
Anticonvulsants and Anti-Mania Drugs

Seizure Overview

- Of the more than two million people with epilepsy in the United States, about 45% do not achieve complete control of seizures with antiepileptic drugs.¹ The treatment of epilepsy most often begins with monotherapy, and drug dosages are increased until seizures are controlled or adverse effects become problematic. If seizures continue, experts generally prescribe at least one and sometimes a second alternative drug as monotherapy before considering use of two or more drugs at the same time.
- When used for the appropriate seizure type, antiepileptic drugs (AEDs) are roughly equivalent in efficacy. The choice of drug is usually based on factors such as ease of use, adverse effects, interactions with other drugs, presence of comorbid conditions, and cost.²

Executive Summary

Current Basic Core Formulary (BCF) Drugs: The Anticonvulsant and Anti-Mania Drug Class has not been previously reviewed for Uniform Formulary (UF) status. Before implementation of the UF Rule in 2005, the following agents were previously designated as BCF: divalproex (Depakote, Depakote ER, Depakote Sprinkles), carbamazepine (Tegretol), phenytoin (Dilantin), and phenobarbital.

Drugs in the Class (Table 1): There are over 40 AEDs available in the United States. Most are available in generic formulations. The AEDs were classified according to their “parent” compound (e.g., levetiracetam, topiramate, carbamazepine, etc.). Several different subclasses were then identified. The clinical and cost-effectiveness reviews focused on the clinical differences within these subclasses.

- Twelve branded agents remain in the class including Keppra XR, Trokendi XR, Qudexy XR, Lamictal XR, Oxtellar XR, Aptiom, Equetro ER, Vimpat, Fycompa, Onfi, Sabril, and Banzel. Generic formulations of Keppra XR and Lamictal XR recently entered the market.
- Out of the 12 branded products with no generic equivalents, five of the AEDs are unique products, with no therapeutic equivalents: Vimpat, Fycompa, Onfi, Sabril, and Banzel.
- Five other products are branded formulations with therapeutic alternatives: topiramate extended release (Trokendi XR, Qudexy XR); oxcarbazepine extended release (Oxtellar XR), eslicarbazepine (Aptiom), and carbamazepine extended release (Equetro XR).
- Other low-cost generic drugs that were not a focus of the clinical and cost reviews included the following products: phenobarbital, primidone (also used for essential tremor), felbamate, and ethosuximide (drug of choice for absence seizures). These products will remain designated as UF, with phenytoin and phenobarbital remaining as BCF. Two other drugs used for seizures, tiagabine and ezogabine (Potiga) are GABA-type drugs, and are classified as part of the Antidepressant and Non-Opioid Pain agents.
- Two new products, levetiracetam oral tablets for suspension (Spritam) and brivaracetam (Briviact) had not been commercially launched at the time of the review and will be reviewed at a later date.

Table 1. Anticonvulsants and Anti-Mania Drugs Available in the United States[†]

Active Ingredient	Brand	Strengths	FDA Approval	Generic available
Levetiracetam	Keppra	tabs: 250, 750, 1000 mg; oral soln: 100 mg/mL	1999	Yes
	Keppra XR	ER tabs: 500, 750 mg	2008	Yes
	Spritam*	tabs for oral susp: 250, 500, 750, 100 mg	2015	No
Brivaracetam	Briviact*	Tabs: 10, 25, 50, 75, 100 mg; oral soln: 10 mg/mL	Feb 2016	No
Topiramate	Topamax	tabs: 25, 50, 10, 200 mg	1996	Yes
	Topamax Sprinkle	sprinkle: 15, 25 mg caps	1998	Yes
	Trokendi XR	ER caps: 25, 50, 100, 200 mg	2013	No
	Qudexy XR	ER caps: 25, 50, 100, 150, 200 mg	2014	Authorized Generics
Divalproex	Depakote	delayed release tabs: 125, 250, 500 mg	1983	Yes
	Depakote ER	ER tabs: 250, 500 mg	2002	Yes
	Depakote Sprinkles	delayed release caps: 125 mg	1989	No
Valproic Acid	Depakene	caps: 250 mg; syrup: 250 mg/5 mL	1978	Yes
	Stavzor**	delayed release caps: 125, 250, 500 mg	2008	No
Lamotrigine	Lamictal	tabs: 25, 100, 150, 200 mg	1994	Yes
	Lamictal ODT	ODT: 25, 50, 100, 200 mg	2009	No
	Lamictal CD	chewable tabs: 2, 5, 25, 100 mg	1998	Yes
	Lamictal XR	ER tabs: 25, 50, 100, 200, 300 mg	2009	Yes
Oxcarbazepine	Trileptal	tabs: 150, 300, 600 mg; susp: 300 mg/5 mL	2000	Yes
	Oxtellar XR	ER tabs: 150, 300, 600 mg	2012	No
Eslicarbazepine	Aptiom	tabs: 200, 400, 600, 800 mg	2013	No
Carbamazepine	Tegretol	tabs: 200 mg; chew tab: 100 mg; susp: 100 mg/5 mL	1968	Yes
	Tegretol XR	ER tabs: 100, 200, 400 mg	1996	Yes
	Carbatrol	ER caps: 100, 200, 400 mg	1997	Yes
	Epitol	tab: 200 mg; chew tab: 100 mg	1986	Teva generic to Tegretol
	Equetro ER	ER caps: 100, 200, 300 mg	2004	No
Lacosamide	Vimpat	tabs: 50, 100, 150, 200 mg; oral soln: 10 mg/mL	2008	No
Perampanel	Fycompa	tabs: 2, 4, 6, 8, 10, 12 mg	Oct 2012	No
Clobazam	Onfi	tabs: 10, 20 mg; susp: 2.5 mg/mL	Oct 2011	No
Vigabatrin	Sabril	tabs: 500 mg; oral packet for soln: 500 mg	Aug 2009	No
Rufinamide	Banzel	tabs: 200, 400 mg; susp: 40 mg/mL	Nov 2008	No
Zonisamide	Zonegran	caps: 25, 50, 100 mg	2000	Yes

Products in bold are branded, with no AB-rated generics available or with recent generic entrants (Keppra XR and Lamictal XR).

* Spritam – not part of May 2016 review – not launched; will be reviewed as a New Drug

* Briviact – not part of May 2016 review – not launched; will be reviewed as Innovator

**Stavzor – discontinued in 2015– not due to safety or efficacy reasons

[†] Note that other products in the class that have generic equivalents and were not reviewed will remain UF: lithium; phenytoin; phenobarbital; primidone; felbamate; ethosuximide.

Also note that tiagabine and ezogabine (Potiga) are GABA drugs and included in the Antidepressants/Non-Opioid Pain Drug Class.

Indications (Table 2): The AEDs are indicated for multiple seizure types; they also range in use for either monotherapy and/or adjunctive therapy.

Table 2. General Indications (package inserts)

Drug	Partial	Complex Partial	Generalized Tonic-Clonic	Lennox-Gastaut	Myoclonic	Atypical Absence	Infantile Spasm	Absence
Carbamazepine	X		X					
Felbamate	X			X				
Lacosamide (Vimpat)	X							
Lamotrigine	X		X	X	X	X		
Levetiracetam	X		X		X			
Oxcarbazepine	X							
Phenobarbital	X		X					
Phenytoin	X		X					
Primidone	X		X					
Rufinamide (Banzel)	X			X				
Topiramate	X		X	X				
Valproic acid	X	X	X		X	X		
Zonisamide	X							
Clobazam (Onfi)				X				
Perampanel (Fycompa)	X		X					
Vigabatrin (Sabril)*		X					X	
Eslicarbazepine (Aptiom)	X							
Ethosuximide*								X

* Note that there are only two treatments FDA-approved for infantile spasm: vigabatrin (Sabril) and adrenocorticotropic hormone (Acthar Gel, which is not included in this review). Also note that ethosuximide is the only AED indicated for absence seizures and was not reviewed here.

Clinical Literature Evaluation/General Information

Well conducted meta-analysis and systematic reviews are difficult to conduct due to AED dosage differences, population differences, and drug availability when clinical trials were conducted. Controlled trials are difficult to conduct in patients with epilepsy, as the use of a placebo would be unethical, and patients whose seizures are controlled by one medication are often reluctant to be randomized to another drug.

- There are no comparative effectiveness reviews for efficacy, tolerability, and safety of older versus newer antiepileptic treatments.
- Clinical practice guidelines in the United States have not been updated to include recommendations regarding adjunctive therapy and do not include newer products (Vimpat, Fycompa, Onfi, Sabril, and Banzel). In general, the newer products are easier to titrate, are usually dosed QD or BID, or are more tolerable, compared to the older products (carbamazepine, phenytoin, divalproex).
- According to the Medical Letter, the following are drugs of choice for epilepsy.²
 - Partial, including secondarily, generalized seizures
 - Drugs of Choice: lamotrigine, carbamazepine, levetiracetam, oxcarbazepine
 - Alternatives: topiramate, valproate, gabapentin, zonisamide, phenytoin, pregabalin (Lyrica), lacosamide (Vimpat), ezogabine
 - Note that gabapentin, pregabalin, and ezogabine are not included in this review.
 - Primary Generalized Tonic-Clonic Seizures
 - Drugs of Choice: valproate, lamotrigine, levetiracetam
 - Alternatives: topiramate, zonisamide, phenytoin

- Absence Seizures
 - Drugs of Choice: ethosuximide, valproate
 - Alternatives: lamotrigine, clonazepam, zonisamide, levetiracetam
- Atypical Absence, Myoclonic, Atonic Seizures
 - Drugs of Choice: valproate, lamotrigine, levetiracetam
 - Alternatives: topiramate, zonisamide, clonazepam, felbamate, clobazam (Onfi), rufinamide (Banzel)
- The International League Against Epilepsy (ILAE) 2013 evidence review recommends the following AEDs for children when used for initial monotherapy:
 - Partial Onset Seizures
 - Level A: oxcarbazepine
 - Level C: carbamazepine, phenobarbital, phenytoin, topiramate, valproate, vigabatrin (Sabril)
 - Generalized Onset Tonic-Clonic Seizures
 - Level C: carbamazepine, phenobarbital, phenytoin, topiramate, valproate
 - Level D: oxcarbazepine
- Choice of treatment should be based on efficacy, tolerability, and individual patient characteristics.

Efficacy Measures

The primary efficacy measures in epilepsy studies include the following: proportion of seizure-free patients; proportion of patients with seizure remission; 25%, 50%, 75% reduction in seizure frequency; median seizure reduction; and, percent responder rates.

Efficacy

Newer Agents: Due to the lack of comparative effectiveness reviews among the AEDs, the unique efficacy and safety characteristics of the newer drugs will be discussed, with a brief summary of the trials used, to obtain FDA approval.

- Lacosamide (Vimpat)³
 - A systematic review consisting of 14 studies and 3,509 patients assessed the use of lacosamide in adult patients with refractory epilepsy. Based on this evidence, lacosamide, used in combination with other AEDs, was well tolerated and reduced seizure frequency by at least 50% in 18%–69% of patients with refractory focal seizures.
- Perampanel (Fycompa)⁴
 - Published randomized controlled trials had small sample sizes, and meta-analyses included too few studies to draw conclusive results for the assessment of tolerability, efficacy, and safety of perampanel.
 - Perampanel resulted in a statistically significant reduction of seizure frequency with respect to the 50% responder rate in patients with partial onset epilepsy. Perampanel is well tolerated at 4 mg and reasonably tolerated at 8 mg and 12 mg.
- Clobazam (Onfi)⁵
 - Patients aged 2–60 years with Lennox-Gastaut were randomized to placebo or clobazam 0.25, 0.5, or 1.0 mg/kg/day. The study consisted of 4-week baseline, 3-week titration, and 12-week maintenance phases, followed by a 2- or 3-week taper or continuation in an open-label extension. Intention to treat population was 217 patients.
 - Average weekly drop seizure rates decreased 12.1% for placebo versus 41.2% ($p=0.0120$), 49.4% ($p=0.0015$), and 68.3% ($p=0.0001$) for the clobazam 0.25, 0.5, and 1.0 mg/kg/day groups, respectively.
- Vigabatrin (Sabril)⁶
 - A 2-week randomized, single-blinded, multicenter study with a 3-year, open-label, dose-ranging follow-up study included patients who were younger than 2 years of age, had a diagnosed duration of infantile spasms of no more than 3 months, and had not previously been treated with adrenocorticotrophic hormone, prednisone, or valproic acid. Treatment responders were those who were free of infantile spasm for 7 consecutive days.
 - Overall, 32 of 142 patients who were able to be evaluated for efficacy were treatment responders (8/75 receiving low-dose vigabatrin versus 24/67 receiving high doses, $p < 0.001$). Vigabatrin was well tolerated and safe; only 9 patients discontinued therapy because of adverse events.
- Rufinamide (Banzel)⁷
 - A double-blind, randomized, placebo-controlled trial was conducted in patients with Lennox-Gastaut syndrome. Eligible patients between 4 and 30 years of age had multiple types of seizures with a minimum of 90 seizures in the month before baseline.
 - After a 28-day baseline period, 138 patients received either rufinamide ($n = 74$) or placebo ($n = 64$) in addition to their other antiepileptic drugs. The median percentage reduction in total seizure frequency was greater in the rufinamide therapy group than in the placebo group (32.7% versus 11.7%, $p = 0.0015$). There was a difference ($p < 0.0001$) in drop attack seizure frequency with rufinamide (42.5% median percentage reduction) versus placebo (1.4% increase).
- Eslicarbazepine (Aptiom)⁸

- A multicenter, parallel-group studied the efficacy and safety of eslicarbazepine as adjunctive treatment in adults with refractory partial onset seizures. Patients were randomized to placebo (n = 102) or once-daily 400 mg (n = 100), 800 mg (n = 98), or 1,200 mg (n = 102) in the double-blind treatment phase.
- Seizure frequency over the maintenance period (primary endpoint) was significantly lower than placebo in the 1,200 mg (p = 0.0003) and 800 mg (p = 0.0028) groups. These doses were well tolerated and more effective than placebo in patients who were refractory to treatment with one or two concomitant AEDs.

Common Adverse Events

With most AEDs, there are mainly dose-related adverse effects that could be considered typical, such as sedation, drowsiness, incoordination, nausea, and fatigue. Careful dose titration with small initial doses can reduce the likelihood of these adverse effects occurring. Information on adverse effects of the older AEDs are well known, but the newer drugs do not have the long-term adverse event data to clearly understand the effects. Table 3 summarizes the major adverse effects of the AEDs.

Table 3. Systemic and Neurologic Side Effects⁹⁻²⁰

Drug	Systemic Side Effects	Neurologic Side Effects
Carbamazepine	nausea, vomiting, diarrhea, hyponatremia, rash, pruritus	drowsiness, dizziness, blurred or double vision, lethargy, headache
Clobazam (Onfi)	increased salivation, nausea, vomiting, constipation	somnolence, aggression, irritability, ataxia, insomnia
Eslicarbazepine (Aptiom)	nausea, vomiting, diarrhea, fatigue, rash	dizziness, drowsiness, headache, diplopia, vertigo, ataxia, attention disturbance, blurred vision, tremor (Note: dizziness, diplopia, and ataxia reported more frequently in combination with carbamazepine)
Lacosamide (Vimpat)	nausea, vomiting, fatigue	ataxia, dizziness, headache, diplopia
Lamotrigine	rash, nausea	dizziness, tremor, diplopia
Levetiracetam	infection	fatigue, somnolence, dizziness, agitation, anxiety, irritability, depression
Oxcarbazepine	nausea, rash, hyponatremia	sedation, headache, dizziness, vertigo, ataxia, diplopia
Perampanel (Fycompa)	weight gain, fatigue, nausea	dizziness, somnolence, irritability, gait disturbance, falls, aggression, mood alteration
Rufinamide (Banzel)	nausea, vomiting, fatigue	dizziness, somnolence, headache
Topiramate	weight loss, paresthesia	fatigue, nervousness, difficulty concentrating, confusion, depression, anorexia, language problems, anxiety, mood problems, tremor
Valproate	weight gain, nausea, vomiting, hair loss, easy bruising	tremor, dizziness
Vigabatrin (Sabril)	vision loss	drowsiness, fatigue, dizziness
Zonisamide	nausea, anorexia	Somnolence, dizziness, ataxia, confusion, difficulty concentrating, depression

Additional Safety Concerns

- Vigabatrin (Sabril) is associated with visual defects. Approximately 40% of patients lose peripheral vision, which can be permanent.
- Perampanel (Fycompa) is the only AED with a black box warning for serious psychiatric and behavioral reactions.
- Suicidality: The FDA reported in 2008 that a meta-analysis of data from placebo-controlled studies of 11 AEDs found an increased risk of suicidal behavior and ideation in patients taking these drugs: 0.43% of patients on AEDs (n=27,863) compared to 0.22% of those on placebo (n=16,029). However, the overall incidence was extremely low and its clinical significance was questionable. The results of a large cohort study among patients in the United States suggest that gabapentin, lamotrigine, oxcarbazepine, and tiagabine may increase the risk of suicidal acts compared with topiramate or carbamazepine.

Product Niches/Place in Therapy

- **Levetiracetam**—approved for primary generalized tonic-clonic seizures in patients as young as 6; generics to Keppra XR recently entered the market.
- **Topiramate IR (Topamax)**—several off-label uses including weight loss, bipolar disorder, alcohol dependency, obsessive compulsive disorder, and post-traumatic stress disorder. In addition to other seizure types (partial onset seizures and primary generalized tonic-clonic seizures), Topamax is approved for patients with Lennox-Gastaut down to the age of 2 years. Also approved for migraine headache.
- **Topiramate ER (Trokendi XR, Qudexy XR)**—The newer extended release products Trokendi XR and Qudexy XR do not offer clinically compelling advantages over generic topiramate IR. Manual Prior Authorization criteria were recommended in August 2014 (implemented December 2014) for Qudexy XR and Trokendi XR, limiting use to the FDA indications for seizures and appropriate age range.
- **Valproic Acid**—alternative to ethosuximide for absence seizures. Depakene generic is approved for multiple seizure types in children down to the age of 10 years. The branded product Stavzor is marketed as easier to swallow because capsules are 40% smaller than divalproex sodium delayed- or extended-release 500 mg capsules. However, this product was discontinued from the market in 2015 and supplies are exhausted.
- **Lamotrigine**—approved for Lennox-Gastaut in patients as young as 2 years. Generic entrants are now available for Lamictal XR.
- **Oxcarbazepine**—generic Trileptal is available and approved for pediatrics down to the age of 2 years with partial seizures and is available in a liquid formulation. Good tolerability profile. Oxtellar XR is dosed once daily. Eslicarbazepine (Aptiom) is also dosed once daily and has less drug interactions than Trileptal. Other than the patient convenience, Oxtellar XR and Aptiom do not offer clinically compelling advantages over the formulary AEDs.
- **Carbamazepine**—generic Tegretol approved for patients as young as 6. The branded carbamazepine product Equetro ER is only approved for mania, and not seizures. Epitol is a branded generic of Tegretol from the manufacturer Teva. There are no clinically compelling advantages for Epitol or Equetro ER over generic carbamazepine formulations.
- **Lacosamide (Vimpat)**—unique mechanisms of action at the sodium channels; well tolerated except for dizziness and somnolence; easy to titrate. Lacosamide is approved for partial onset seizures in patients down to age 17 years. An oral solution and tablets are available.
- **Perampanel (Fycompa)**—unique mechanism of action at the glutamate receptor. Its place in therapy is for refractory patients with secondary generalized seizures or exclusively for focal seizures as a second- or third-line agent. Fycompa is the only AED with a black box warning for hostility, aggression, and homicidal ideation. Its long duration of action can prolong adverse effects of sedation, headache, and dizziness.
- **Clobazam (Onfi)**—approved as adjunctive therapy for Lennox-Gastaut seizures in patients as young as 2 years. It is a derivative of benzodiazepines that targets alpha 2 receptors over alpha 1 receptors, which causes less sedation than typical benzodiazepines. Frequently used in pediatric patients with refractory seizures.
- **Vigabatrin (Sabril)**—approved for infantile spasms (down to age of 1 year) and refractory complex partial seizures (down to the age of 10 years). Risk of vision loss requires restricted distribution and enrolling in a patient registry.
- **Rufinamide (Banzel)**—approved for Lennox-Gastaut down to the age of 1 year, but there are concerns of shortened QT interval and the risk of inducing status epilepticus.
- **Zonisamide**—generics available; several off-label uses, including treatment of migraine headache, weight loss, and mood disturbances. In children, it is frequently used as monotherapy or add-on therapy.
- **Ethosuximide**—approved for absence seizures.

Conclusion

- No drug has been proven superior overall at treating seizures. When used for the appropriate seizure type, the AEDs are roughly equivalent in efficacy.
- Clinical guidelines indicate that a variety of medications are needed to treat seizures effectively.
- AED treatment selection should be based on drug characteristics, including side effect profile, ease of administration, potential drug interactions, as well as other characteristics, including seizure type and epilepsy syndrome.

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