# Carbamazepine

Week 8

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## Overview

- Carbamazepine is an anticonvulsant compound that is structurally similar to the tricyclic antidepressant agents.
- It blocks voltage-dependent sodium channels.
- It is the drug of choice or the treatment of trigeminal neuralgia, and is used in the treatment of a variety of seizure disorders.
- It has FDA approval for generalized tonic–clonic and partial seizures, bipolar disorders, and in acute mania and mixed episodes.

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# Overview

- Carbamazepine is used off-label in a variety of other conditions, including pain syndromes, migraine headaches, and other neurologic disorders.
- Carbamazepine is available in many dosage forms, including oral suspension, chewable tablet, oral tablet, extended-release tablets, and extended-release capsules.

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# Parameters

| | |
|---|---|
| Therapeutic plasma concentrations | 4–12 mg/L |
| F | 80% tablets |
| S | 1.0 |
| V[a] | 1.1 L/kg |
| Cl[a,b] | |
| Monotherapy | 0.064 L/kg/hr |
| Polytherapy | 0.10 L/kg/hr |
| Children (monotherapy) | 0.11 L/kg/hr |
| Free fraction | 0.2–0.3 |
| t½ | |
| Adult monotherapy | 15 hr |
| Adult polytherapy[b] | 10 hr |

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# Dose

- The most commonly used dose for children less than 6 years of age is 10 to 20 mg/kg/day initially but, at steady state, is likely to be 20 to 30 mg/kg/day orally divided twice daily.
- Effective doses for adults with seizure disorders are in the range of 15 to 25 mg/kg/day (or 800 to 1200 mg/day) at steady state.
- Migraine prophylaxis doses are usually in the range of 10 to 20 mg/kg/day given twice daily with extended-release products.

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- Carbamazepine is approximately 75% bound to plasma albumin and α -acid glycoprotein.
- Usual half-life of carbamazepine, 24 to 30 hours, as monotherapy would suggest achievement of steady state within a week.
- However, time to achieve steady state is highly variable with reports of 4 to 5 days owing to auto-induction.

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- Carbamazepine is metabolized by CYP3A4 and CYP3A5 producing a carbamazepine 10, 11-epoxide, metabolite responsible or both therapeutic and adverse effects.
- The half-life of the 10, 11-epoxide is approximately 34 hours.
- The carbamazepine- 10,11 –epoxide to carbamazepine ratios are higher in infants and preschool children.
- Simultaneous administration of quetiapine, phenytoin, and valproate sodium can increase the formation of the 10,11 –epoxide.

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## Adverse Effects

- The most common adverse effects associated with carbamazepine involve the central nervous system (CNS) and include dizziness, nystagmus, ataxia, blurred vision, diplopia, dry mouth, nausea, vomiting, drowsiness, and suicidality.
- Cardiovascular, renal, and hepatic effects vary in severity and include tachycardia, hyponatremia, hepatic porphyria, and hepatotoxicity.
- Idiosyncratic dermatologic and hematologic reactions associated with carbamazepine include agranulocytosis, aplastic anemia, mild maculopapular eruption and drug hypersensitivity syndrome or drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens–Johnson syndrome (SJS), and toxic epidermal necrolysis ( EN)

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# Clearance

- Carbamazepine is eliminated almost exclusively by metabolism, with less than 2% of an oral dose being excreted remain unchanged in the urine.
- Carbamazepine is metabolized in the liver by CYP3A4/5 isoenzymes and induces CYP 1A2 (strong), CYP2B6 (moderate), CYP2C8/9 (strong), 2C9 (strong), and CYP 3A4 (strong) to accelerate the hepatic metabolism of other drugs.
- In patients who are taking other enzyme-inducing antiepileptic drugs concurrently (polytherapy), the clearance is increased from 0.064 L/kg/hr to 0.1 L/kg/hr.
- Clearance in chronic therapy is increased owing to auto-induction of its metabolic enzymes.

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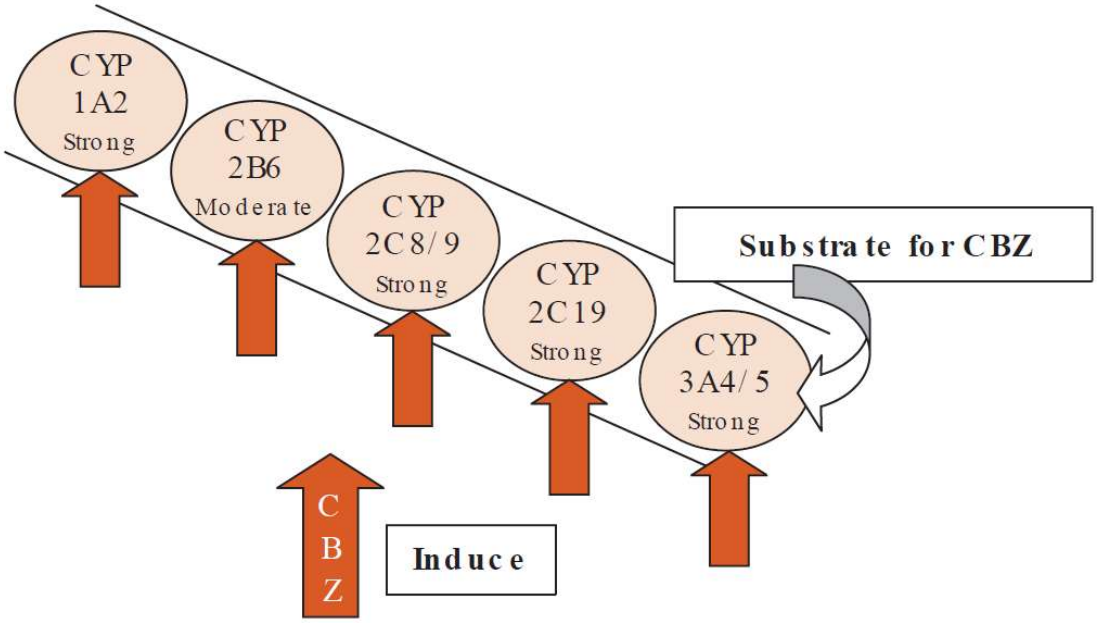


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# Drug Interactions

- Carbamazepine has many drug interactions resulting both from CYP inhibition and from induction that alter observed concentrations.
- Carbamazepine has been shown to induce the metabolism of warfarin through CYP2C9.
- Carbamazepine greatly reduces the serum concentrations of atorvastatin and rosuvastatin.

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CYP3A4 **inhibitors** that inhibit carbamazepine metabolism and increase plasma carbamazepine include

INCREASED PLASMA CARBAMAZEPINE

Azole antifungals
fluconazole, itraconazole, ketoconazole, voriconazole
Cimetidine
Clarithromycin[a]
Chloroquin, mefloquine
Dalfopristin/Quinupristin
Diltiazem
Erythromycin[a]
Fluoxetine
Fluvoxamine
Grapefruit juice
Isoniazid
Lithium
Loratadine
Loxapine
Niacinamide
Protease inhibitors
indinavir, nelfinavir, ritonavir
Quetiapine
Quinine
Ranolazine
Troleandomycin
Valproate[a]
Verapamil
Zileuton

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CYP3A4 **inducers** that induce the rate of carbamazepine metabolism and decrease plasma carbamazepine include

DECREASED PLASMA CARBAMAZEPINE

Carbamazepine[b]
Cisplatin
Doxorubicin
Felbamate
Phenobarbital
Phenytoin
Primidone
Rifampin
Theophylline

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## The Effects of Carbamazepine on Other Select Drugs

| DRUG(S) | MECHANISM | EFFECT | RECOMMENDATION |
|---|---|---|---|
| Delavirdine/other NNRTIs | Induction of CYP3A4 by carbamazepine | Reduction in plasma concentration of NNRTI and loss of virologic response | Monitor carbamazepine concentrations and adjust. Consider alternative AED agent |
| Lithium | Pharmacodynamic effect | Neurotoxic effect and adverse effects | A reduced lithium dose may be needed |
| Oral contraceptives | Induction of CYP3A4 by carbamazepine | Enhanced metabolism of EE and norethindrone resulting in contraceptive failure | Backup method of contraception required; barrier or IUD |
| Phenytoin primidone | Hepatic metabolism induced | Combination may alter levels of both drugs; may increase CNS depression | Monitor serum concentrations of phenytoin and carbamazepine |

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- Carbamazepine induces its own metabolism through time- and dose-dependent auto-induction.
- Therefore, the use of clearance values from single-dose studies is impractical in the calculation of a maintenance dose and may lead to errors.
- It is important to initiate patients on relatively low doses to avoid side effects early in therapy.
- The maintenance dose can be increased at 1- to 2-week intervals by 200 mg/day.

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## Oxcarbazepine (Trileptal)

- Oxcarbazepine (Trileptal) was developed as chemically similar to carbamazepine with an improved safety profile.
- Oxcarbazepine is a prodrug of 10-monohydroxycarbazepine (MHD), the active metabolite that is responsible for the majority of drug actions.
- Oxcarbazepine is completely absorbed and converted to MHD.
- Steady state is reached in 2 to 3 days.
- Oxcarbazepine biotransformation does not involve epoxide metabolite formation.

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## Oxcarbazepine (Trileptal)

- No dose adjustment is required for liver dysfunction, but is for creatinine clearance < 30 mL/min.
- Oxcarbazepine can inhibit CYP2C 9 and induce CYP3A4/5 with potentially important e ects on plasma concentrations of other drugs.
- No auto-induction has been observed with oxcarbazepine.

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## Eslicarbazepine (Aptiom)

- Eslicarbazepine is approved for both adjunctive and monotherapy for partial-onset seizures in adults and children.
- It is structurally different from carbamazepine and oxcarbazepine.
- It has a low potential for drug interactions.
- Like oxcarbazepine, it is not metabolized to an epoxide.
- A common concern of the three agents is hyponatremia.
- Hyponatremia appears to be caused by syndrome of inappropriate antidiuretic hormone secretion and is dose related.

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- **Question #1** N.S., a 36-year-old, 60 kg female, is to be started on carbamazepine as an anticonvulsant agent. How would you initiate therapy? Explain your rationale. Estimate the amount needed at steady state and then propose how to start the patient on therapy. Calculate a daily dose that will produce an average steady-state plasma concentration of approximately 6 mg/L. ($Cl_{monotherapy}$=0.064L/kg, S=1, F=0.8)

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- **Question #2** After 2 months, the carbamazepine dose of N.S. has been increased to 300 mg orally two times a day. On this regimen, she has had some reduction in seizure frequency; however, seizure control is still considered unsatisfactory. The steady-state carbamazepine level at this time is reported to be 4 mg/L. What are possible explanations for this observed plasma level? What dose would be required to achieve a new steady-state carbamazepine level of 6 mg/L?

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- **Question #3** A.B. is a 60-year-old male (65 kg) currently receiving the following:

| Medication | Steady-state concentration (mcg/ml) |
|---|---|
| Carbamazepine 200 mg three times a day | 7 |
| Phenytoin extended 300 mg orally at bedtime | 11 |

- Despite these agents, seizures persist, and the decision is made to add valproic acid of 250 mg orally three times a day. One month following the addition of valproic acid, A.B. complains of drowsiness. Drug concentrations are drawn, and the levels obtained are carbamazepine 7.6 mcg/mL, phenytoin 8 mcg/mL, and valproic acid 50 mcg/mL. The serum albumin level reported is 4.2 g/dL. What is your explanation for the patient complaints?

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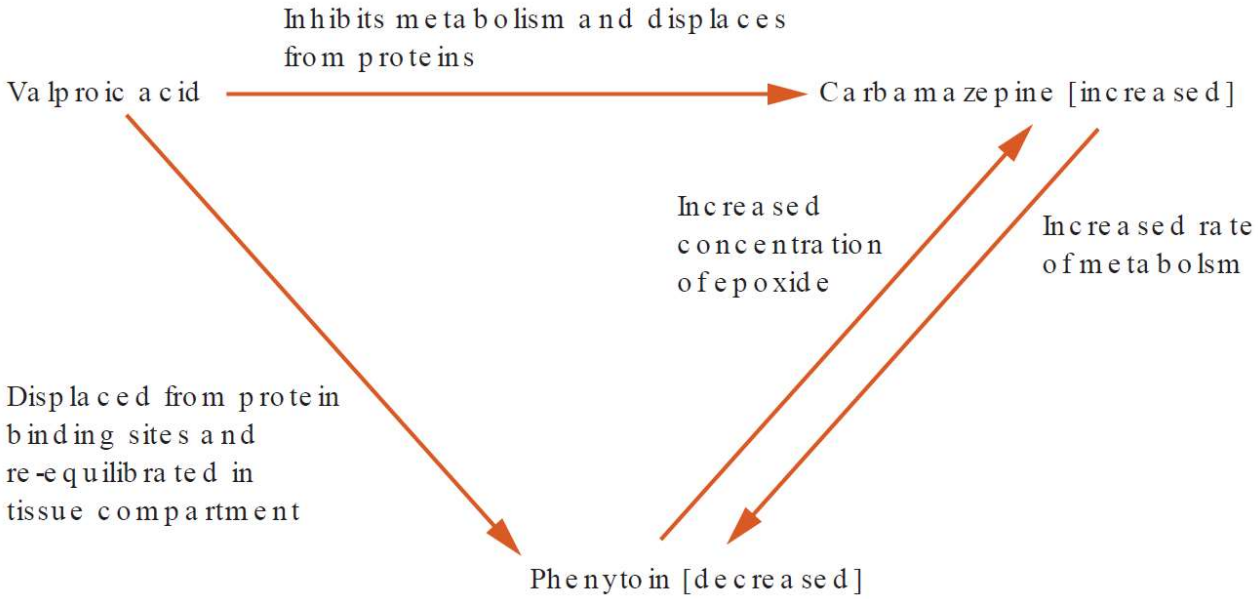


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