsules 250 mg/5 mL syrup/solution
methsuximide (Celontin)[229]	300 mg daily	1.2 gm/day or until control is achieved with minimal side effects (two to four times a day)	dosing not specified in label	300 mg capsules
Benzodiazepines				
clonazepam (Klonopin)[230]	0.5 mg three times a day	20 mg/day (three times a day)	0.1-0.2 mg/kg/day	0.5, 1, 2 mg tablets 0.125, 0.25, 0.5, 1, 2 mg orally disintegrating tablets (wafers)
diazepam rectal gel (Diastat)[231]	0.2 mg/kg one time and may repeat in four to 12 hours if needed	One episode every five days or five episodes every month	0.2-0.5 mg/kg	2.5 mg Twin Pack 10, 20 mg Acudial

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Dosages (continued)

Drug	Initial Dose	Maximum Daily Dose	Pediatric Dose	How Supplied
Carbamazepine Derivatives				
carbamazepine (Tegretol/XR, Carbatrol, Epitol)[232,233,234]	**Epilepsy:** 400 mg/day (200 mg twice daily for both IR and ER; give suspension as 100 mg four times daily). May increase dose weekly by adding up to 200 mg/day; use a twice daily regimen for ER tablets or three to four times daily for other formulations. **Trigeminal neuralgia:** 200 mg/day (100 mg twice daily for both IR and XR; give Carbatrol 200 mg one time on first day; give suspension 50 mg four times daily)	**Epilepsy:** 1,600 mg/day (twice daily for XR/ER and three to four times a day for IR) Trigeminal neuralgia: 1,200 mg/day	**Children < 6 years:** Initially, 10 to 20 mg/kg/day twice daily or three times daily as tablets or four times daily as suspension. May increase dose weekly up to 35 mg/kg/day. **Children 6-12 years:** Initially, 100 mg twice daily IR or ER tablets or 2.5 mL four times daily for suspension. May increase dose weekly by adding up to 100 mg/day using twice daily regimen of ER tablets or three to four times daily of other formulations up to 1,000 mg/day.	200 mg tablets 100 mg chewable tablets 100 mg/5 mL suspension 100, 200, 400 mg XR tablets 100, 200, 300 mg ER capsules
carbamazepine (Equetro)[235]	**Bipolar Disorder:** 400 mg/day (twice a day)	**Bipolar Disorder:** 1,600 mg/day (twice a day)	--	100, 200, 300 mg ER capsules
oxcarbazepine (Trileptal)[236]	300 mg twice a day	2,400 mg/day (twice a day)	Weight dependent targets range 900-2,100 mg/day	150, 300, 600 mg tablets 300 mg/5 mL suspension
Valproic acid and derivatives				
valproic acid (Depakene)[237]	10-15 mg/kg/day (doses greater than 250 mg/day should be given in divided doses)	60 mg/kg/day (doses greater than 250 mg/day should be given in divided doses)	10-15 mg/kg/day	250 mg capsules 250 mg/5 mL syrup
valproic acid ER (Stavzor)[238]	10-15 mg/kg/day (doses greater than 250 mg/day should be given in divided doses)	60 mg/kg/day (doses greater than 250 mg/day should be given in divided doses)	≥10 years: 10-15 mg/kg/day	125, 250, 500 mg delayed-release capsules
divalproex (Depakote/ER)[239, 240,241]	10-15 mg/kg/day	60 mg/kg/day (delayed release dosed twice a day; ER dosed once daily)	≥10 years: 10-15 mg/kg/day	125, 250, 500 mg delayed-release tablets 125 mg Sprinkle capsules 250, 500 mg ER tablets

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Dosages (continued)

Drug	Initial Dose	Maximum Daily Dose	Pediatric Dose	How Supplied
Other Anticonvulsants				
felbamate (Felbatol)[242]	1,200 mg/day (three to four times a day)	3,600 mg/day (three to four times a day)	15 to 45 mg/kg/day	400, 600 mg tablets 600 mg/5 mL suspension
gabapentin (Fanatrex, Neurontin)[243]	300 mg three times a day	3,600 mg/day (three times a day)	up to 50 mg/kg/day	100, 300, 400 mg capsules 600, 800 mg tablets 250 mg/5 mL, 250 mg/10 mL solution
gabapentin (Gralise)[244]	300 mg/day	1,800 mg/day (once daily)	--	300, 600 mg tablets
lacosamide (Vimpat)[245]	50 mg twice daily	200-400 mg daily in two divided doses	--	50, 100, 150, 200 mg tablets 10 mg/mL solution
lamotrigine (Lamictal)[246]	50 mg/day (as adjunct) 25 mg every other day (with valproate)	700 mg/day (as adjunct) 200 mg/day (with valproate) twice a day	5-15 mg/kg/day (with select as adjunct) 1-3 mg/kg/day (with valproate)	25, 100, 150, 200 mg tablets 5, 25 mg chewable tablets 25, 50, 100, 200 mg ODT
lamotrigine (Lamictal XR)[247]	one tablet daily	one tablet daily	one tablet daily	25, 50, 100, 200 mg tablets
levetiracetam (Keppra)[248]	500 mg twice a day	3,000 mg/day (twice a day)	20 to 60 mg/kg/day	250, 500, 750, 1,000 mg tablets 100 mg/mL solution
levetiracetam XR (Keppra XR)[249]	1,000 mg once daily	3,000 mg once daily	--	500, 750 mg tablets
pregabalin (Lyrica)[250]	**DPNP:** 150 mg/day in three divided doses **PHN/ Adjunctive therapy for partial seizures:** 150 mg/day in two to three divided doses **Fibromyalgia:** 150 mg/day in two divided doses	**DPNP:** 300 mg/day **PHN/Adjunctive therapy for partial seizures:** 600 mg/day **Fibromyalgia:** 450 mg/day	--	25, 50, 75, 100, 150, 200, 225, 300 mg capsules 20 mg/mL solution
rufinamide (Banzel)[251]	400-800 mg/day in two equally divided doses with food.	3,200 mg/day in two equally divided doses with food.	≥4 years: 10 mg/kg/day in two equally divided doses. Maximum 45 mg/kg/day or 3,200 mg in two equally divided doses with food.	200, 400 mg tablets 40 mg/mL suspension

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Dosages (continued)

Drug	Initial Dose	Maximum Daily Dose	Pediatric Dose	How Supplied
tiagabine (Gabitril)[252]	4 mg/day (with enzyme-inducing antiepileptic drugs	56 mg/day (with enzyme-inducing antiepileptic drugs) (two to four times a day)	12-18 years up to 32 mg/day (with enzyme-inducing antiepileptic drugs)	2, 4, 12, 16 mg tablets
topiramate (Topamax)[253]	25-50 mg/day in two divided doses	400 mg/day in two divided doses	5-9 mg/kg/day in two divided doses	25, 50, 100, 200 mg tablets 15, 25 mg sprinkle capsules
vigabatrin (Sabril)[254]	500 mg twice daily	1.5 g twice daily	50 mg/kg/day in two divided doses, titrated to a maximum of 150 mg/kg/day	500 mg tablets 500 mg powder for oral solution
zonisamide (Zonegran)[255]	100 mg daily	600 mg/day (one to two times a day)	--	25, 50, 100 mg capsules

Dosage changes may need to be made for each agent based on the other anticonvulsants that the patient is currently receiving, decreased renal and/or hepatic function, and tolerability of the agent. Please consult package inserts for additional information.

carbamazepine: When converting patients from carbamazepine IR to Tegretol XR or Carbatrol, the same total daily dose should be administered. Tegretol XR tablets must be swallowed whole and never crushed or chewed.

phenytoin: Dilantin Kapseals and Phenytek are extended-release capsules formulated with the sodium salt of phenytoin. They are initiated three times daily, and then the patient is converted to once daily dosing when adequate seizure control is attained. The free acid form of phenytoin is used in the Dilantin-125 Suspension and Dilantin Infatab formulations. There is an eight percent increase in drug with the free acid products. They are not to be used for once daily dosing.

valproic acid and derivatives: There are several derivatives of valproic acid available. Each equivalent dosage form (Depakene versus Depakote) delivers the same amount of valproate ion. Depakote causes fewer gastrointestinal adverse effects than Depakene.

When converting patients from twice daily Depakote to once daily Depakote ER, an 8 to 20 percent higher total daily dose of Depakote ER should be given. They are not bioequivalent.

In addition to its use in epilepsy, divalproex ER (Depakote ER) is indicated for use in acute manic or mixed episodes associated with bipolar disorder, with or without psychotic features. The initial dose is 25 mg/kg/day and can be increased to a maximum of 60 mg/kg/day to achieve therapeutic response. It is also indicated for migraine prophylaxis; the starting dose is 500 mg daily for one week, and then 1,000 mg daily.

vigabatrin: Vigabatrin is only available through a special restricted distribution program called SHARE program.

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CLINICAL TRIALS

Search Strategy

Due to the multiple indications for use of the anticonvulsant medications, many of the comparative clinical trials currently available do not specifically focus on treatment of seizure disorder. However, the studies identified in this review attempt to isolate those comparative studies that facilitate identification of the clinically proven therapies in the treatment of seizure disorder that meet the goals of treatment for seizure disorder: reducing the frequency of seizures and providing the optimal quality of life for the patient. When comparative trial information was unavailable, well-designed placebo-controlled studies have been included.

Articles were identified through searches performed on PubMed and review of information sent by the manufacturers. The search strategy included the use of all drugs in this class and the keywords "seizure" and "anticonvulsants". Randomized, controlled, comparative trials of FDA-approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

There are no comparative clinical trials evaluating pregabalin to gabapentin, duloxetine, or milnacipran for the treatment of fibromyalgia. Pregabalin has not been compared to other active treatment in the management of neuropathic pain. Good quality, double-blind, comparative trials have not been performed with divalproex, carbamazepine, and lamotrigine in the management of bipolar disorder.

ethosuximide (Zarontin), valproic acid (Depakene), and lamotrigine (Lamictal)

In a double-blind, randomized, controlled clinical trial, the efficacy, tolerability, and neuropsychological effects of ethosuximide, valproic acid, and lamotrigine in children with newly diagnosed childhood absence epilepsy (n=453) were compared.[256] Drug doses were increased until the child was free of seizures, the maximal allowable or highest tolerable dose was reached, or a criterion indicating treatment failure was met. The primary outcome was freedom from treatment failure after 16 weeks of therapy. Differential drug effects were determined by means of pairwise comparisons. After 16 weeks of therapy, the freedom-from-failure rates for ethosuximide and valproic acid were similar (53 and 58 percent, respectively; $p=0.35$) and were higher than the rate for lamotrigine (29 percent; $p<0.001$ for both comparisons). There were no significant differences among the three drugs with regard to discontinuation because of adverse events. Lamotrigine is not indicated for the treatment of absence seizures.

gabapentin (Neurontin) and carbamazepine (Tegretol)

Gabapentin and carbamazepine have been compared in a randomized, double-blind manner for the treatment of partial or generalized epilepsy in 292 patients.[257] They were similar in efficacy with more

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carbamazepine patients discontinuing therapy due to adverse effects than gabapentin patients (24 percent versus 13.5 percent).

lamotrigine (Lamictal), carbamazepine (Tegretol), and phenytoin (Dilantin)

Lamotrigine has been compared to carbamazepine (n=150) and to phenytoin (n=181) in two separate randomized, double-blind trials for treatment of partial or generalized epilepsy.[258,259] Similar efficacy is noted among the agents with lamotrigine better tolerated. Nineteen percent of carbamazepine patients reported rash versus three percent of lamotrigine patients. In the comparative trial with phenytoin, 14 percent of lamotrigine and nine percent of phenytoin patients reported a rash. In the study, the 100 mg per day starting dose for lamotrigine was higher than currently recommended.

gabapentin (Neurontin), lamotrigine (Lamictal) and carbamazepine (Tegretol)

An 18-center, randomized, double-blind, double-dummy, parallel study of 593 elderly patients with newly diagnosed seizure disorder was conducted to determine the relative tolerability and efficacy of two anticonvulsants, lamotrigine and gabapentin, as compared to carbamazepine.[260] Patients (mean age 72 years) were randomly assigned to one of three treatment groups: gabapentin 1,500 mg daily, lamotrigine 150 mg daily, and carbamazepine 600 mg daily. The primary outcome measure was retention in the trial for at least 12 months. Most patients had multiple medical conditions, received an average of seven concomitant medications, and had a history of cerebral infarction. There was no significant difference in seizure-free rate at 12 months. However, the incidence of adverse effects that resulted in termination of therapy was 12.1 percent for lamotrigine, 21.6 percent for gabapentin, and 31 percent for carbamazepine (p=0.001). The study concluded that lamotrigine and gabapentin should be considered as initial therapy for older patients with newly diagnosed seizures.

lamotrigine (Lamictal) and valproic acid (Depakene)

Lamotrigine has also been compared to valproic acid as monotherapy in refractory partial epilepsy in a randomized, double-blind trial.[261] Lamotrigine 500 mg proved superior to 1,000 mg of valproic acid with 56 percent of the 156 patients completing the study versus 20 percent on valproic acid. Exit criteria were based on worsening seizure activity. Rash was reported by eight percent of valproic acid-treated patients and 11 percent of lamotrigine-treated patients (one with Stevens-Johnson syndrome). The lamotrigine titration rate was higher than currently recommended.

levetiracetam (Keppra) and controlled-release carbamazepine

Adults with two or more partial or generalized tonic-clonic seizures in the previous year were randomly assigned to levetiracetam 500 mg twice daily (n=288) or controlled-release carbamazepine 200 mg twice daily (n=291) in a multicenter, double-blind, noninferiority, parallel-group trial.[262] The dosage could be increased incrementally to a maximum of levetiracetam 1,500 mg twice daily or controlled-release carbamazepine 600 mg twice daily. Patients achieving the primary endpoint of a six-month seizure-free period continued on further treatment for a six-month maintenance period. At per-protocol analysis, 73 percent of levetiracetam patients were seizure-free at six months and 56.6 percent were at one year versus 72.8 percent controlled-release carbamazepine patients were seizure-free at six months and 58.5 percent at one year. Of all patients achieving six-month or one-year remission, 80.1 percent and 86.0 percent in the levetiracetam group and 85.4 percent and 89.3 percent in the carbamazepine group did so at the lowest dose level. Withdrawal rates for adverse events were 14.4 percent with levetiracetam and 19.2 percent with controlled-release carbamazepine.

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oxcarbazepine (Trileptal), phenytoin (Dilantin), and valproic acid (Depakene)

Oxcarbazepine has been compared to phenytoin and valproic acid for the treatment of either partial or generalized seizures.[263,264,265] The randomized, double-blind studies show the agents have similar seizure control. More phenytoin patients discontinued therapy due to adverse effects. The early discontinuation rates due to adverse events were similar in the valproic acid study.

Oxcarbazepine has also been compared to carbamazepine for generalized tonic-clonic seizures in newly diagnosed patients in a similar double-blind study (n=235).[266] Sixty percent of patients on carbamazepine and 52 percent of patients on oxcarbazepine remained seizure-free. Twenty-six percent of carbamazepine patients discontinued treatment as compared to 14 percent of oxcarbazepine patients.Z

topiramate (Topamax) and phenytoin

A randomized, double-blind, 28-day trial of topiramate 100 mg/day versus phenytoin 300 mg/day (after 1,000 mg loading dose) was conducted in 261 patients with new-onset epilepsy.[267] The primary endpoint was time to seizure, and the primary objective was to establish non-inferiority of topiramate to phenytoin in the risk of seizure. At day 28, the estimated seizure-free rate was 81.1 percent for topiramate compared to 90.3 percent for phenytoin. Non-inferiority of topiramate to phenytoin could not be established [hazard ratio 2.0, 95% confidence interval, 0.98 to 4.12, p=0.366; phenytoin was not superior to topiramate. A higher percentage of patients discontinued phenytoin compared to topiramate for all reasons (21.1 versus 12.8 percent) and due to adverse events (13.4 versus 6.8 percent). The most common treatment-related adverse events in both groups were dizziness, paresthesia, and somnolence.

topiramate (Topamax) and sodium valproate

In 24-week, randomized, double-blind, crossover clinical trial, topiramate and sodium valproate were compared for efficacy in the prevention of migraine.[268] A total of 64 patients were randomized to topiramate (25 mg daily increment over one week to 50 mg) for a total of two months. The second group received sodium valproate (200 mg daily increment over one week to 400 mg) for two months. Both treatments appeared to be equivalent in efficacy and safety to sodium valproate with a significant decrease in duration, monthly frequency, and intensity of headache. For the sodium valproate group, the mean monthly migraine frequency decreased from 5.4 to 4.0 episode per month, headache intensity from 7.7 to 5.8 by visual analog scale, and headache duration from 21.3 to 12.3 hours ($p<0.001$). In the topiramate group, mean monthly headache frequency decreased from 5.4 to 3.2 per month, headache intensity from 6.9 to 3.7, and headache duration from 17.3 to 3.9 hours ($p<0.001$). Overall, topiramate and sodium valproate had a similar benefit.

META-ANALYSES

A systematic review evaluated anticonvulsants for effectiveness in the prophylaxis of migraine.[269] All prospective, controlled studies of anticonvulsants in prevention of migraines published through April 2006 were evaluated. Anticonvulsants, considered as a class, reduce migraine frequency by about 1.3 attacks per 28 days compared with placebo, and more than double the number of patients for whom migraine frequency is reduced by > or = 50 percent relative to placebo. Valproate derivatives (Depakene, Depakote/ER, Stavzor) and topiramate (Topamax) were better than placebo, whereas

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clonazepam (Klonopin) and lamotrigine (Lamictal) were not. Gabapentin (Neurontin) was included in the review, but more research needs to be completed.

A systematic review of treatment of bipolar disorder included a total of 583 articles and 913 papers for randomized controlled trials.[270] Findings suggest that lithium is a useful agent in the acute manic and maintenance phase. Both first- and second-generation antipsychotics are efficacious in the treatment of acute mania. For bipolar depression, quetiapine (Seroquel®) and olanzapine/fluoxetine (Symbyax®) are also effective for treating bipolar depression, while olanzapine (Zyprexa®), quetiapine, and aripiprazole (Abilify®) are effective during the maintenance phase. Valproate and carbamazepine have antimanic properties, whereas lamotrigine may be preferably effective in the treatment of depression but not mania.

PERTINENT CLINICAL COMPARISONS[271,272,273,274,275,276,277,278,279]

There is evidence from clinical trials that carbamazepine (Tegretol, Tegretol XR, Carbatrol), gabapentin, lamotrigine, oxcarbazepine (Trileptal), topiramate, and valproate are efficacious as monotherapy in newly diagnosed patients with either partial or mixed seizure disorders. Newly diagnosed patients can be initiated on standard therapy with older agents or on one of the newer drugs mentioned above. For refractory patients with partial seizures, monotherapy with lamotrigine 500 mg per day (on enzyme inducers) is superior to valproic acid 1,000 mg per day. Oxcarbazepine (2,400 mg per day) and topiramate (1,000 mg per day) are also effective as monotherapy.

In a post-hoc analysis, data from five comparative, double-blind, single-drug studies to evaluate the efficacy of treatment of patients with partial seizures with oxcarbazepine (Trileptal) versus carbamazepine, phenobarbital, phenytoin (Dilantin, Phenytek), and valproate for approximately one year were pooled to investigate same-patient seizure outcome at six and 12 months.[280] The main conclusion was that response at six months is an excellent predictor of response at 12 months.

For pediatric patients, the pathophysiology of partial seizures is similar to that of adults and will probably respond to the same drugs. However, gabapentin, lamotrigine, oxcarbazepine, and topiramate are the preferred adjunctive therapies in pediatric patients.

Overall, generalized seizures are easily treated, and refractory patients are rare. Topiramate has clinical support for effectiveness in this population which also extends to pediatrics.

There is evidence that lamotrigine is effective in absence seizures and can be an option for newly diagnosed patients.

The barbiturates and benzodiazepines are C-IV controlled substances; lacosamide (Vimpat) and pregabalin (Lyrica) are C-V.

SUMMARY

Anticonvulsants have very little or no direct comparative data in the treatment of seizures or any other indication. Selection of drugs for epilepsy treatment frequently depends on particular seizure type. For instance, carbamazepine (Tegretol, Tegretol XR, Carbatrol, Epitol) is frequently the first choice for partial seizures. Phenytoin (Dilantin, Phenytek), lamotrigine (Lamictal), valproic acid/divalproex (Depakene, Depakote, Depakote ER, Stavzor), and oxcarbazepine (Trileptal) are also available. The drugs typically chosen first to treat generalized seizures are valproic acid/divalproex, phenytoin, and carbamazepine. For the treatment of absence seizures, valproic acid/divalproex and ethosuximide

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(Zarontin) are the agents most frequently selected. Valproic acid/divalproex has become utilized the most for patients with combined seizure disorders because it has demonstrated efficacy against many other seizure types, such as generalized and partial seizures, in addition to absence seizures. The agents available for use in Lennox-Gastaut Syndrome are lamotrigine (Lamictal), topiramate (Topamax), rufinamide (Banzel), felbamate (Felbatol), and clonazepam (Klonopin). Felbamate should be reserved for use if all other options have been exhausted, and the benefits outweigh the risks of aplastic anemia and hepatotoxicity. Vigabatrin (Sabril) is the only product indicated for the treatment of infantile spasms.

Many drug interactions exist for the anticonvulsants including interactions among adjunctive anticonvulsants. Phenobarbital, phenytoin, primidone (Mysoline), and carbamazepine are potent inducers of CYP 450 and other enzyme systems.

About 70 percent of patients can be maintained on one drug but not all are seizure-free. The most common reason for treatment failure is noncompliance, which may occur in up to 60 percent of patients. If control is not achieved with one drug, an alternative medication should be attempted before others are added to current therapy. Reduced renal function can lead to an accumulation of renally excreted anticonvulsants, such as gabapentin, topiramate, levetiracetam (Keppra, Keppra XR), and pregabalin (Lyrica). Gabapentin (Neurontin), topiramate, and levetiracetam are preferred for treatment of patients with hepatic dysfunction whereas valproate and felbamate are potentially hepatotoxic and should be avoided in these patients.

Utilization of anticonvulsants in epileptic women who use oral contraceptives, who desire to become pregnant, or who are pregnant require considerations related to drug interactions and pregnancy risk factors. The elderly population also requires special considerations related to medication selection and dosage due to age-related factors and their utilization of multiple medications for comorbidities.

It is difficult to make distinctions amongst any of these drugs for any FDA-approved indication. There are small amounts of comparative data, but extensive clinical trials between the agents have not been done. Overall, the agents have similar efficacy with the newer drugs having fewer serious adverse effects and drug interactions.

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