

Anticonvulsant Medications: Use in Adults



The Centers for Medicare & Medicaid Services (CMS), Medicaid Integrity Group (MIG) has identified issues with the utilization of medications in the anticonvulsant drug therapy class. The U.S. Food and Drug Administration (FDA) approves product labeling for prescription drugs. The MIG has identified that some providers may have prescribed anticonvulsant medications outside of FDA-approved product labeling for indication, age, dosage, or duration of therapy. Therefore, CMS's goal is to improve quality of care and enhance patient safety by educating providers on the proper use of anticonvulsant medications in adults.

This fact sheet summarizes the current FDA-approved product labeling for the use of anticonvulsant medications in adults. After reading this fact sheet, providers should be able to accurately:

- Identify the FDA-approved indications for the use of anticonvulsant medications in adults;
- Identify the available treatment guidelines for the management of seizures in adults; and
- Summarize the adverse reactions and risks of anticonvulsant medications.

FDA-Approved Indications for Anticonvulsant Medications in Adults

Anticonvulsant medications are used for the prevention and treatment of seizures that may or may not be a result of epilepsy, a neurological disorder that affects approximately 2.3 million people in the United States.[1] Patients diagnosed with epilepsy experience recurrent seizures; however, not all seizures are a result of epilepsy. A seizure may last from a few seconds to several minutes, and can also be caused by low blood sugar, alcohol or drug withdrawal, high fever, or head trauma.[2]

Anticonvulsant medications are FDA approved to treat seizures and many other medical conditions unrelated to seizure disorders. However, not all anticonvulsants are FDA approved for every indication. The FDA-approved indications for the use of anticonvulsant medications in adult patients are:

- Bipolar I disorder;
- Epilepsy;
- Mania;
- Migraines;
- Postherpetic neuralgia;
- Prevention and treatment of seizures occurring during and following neurosurgery;
- Restless leg syndrome (RLS);
- Seizures (absence, myoclonic, partial-onset, and tonic-clonic);
- Seizures associated with Lennox-Gastaut syndrome (LGS); and
- Trigeminal neuralgia.



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ACRONYMS

AHRQ	Agency for Healthcare Research and Quality
CDER	Center for Drug Evaluation and Research
CMS	Centers for Medicare & Medicaid Services
FDA	U.S. Food and Drug Administration
LFT	liver function test
LGS	Lennox-Gastaut syndrome
MIG	Medicaid Integrity Group
OTC	over the counter
RLS	restless leg syndrome
SHARE	Support, Help, and Resources for Epilepsy
SJS	Stevens-Johnson syndrome
TEN	toxic epidermal necrolysis
WBC	white blood cell

Dosing schedules for anticonvulsant medications are guided by the specific indication for use. Some anticonvulsant medications require dosage adjustments for renal function, hepatic function, and other patient factors. When anticonvulsant medications are used in combination, or when a patient is transitioned from one anticonvulsant to another, a dosage adjustment may be required. Specific recommendations for dosage adjustments can be found in the prescribing information for each medication.

LGS is a rare condition that primarily affects young children. Because seizures associated with LGS are difficult to control with medication and treatment regimens are highly individualized, the FDA-approved anticonvulsant medications for the treatment of LGS are not included in this fact sheet.[3] The benzodiazepines and barbiturates are also not discussed in this fact sheet because they are infrequently used for the long-term treatment of seizures.

The indications and dosages for the anticonvulsant medications discussed in this fact sheet are provided in the “Anticonvulsant Medications: U.S. Food and Drug Administration-Approved Indications and Most Common Dosages for Adults” document.

Monitoring Parameters for Select Anticonvulsant Medications

Some of the anticonvulsant medications require monitoring of drug levels to ensure their safe use. The therapeutic drug levels of the anticonvulsant medications that require drug level monitoring are provided in Table 1 below.

Table 1. Therapeutic Drug Levels for Anticonvulsant Medications

Medication	Therapeutic Level
carbamazepine[4]	4 mcg per ml to 12 mcg per ml
ethosuximide[5]	40 mcg per ml to 100 mcg per ml
phenytoin[6]	10 mcg per ml to 20 mcg per ml
valproic acid[7]	50 mcg per ml to 125 mcg per ml (mania)
valproic acid	50 mcg per ml to 100 mcg per ml (epilepsy)

Treatment Guidelines for the Use of Anticonvulsant Medications in Adults

The Agency for Healthcare Research and Quality (AHRQ) hosts a database of treatment guidelines. The AHRQ is a branch of the U.S. Department of Health and Human Services. Please visit <http://www.guideline.gov> for the AHRQ’s National Guideline Clearinghouse. Links to some of the treatment guidelines for the management of seizures and the use of anticonvulsant medications in adults are provided in Table 2.

Table 2. Treatment Guidelines for Anticonvulsant Medications

Sponsoring Organization	Title of Guideline	Link to Guideline
American Academy of Neurology, Quality Standards Subcommittee	Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors.	http://www.guideline.gov/content.aspx?id=2823
American Academy of Neurology and American Epilepsy Society, Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee	Practice parameter update: management issues for women with epilepsy--focus on pregnancy (an evidence-based review): obstetrical complications and change in seizure frequency.	http://www.guideline.gov/content.aspx?id=14681
Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons	Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents—second edition.	http://www.guideline.gov/content.aspx?id=36899

Adverse Reactions and Risks of Anticonvulsant Medications

The prescribing information for each anticonvulsant medication provides details on the adverse reactions and risks of that medication. The adverse reactions and risks vary with each medication. Prescribing information can be found by searching the medication name at either <http://www.accessdata.fda.gov/scripts/cder/drugsatfda> on the FDA website or <http://dailymed.nlm.nih.gov> on the DailyMed website.

Several of the anticonvulsant medications have boxed warnings that draw attention to serious and potentially life-threatening adverse reactions. The anticonvulsant medications with boxed warnings are carbamazepine, valproic acid, lamotrigine, vigabatrin, and perampanel.

Risk of Suicidality

Anticonvulsant medications have shown an increased risk of suicidality. In pooled analyses that included 11 anticonvulsant medications, results showed that patients taking an anticonvulsant were almost twice as likely to experience suicidal behavior or ideation as those patients taking a placebo.[8] The FDA requires the manufacturers of anticonvulsant medications to include a warning in the prescribing information.

A Medication Guide has also been developed to alert patients and caregivers to the risk of suicidality. The Medication Guide is dispensed with every new and refilled prescription. Links to the required Medication Guides can be found at <http://www.fda.gov/Drugs/DrugSafety/ucm085729.htm> on the FDA website.

Carbamazepine

Carbamazepine may cause dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS). These reactions can be fatal. The medication should be discontinued if a patient presents with a drug-induced rash.[9] If anticonvulsant therapy is required, the patient should be treated with a different anticonvulsant medication.

Aplastic anemia and agranulocytosis have also been associated with carbamazepine therapy. Baseline white blood cell (WBC) and platelet counts should be obtained before starting carbamazepine and should be monitored periodically based on clinical judgment.[10] Boxed warnings have been added to alert patients and providers to these risks.

The boxed warnings for carbamazepine state:[11]

WARNINGS

SERIOUS DERMATOLOGIC REACTIONS AND HLA-B*1502 ALLELE

SERIOUS AND SOMETIMES FATAL DERMATOLOGIC REACTIONS, INCLUDING TOXIC EPIDERMAL NECROLYSIS (TEN) AND STEVENS-JOHNSON SYNDROME (SJS), HAVE BEEN REPORTED DURING TREATMENT WITH TEGRETOL. THESE REACTIONS ARE ESTIMATED TO OCCUR IN 1 TO 6 PER 10,000 NEW USERS IN COUNTRIES WITH MAINLY CAUCASIAN POPULATIONS, BUT THE RISK IN SOME ASIAN COUNTRIES IS ESTIMATED TO BE ABOUT 10 TIMES HIGHER. STUDIES IN PATIENTS OF CHINESE ANCESTRY HAVE FOUND A STRONG ASSOCIATION BETWEEN THE RISK OF DEVELOPING SJS/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 TEGRETOL. PATIENTS TESTING POSITIVE FOR THE ALLELE SHOULD NOT BE TREATED WITH TEGRETOL UNLESS THE BENEFIT CLEARLY OUTWEIGHS THE RISK (SEE **WARNINGS AND PRECAUTIONS, LABORATORY TESTS**).

APLASTIC ANEMIA AND AGRANULOCYTOSIS

APLASTIC ANEMIA AND AGRANULOCYTOSIS HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF TEGRETOL. DATA FROM A POPULATION-BASED CASE CONTROL STUDY DEMONSTRATE THAT THE RISK OF DEVELOPING THESE REACTIONS IS 5-8 TIMES GREATER THAN IN THE GENERAL POPULATION. HOWEVER, THE OVERALL RISK OF THESE REACTIONS IN THE UNTREATED GENERAL POPULATION IS LOW, APPROXIMATELY SIX PATIENTS PER ONE MILLION POPULATION PER YEAR FOR AGRANULOCYTOSIS AND TWO PATIENTS PER ONE MILLION POPULATION PER YEAR FOR APLASTIC ANEMIA.

ALTHOUGH REPORTS OF TRANSIENT OR PERSISTENT DECREASED PLATELET OR WHITE BLOOD CELL COUNTS ARE NOT UNCOMMON IN ASSOCIATION WITH THE USE OF TEGRETOL, DATA ARE NOT AVAILABLE TO ESTIMATE ACCURATELY THEIR INCIDENCE OR OUTCOME. HOWEVER, THE VAST MAJORITY OF THE CASES OF LEUKOPENIA HAVE NOT PROGRESSED TO THE MORE SERIOUS CONDITIONS OF APLASTIC ANEMIA OR AGRANULOCYTOSIS.

BECAUSE OF THE VERY LOW INCIDENCE OF AGRANULOCYTOSIS AND APLASTIC ANEMIA, THE VAST MAJORITY OF MINOR HEMATOLOGIC CHANGES OBSERVED IN MONITORING OF PATIENTS ON TEGRETOL ARE UNLIKELY TO SIGNAL THE OCCURRENCE OF EITHER ABNORMALITY. NONETHELESS, COMPLETE PRETREATMENT HEMATOLOGICAL TESTING SHOULD BE OBTAINED AS A BASELINE. IF A PATIENT IN THE COURSE OF TREATMENT EXHIBITS LOW OR DECREASED WHITE BLOOD CELL OR PLATELET COUNTS, THE PATIENT SHOULD BE MONITORED CLOSELY. DISCONTINUATION OF THE DRUG SHOULD BE CONSIDERED IF ANY EVIDENCE OF SIGNIFICANT BONE MARROW DEPRESSION DEVELOPS.

Valproic Acid and Divalproex

Valproic acid and its derivatives, including divalproex, have been associated with hepatotoxicity, teratogenicity, and pancreatitis. Patients requiring valproic acid therapy should be made aware of these risks prior to the initiation of therapy. Hepatotoxicity usually occurs in children younger than two years old and within the first six months of therapy, although it may occur at any time and may occur in patients older than two years old. Liver function tests (LFTs) should be monitored prior to initiation of therapy and periodically throughout the course of treatment.[12]

The risks of treatment with valproic acid and its derivatives should be discussed with the patient and weighed against the potential benefits. Valproic acid is a known teratogen. Female patients in their childbearing years should also be provided with the medication guide (included in the prescribing information) that describes the teratogenic potential of valproic acid.[13] In addition, studies indicate that exposure to valproic acid in utero causes adverse effects on cognitive function in children; they “have lower cognitive test scores than children exposed in utero to either another antiepileptic drug or to no antiepileptic drugs.”[14] Female patients who become pregnant while taking valproic acid should be encouraged to enroll in the North American Antiepileptic Drug Pregnancy Registry. Information on the registry can be found at <http://www.massgeneral.org/aed> on the Massachusetts General Hospital website.[15]

Pancreatitis may occur in children and adults. Patients should be educated about the warning signs of pancreatitis and encouraged to seek treatment if they occur.[16]

The boxed warnings for valproic acid state:[17]

WARNING: LIFE THREATENING ADVERSE REACTIONS

Hepatotoxicity

Hepatic failure resulting in fatalities has occurred in patients receiving valproate and its derivatives. Children under the age of two years are at a considerably 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 Depakote 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. The incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.

These incidents usually have occurred during the first six months of treatment. Serious or fatal hepatotoxicity may be preceded by non-specific 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 [see Warnings and Precautions (5.1)].

Fetal Risk

Valproate can cause major congenital malformations, particularly neural tube defects (e.g., spina bifida). In addition, valproate can cause decreased IQ scores following *in utero* exposure.

Valproate is therefore contraindicated in pregnant women treated for prophylaxis of migraine [see Contraindications (4)]. Valproate should only be used to treat pregnant women with epilepsy or bipolar disorder if other medications have failed to control their symptoms or are otherwise unacceptable.

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Valproate should not be administered to a woman of childbearing potential unless the drug is essential to the management of her medical condition. This is especially important when valproate use is considered for a condition not usually associated with permanent injury or death (e.g., migraine). Women should use effective contraception while using valproate [see *Warnings and Precautions* (5.2, 5.3, 5.4)].

A Medication Guide describing the risks of valproate is available for patients [see *Patient Counseling Information* (17)].

Pancreatitis

Cases of life-threatening pancreatitis have been reported in both children and adults receiving valproate. 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 ordinarily be discontinued. Alternative treatment for the underlying medical condition should be initiated as clinically indicated [see *Warnings and Precautions* (5.5)].

Lamotrigine

Serious skin rashes have been associated with lamotrigine. The risk of occurrence may be related to concomitant valproate therapy, exceeding the recommended initial dose, or rapidly increasing the dose. The medication should be discontinued if a patient presents with a drug-induced rash.[18]

The boxed warning for lamotrigine states:[19]

WARNING: SERIOUS SKIN RASHES

LAMICTAL® can cause serious rashes requiring hospitalization and discontinuation of treatment. The incidence of these rashes, which have included Stevens-Johnson syndrome, is approximately 0.8% (8 per 1,000) in pediatric patients (2 to 16 years of age) receiving LAMICTAL as adjunctive therapy for epilepsy and 0.3% (3 per 1,000) in adults on adjunctive therapy for epilepsy. In clinical trials of bipolar and other mood disorders, the rate of serious rash was 0.08% (0.8 per 1,000) in adult patients receiving LAMICTAL as initial monotherapy and 0.13% (1.3 per 1,000) in adult patients receiving LAMICTAL as adjunctive therapy. In a prospectively followed cohort of 1,983 pediatric patients (2 to 16 years of age) with epilepsy taking adjunctive LAMICTAL, there was 1 rash-related death. In worldwide postmarketing experience, rare cases of toxic epidermal necrolysis and/or rash-related death have been reported in adult and pediatric patients, but their numbers are too few to permit a precise estimate of the rate.

Other than age, there are as yet no factors identified that are known to predict the risk of occurrence or the severity of rash caused by LAMICTAL. There are suggestions, yet to be proven, that the risk of rash may also be increased by (1) coadministration of LAMICTAL with valproate (includes valproic acid and divalproex sodium), (2) exceeding the recommended initial dose of LAMICTAL, or (3) exceeding the recommended dose escalation for LAMICTAL. However, cases have occurred in the absence of these factors.

Nearly all cases of life-threatening rashes caused by LAMICTAL have occurred within 2 to 8 weeks of treatment initiation. However, isolated cases have occurred after prolonged treatment (e.g., 6 months). Accordingly, duration of therapy cannot be relied upon as means to predict the potential risk heralded by the first appearance of a rash.

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Although benign rashes are also caused by LAMICTAL, it is not possible to predict reliably which rashes will prove to be serious or life-threatening. Accordingly, LAMICTAL should ordinarily be discontinued at the first sign of rash, unless the rash is clearly not drug-related. Discontinuation of treatment may not prevent a rash from becoming life threatening or permanently disabling or disfiguring [see *Warnings and Precautions (5.1)*].

Vigabatrin

Vision loss has been associated with vigabatrin therapy. Patients should have their vision tested within four weeks of starting vigabatrin and every three months during the course of therapy. Because of the risk of vision loss, vigabatrin is only available through Support, Help, and Resources for Epilepsy (SHARE), a restricted distribution program.[20]

The boxed warning for vigabatrin, which includes information on the SHARE restricted distribution program, states:[21]

WARNING: VISION LOSS

- SABRIL causes permanent bilateral concentric visual field constriction in 30 percent or more of patients that ranges in severity from mild to severe, including tunnel vision to within 10 degrees of visual fixation, and can result in disability. In some cases, SABRIL also can damage the central retina and may decrease visual acuity.
- The onset of vision loss from SABRIL is unpredictable, and can occur within weeks of starting treatment or sooner, or at any time during treatment, even after months or years.
- The risk of vision loss increases with increasing dose and cumulative exposure, but there is no dose or exposure known to be free of risk of vision loss.
- Vision testing at baseline (no later than 4 weeks after starting SABRIL) and at least every 3 months during therapy is required for adults on SABRIL. Vision testing is also required about 3 to 6 months after the discontinuation of SABRIL therapy. Once detected, vision loss due to SABRIL is not reversible. It is expected that, even with frequent monitoring, some patients will develop severe vision loss.
- It is possible that vision loss can worsen despite discontinuation of SABRIL.
- Because of the risk of vision loss, SABRIL should be withdrawn from patients who fail to show substantial clinical benefit within 3 months of initiation, or sooner if treatment failure becomes obvious. Patient response to and continued need for SABRIL should be periodically reassessed.
- Symptoms of vision loss from SABRIL are unlikely to be recognized by patients or caregivers before vision loss is severe. Vision loss of milder severity, while often unrecognized by the patient, can still adversely affect function.
- SABRIL should not be used in patients with, or at high risk of, other types of irreversible vision loss unless the benefits of treatment clearly outweigh the risks. The interaction of other types of irreversible vision damage with vision damage from SABRIL has not been well-characterized, but is likely adverse.
- SABRIL should not be used with other drugs associated with serious adverse ophthalmic effects such as retinopathy or glaucoma unless the benefits clearly outweigh the risks.
- The lowest dose and shortest exposure to SABRIL should be used that is consistent with clinical objectives.

Because of the risk of permanent vision loss, SABRIL is available only through a special restricted distribution program called SHARE, by calling 1-888-45-SHARE. Only prescribers and pharmacies registered with SHARE may prescribe and distribute SABRIL. In addition, SABRIL may be dispensed only to patients who are enrolled in and meet all conditions of SHARE [see **WARNINGS AND PRECAUTIONS, Distribution Program for SABRIL (5.2)**].

Perampanel

Perampanel has been associated with serious psychiatric and behavioral reactions. Patients should be monitored for signs and symptoms of psychiatric and behavioral adverse reactions including aggression, anger, irritability, hostility, and homicidal ideation and threats. Patients and caregivers should be instructed to contact a healthcare provider if any of these reactions or changes in behavior are observed.[22]

The boxed warning for perampanel states:[23]

WARNING: SERIOUS PSYCHIATRIC AND BEHAVIORAL REACTIONS

- **Serious or life-threatening psychiatric and behavioral adverse reactions including aggression, hostility, irritability, anger, and homicidal ideation and threats have been reported in patients taking FYCOMPA (5.1)**
- **These reactions occurred in patients with and without prior psychiatric history, prior aggressive behavior, or concomitant use of medications associated with hostility and aggression (5.1)**
- **Advise patients and caregivers to contact a healthcare provider immediately if any of these reactions or changes in mood, behavior, or personality that are not typical for the patient are observed while taking FYCOMPA or after discontinuing FYCOMPA (5.1)**
- **Closely monitor patients particularly during the titration period and at higher doses (5.1)**
- **FYCOMPA should be reduced if these symptoms occur and should be discontinued immediately if symptoms are severe or are worsening (5.1)**

Resources

Please visit <http://www.medicaid.gov/Medicaid-CHIP-Program-Information/By-State/By-State.html> for links to State Medicaid program websites.

The Center for Drug Evaluation and Research (CDER) hosts a website providing health professionals with current information on over-the-counter (OTC) and prescription drugs. Visit <http://www.fda.gov/Drugs/ResourcesForYou/HealthProfessionals> to access drug-related databases, information on drug recalls and alerts, current information on new and generic drug approvals, and information on drug safety and availability.

Section 1927(g)(1)(B) of the Social Security Act identifies the predetermined standards that the State's drug use review program must use to assess data on drug use. Visit http://www.ssa.gov/OP_Home/ssact/title19/1927.htm for information on the compendia.

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