**CARBAMAZEPINE**

**Therapeutics**

**Brands**
- Tegretol
- Carbatrol
- Equetro

*see index for additional brand names*

**Generic?**
Yes (not for extended-release formulation)

**Class**
- Neuroscience-based Nomenclature: glutamate, voltage-gated sodium and calcium channel blocker (Glu-CB)
- Anticonvulsant, antineuralgic for chronic pain, voltage-sensitive sodium channel antagonist

**Commonly Prescribed for**
(bold for FDA approved)
- 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 have only 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 side 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, MAOIs)
SIDES EFFECTS

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

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

Life-Threatening or Dangerous Side Effects
- Rare aplastic anemia, agranulocytosis (unusual bleeding or bruising, mouth sores, infections, fever, sore throat)
- Rare severe dermatologic reactions (purpura, 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)

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

What to Do About Side Effects
- Wait
- Take with food or split dose to avoid gastrointestinal 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 Side Effects
- Many side effects cannot be improved with an augmenting agent

Tests
- 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
- Can wear off with time, but commonly does not wear off at high doses
- CNS side effects significantly lower with controlled-release formulation (e.g., Equetro, Carbatrol)

DOSING AND USE

Usual Dosage Range
- 400–1,200 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/5mL (450 mL)
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 CYP450 3A4
- 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 CYP450 3A4, but also an inducer of CYP450 3A4
- Thus, carbamazepine induces its own metabolism, often requiring an upward dosage adjustment
- Is also an inducer of CYP450 2C9 and weakly of 1A2 and 2C19
- Food does not affect absorption
CARBAMAZEPINE (continued)

**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.
- CYP450 3A4 inducers, such as carbamazepine itself, can lower the plasma levels of carbamazepine.
- CYP450 3A4 inhibitors, such as nefazodone, fluvoxamine, and fluoxetine, can increase plasma levels of carbamazepine.
- Carbamazepine can increase plasma levels of clotrimazole, phenytoin, primidone.
- Carbamazepine can decrease plasma levels of acetaminophen, clozapine, benzodiazepines, dicumarol, doxycycline, theophylline, warfarin, and haloperidol.
- Carbamazepine can increase plasma levels of clomipramine, phenytoin, primidone.
- Carbamazepine can decrease plasma levels of acetaminophen, clozapine, benzodiazepines, dicumarol, doxycycline, theophylline, warfarin, and haloperidol.
- 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 syndrome of inappropriate antidiuretic hormone secretion, 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 side effects immediately.

**Do Not Use**
- 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.
- Suspension: in patients with hereditary problems with fructose intolerance.

**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, use with caution with MAOIs, including 14 days after MAOIs are stopped (for the expert).
- May exacerbate angle-closure glaucoma.
- Because carbamazepine can lower plasma levels of hormonal contraceptives, it may also reduce their effectiveness.
- Do Not Use
  - 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.
  - Suspension: in patients with hereditary problems with fructose intolerance.

**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 adverse effects

**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 (suspension); 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 1,000 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/day

**Pregnancy**
- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- 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 anticonvulsants in combination may cause a higher prevalence of teratogenic effects than anticonvulsant 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 anticonvulsants 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 adverse effects, 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 anticonvulsants such as valproate may be safer than carbamazepine during the postpartum period when breast feeding
### THE ART OF PSYCHOPHARMACOLOGY

#### 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 anticonvulsant 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 side effects is greatest in the first few months of treatment
- Common side effects 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

#### Suggested Reading


