Brands
- Tegretol
- Carbatrol
- Equetro
see index for additional brand names

Generic?
Yes (not for extended-release formulation)

Class
- Antiepileptic (AED), antineuralgic for chronic pain, voltage-sensitive sodium channel antagonist

Commonly Prescribed For
(FDA approved in bold)
- Partial seizures with complex symptomatology
- Generalized tonic–clonic seizures (grand mal)
- Mixed seizure patterns
- Pain associated with true trigeminal neuralgia
- Acute mania/mixed mania (Equetro)
- Glossopharyngeal neuralgia
- Bipolar depression
- Bipolar maintenance
- Psychosis, schizophrenia (adjunctive)

How the Drug Works
- Acts as a use-dependent blocker of voltage-sensitive sodium channels
- Interacts with the open channel conformation of voltage-sensitive sodium channels
- Interacts at a specific site of the alpha pore-forming subunit of voltage-sensitive sodium channels
- Inhibits release of glutamate

How Long until It Works
- For acute mania, effects should occur within a few weeks
- May take several weeks to months to optimize an effect on mood stabilization
- Should reduce seizures by 2 weeks

If It Works
- The goal of treatment is complete remission of symptoms (e.g. seizures, mania, pain)
- Continue treatment until all symptoms are gone or until improvement is stable and then continue treating indefinitely as long as improvement persists
- Continue treatment indefinitely to avoid recurrence of mania and seizures

Treatment of chronic neuropathic pain most often reduces but does not eliminate pain and is not a cure since symptoms usually recur after medicine stopped

If It Doesn’t Work (for bipolar disorder)
- Many patients only have a partial response where some symptoms are improved but others persist or continue to wax and wane without stabilization of mood
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Consider increasing dose, switching to another agent or adding an appropriate augmenting agent
- Consider adding psychotherapy
- Consider biofeedback or hypnosis for pain
- For bipolar disorder, consider the presence of noncompliance and counsel patient
- Switch to another mood stabilizer with fewer adverse effects or to extended-release carbamazepine
- Consider evaluation for another diagnosis or for a comorbid condition (e.g. medical illness, substance abuse, etc.)

Best Augmenting Combos
for Partial Response or Treatment Resistance
- Lithium
- Atypical antipsychotics (especially risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole)
- Valproate (carbamazepine can decrease valproate levels)
- Lamotrigine (carbamazepine can decrease lamotrigine levels)
- Antidepressants (with caution because antidepressants can destabilize mood in some patients, including induction of rapid cycling or suicidal ideation; in particular consider bupropion; also SSRIs, SNRIs, others; generally avoid TCAs, MAO inhibitors)

Tests
- Before starting: blood count, liver, kidney, and thyroid function tests
- During treatment: blood count every 2–4 weeks for 2 months, then every 3–6 months throughout treatment
- During treatment: liver, kidney, and thyroid function tests every 6–12 months
- Consider monitoring sodium levels because of possibility of hyponatremia
Before starting: individuals with ancestry across broad areas of Asia should consider screening for the presence of the HLA-B*1502 allele; those with HLA-B*1502 should not be treated with carbamazepine.

**ADVERSE EFFECTS (AEs)**

**How Drug Causes AEs**
- CNS AEs theoretically due to excessive actions at voltage-sensitive sodium channels
- Major metabolite (carbamazepine-10,11-epoxide) may be the cause of many AEs
- Mild anticholinergic effects may contribute to sedation, blurred vision

**Notable AEs**
- Sedation, dizziness, confusion, unsteadiness, headache
- Nausea, vomiting, diarrhea
- Blurred vision
- Benign leukopenia (transient; in up to 10%)
- Rash

**Life-Threatening or Dangerous AEs**
- Rare aplastic anemia, agranulocytosis (unusual bleeding or bruising, mouth sores, infections, fever, sore throat)
- Rare severe dermatologic reactions (Stevens–Johnson syndrome)
- Rare cardiac problems
- Rare induction of psychosis or mania
- SIADH (syndrome of inappropriate antidiuretic hormone secretion) with hyponatremia
- Increased frequency of generalized convulsions (in patients with atypical absence seizures)
- Rare activation of suicidal ideation and behavior (suicidality)

**Weight Gain**
- Occurs in significant minority

**Sedation**
- Frequent and can be significant in amount
- Some patients may not tolerate it
- Dose-related

**DOSING AND USE**

**Usual Dosage Range**
- 400–1200 mg/day
- Under age 6: 10–20 mg/kg per day

**Dosage Forms**
- Tablet: 100 mg chewable, 200 mg chewable, 200 mg
- Extended-release tablet: 100 mg, 200 mg, 400 mg
- Extended-release capsule: 100 mg, 200 mg, 300 mg
- Oral suspension: 100 mg/5 mL (450 mL)

**How to Dose**
- For bipolar disorder and seizures (ages 13 and older): initial 200 mg twice daily (tablet) or 1 teaspoon (100 mg) 4 times a day (suspension); each week increase by up to 200 mg/day in divided doses (2 doses for extended-release formulation, 3–4 doses for other tablets); maximum dose generally 1200 mg/day for adults and 1000 mg/day for children under age 15; maintenance dose generally 800–1200 mg/day for adults; some patients may require up to 1600 mg/day
- Seizures (under age 13): see Children and Adolescents
- Trigeminal neuralgia: initial 100 mg twice daily (tablet) or 0.5 teaspoon (50 mg) 4 times a day; each week increase by up to 200 mg/day in divided doses (100 mg every 12 hours for tablet formulations, 50 mg 4 times a day for suspension formulation); maximum dose generally 1200 mg/day

**What to Do about AEs**
- Wait
- Take with food or split dose to avoid GI effects
- Extended-release carbamazepine can be sprinkled on soft food
- Take at night to reduce daytime sedation
- Switch to another agent or to extended-release carbamazepine

**Best Augmenting Agents for AEs**
- Many AEs cannot be improved with an augmenting agent
Lower initial dose and slower titration should be used for carbamazepine suspension

Dosing Tips
- Higher peak levels occur with the suspension formulation than with the same dose of the tablet formulation, so suspension should generally be started at a lower dose and titrated slowly
- Take carbamazepine with food to avoid GI effects
- Slow dose titration may delay onset of therapeutic action but enhance tolerability to sedating AEs
- Controlled-release formulations (e.g., Equetro, Carbatrol) can significantly reduce sedation and other CNS AEs
- Should titrate slowly in the presence of other sedating agents, such as other antiepileptics, in order to best tolerate additive sedative AEs
- Can sometimes minimize the impact of carbamazepine upon the bone marrow by dosing slowly and monitoring closely when initiating treatment; initial trend to leukopenia/neutropenia may reverse with continued conservative dosing over time and allow subsequent dosage increases with careful monitoring
- Carbamazepine often requires a dosage adjustment upward with time, as the drug induces its own metabolism, thus lowering its own plasma levels over the first several weeks to months of treatment
- Do not break or chew carbamazepine extended-release tablets as this will alter controlled-release properties

Overdose
- Can be fatal (lowest known fatal dose in adults is 3.2 g, in adolescents is 4 g, and in children is 1.6 g); nausea, vomiting, involuntary movements, irregular heartbeat, urinary retention, trouble breathing, sedation, coma

Long-Term Use
- May lower sex drive
- Monitoring of liver, kidney, thyroid functions, blood counts and sodium may be required

Habit Forming
- No

How to Stop
- Taper; may need to adjust dosage of concurrent medications as carbamazepine is being discontinued

Rapid discontinuation may increase the risk of relapse in bipolar disorder
- Epilepsy patients may seize upon withdrawal, especially if withdrawal is abrupt
- Discontinuation symptoms uncommon

Pharmacokinetics
- Metabolized in the liver, primarily by cytochrome P450 CYP3A4
- Renally excreted
- Active metabolite (carbamazepine-10,11-epoxide)
- Initial half-life 26–65 hours (35–40 hours for extended-release formulation); half-life 12–17 hours with repeated doses
- Half-life of active metabolite is approximately 34 hours
- Is not only a substrate for CYP3A4, but also an inducer of CYP3A4
- Thus, carbamazepine induces its own metabolism, often requiring an upward dosage adjustment

Drug Interactions
- Enzyme-inducing antiepileptic drugs (carbamazepine itself as well as phenobarbital, phenytoin, and primidone) may increase the clearance of carbamazepine and lower its plasma levels
- CYP3A4 inducers, such as carbamazepine itself, can lower the plasma levels of carbamazepine
- CYP3A4 inhibitors, such as nefazodone, fluvoxamine, and fluoxetine, can increase plasma levels of carbamazepine
- Carbamazepine can increase plasma levels of clomipramine, phenytoin, primidone
- Carbamazepine can decrease plasma levels of acetaminophen, clozapine, benzodiazepines, dicoumarol, doxycycline, theophylline, warfarin, and haloperidol as well as other antiepileptics such as phensuximide, methsuximide, ethosuximide, phenytoin, tiagabine, topiramate, lamotrigine, and valproate
- Carbamazepine can decrease plasma levels of hormonal contraceptives and adversely affect their efficacy
- Combined use of carbamazepine with other antiepileptics may lead to altered thyroid function
- Combined use of carbamazepine and lithium may increase risk of neurotoxic effects
- Depressive effects are increased by other CNS depressants (alcohol, MAOIs, other antiepileptics, etc.)
Combined use of carbamazepine suspension with liquid formulations of chlorpromazine has been shown to result in excretion of an orange rubbery precipitate; because of this, combined use of carbamazepine suspension with any liquid medicine is not recommended.

Other Warnings/Precautions

- Patients should be monitored carefully for signs of unusual bleeding or bruising, mouth sores, infections, fever, or sore throat, as the risk of aplastic anemia and agranulocytosis with carbamazepine use is 5–8 times greater than in the general population (risk in the untreated general population is 6 patients per 1 million per year for agranulocytosis and 2 patients per 1 million per year for aplastic anemia).
- Because carbamazepine has a tricyclic chemical structure, it is not recommended to be taken with MAOIs, including 14 days after MAOIs are stopped; do not start an MAOI until 2 weeks after discontinuing carbamazepine.
- May exacerbate narrow-angle-closure glaucoma.
- Because carbamazepine can lower plasma levels of hormonal contraceptives, it may also reduce their effectiveness.
- May need to restrict fluid intake because of risk of developing SIADH or hyponatremia and its complications.
- Use with caution in patients with mixed seizure disorders that include atypical absence seizures because carbamazepine has been associated with increased frequency of generalized convulsions in such patients.
- Individuals with the HLA-B*1502 allele are at increased risk of developing Stevens–Johnson syndrome and toxic epidermal necrolysis.
- Warn patients and their caregivers about the possibility of activation of suicidal ideation and advise them to report such AEs immediately.

Do Not Use

- If patient is taking an MAOI.
- If patient has history of bone marrow suppression.
- If patient tests positive for the HLA-B*1502 allele.
- If there is a proven allergy to any tricyclic compound.
- If there is a proven allergy to carbamazepine.

SPECIAL POPULATIONS

Renal Impairment
- Carbamazepine is renally secreted, so the dose may need to be lowered.

Hepatic Impairment
- Drug should be used with caution.
- Rare cases of hepatic failure have occurred.

Cardiac Impairment
- Drug should be used with caution.

Elderly
- Some patients may tolerate lower doses better.
- Elderly patients may be more susceptible to AEs.

Children and Adolescents
- Approved use for epilepsy; therapeutic range of total carbamazepine in plasma is considered the same for children and adults.
- Ages 6–12: initial dose 100 mg twice daily (tablets) or 0.5 teaspoon (50 mg) 4 times a day (susension); each week increase by up to 100 mg/day in divided doses (2 doses for extended-release formulation, 3–4 doses for all other formulations); maximum dose generally 1000 mg/day; maintenance dose generally 400–800 mg/day.
- Ages 5 and younger: initial 10–20 mg/kg per day in divided doses (2–3 doses for tablet formulations, 4 doses for suspension); increase weekly as needed; maximum dose generally 35 mg/kg per day.

Pregnancy
- Risk Category D (positive evidence of risk to human fetus; potential benefits may still justify its use during pregnancy).
- Use during first trimester may raise risk of neural tube defects (e.g. spina bifida) or other congenital anomalies.
- Use in women of childbearing potential requires weighing potential benefits to the mother against the risks to the fetus.
- If drug is continued, perform tests to detect birth defects.
- If drug is continued, start on folate 1 mg/day early in pregnancy to reduce risk of neural tube defects.
- Antiepileptic Drug Pregnancy Registry: (888) 233–2334.
Use of antiepileptics in combination may cause a higher prevalence of teratogenic effects than antiepileptic monotherapy.

Taper drug if discontinuing.

Seizures, even mild seizures, may cause harm to the embryo/fetus.

For bipolar patients, carbamazepine should generally be discontinued before anticipated pregnancies.

Recurrent bipolar illness during pregnancy can be quite disruptive.

For bipolar patients, given the risk of relapse in the postpartum period, some form of mood stabilizer treatment may need to be restarted immediately after delivery if patient is unmedicated during pregnancy.

Atypical antipsychotics may be preferable to lithium or antiepileptics such as carbamazepine if treatment of bipolar disorder is required during pregnancy.

Bipolar symptoms may recur or worsen during pregnancy and some form of treatment may be necessary.

Breast-Feeding

Some drug is found in mother’s breast milk.

Recommended either to discontinue drug or bottle feed.

If drug is continued while breast-feeding, infant should be monitored for possible AEs, including hematological effects.

If infant shows signs of irritability or sedation, drug may need to be discontinued.

Some cases of neonatal seizures, respiratory depression, vomiting, and diarrhea have been reported in infants whose mothers received carbamazepine during pregnancy.

Bipolar disorder may recur during the postpartum period, particularly if there is a history of prior postpartum episodes of either depression or psychosis.

Relapse rates may be lower in women who receive prophylactic treatment for postpartum episodes of bipolar disorder.

Atypical antipsychotics and antiepileptics such as valproate may be safer than carbamazepine during the postpartum period when breast-feeding.

THE ART OF PAIN PHARMACOLOGY

Potential Advantages

- Treatment-resistant bipolar and psychotic disorders

Potential Disadvantages

- Patients who do not wish to or cannot comply with blood testing and close monitoring.
- Patients who cannot tolerate sedation.
- Pregnant patients.

Primary Target Symptoms

- Incidence of seizures.
- Unstable mood, especially mania.
- Pain.

Pearls

- Carbamazepine was the first antiepileptic widely used for the treatment of bipolar disorder and is now formally approved for acute mania and mixed mania.
- An extended-release formulation has better evidence of efficacy and improved tolerability in bipolar disorder than does immediate-release carbamazepine.
- Dosage frequency as well as sedation, diplopia, confusion, and ataxia may be reduced with extended-release carbamazepine.
- Risk of serious AEs is greatest in the first few months of treatment.
- Common AEs such as sedation often abate after a few months.
- May be effective in patients who fail to respond to lithium or other mood stabilizers.
- May be effective for the depressed phase of bipolar disorder and for maintenance in bipolar disorder.
- Can be complicated to use with concomitant medications.
- Carbamazepine is still considered the drug of choice as a “first-line” agent for the treatment of trigeminal neuralgia.
Suggested Reading


