**Carbamazepine**

**Comment**

See FDA Black Box Warning

First-line or adjunctive therapy of focal seizures. Improves GTCS in IGE, but usually not used due to concern that CBZ may worsen absence and myoclonic seizures, and may precipitate NCSE in these patients. Newer anti epileptic medicines are better tolerated compared to immediate-release CBZ - it is unclear if this applies to extended-release CBZ. Difficulties include transient adverse effects on starting therapy. Enzyme-inducing effects and high drug interaction potential.

**FDA indications**

Epilepsy, Partial, generalized, and mixed types - adults and children

**Mechanism**

Blockade of voltage-gated sodium channels, that interferes with high-frequency neuronal firing.

**Usual dose**

Starting dose is 100-200 mg/day, then increased in 4 weeks due to enzyme (auto)induction to 400-600 mg/day. Maintenance dosages are usually in the range of 400-1600 mg/day (patients on other enzyme inducers may require higher doses). Children: starting dose is up to 5 mg/kg/day, increased over 24 weeks to 1020 mg/kg/day. Maintenance dosages are usually in the range of 5-30mg/kg/day

**Dosing frequency**

2x/d for extended release; 4x/d for immediate release (for compliance, and side effects the ER formulation is clearly preferred)

**Serum levels, labs**

4-12 ug/mL. CBZ is metabolized to CBZ-10,11-epoxide, that accumulates and is an anti epileptic but also causes nonspecific neuropsychological side effects at higher doses. Check CBC, LFTs, basic chemistries as baseline and in 2-4 months after starting CBZ. Check serum levels of CBZ and CBZ-10,11-epoxide if dose-related side effects are suspected.

**Important interactions.**

Phenytoin and barbiturates decrease serum CBZ levels. Valproic acid increases serum CBZ-10,11-epoxide levels. Felbamate decreases the serum levels of CBZ and increases the levels of CBZ-10,11-epoxide.

CYP 3A4 inhibitors inhibit carbamazepine metabolism and can increase plasma carbamazepine levels:
- cimetidine, danazol, diltiazem, macrolides, erythromycin, troleandomycin, clarithromycin, fluoxetine, fluvoxamine, nefazodone, loratadine, terfenadine, isoniazid, niacinamide, nicotinamide, propoxyphene, azoles (e.g., ketoconazole, itraconazole, fluconazole), acetazolamide, verapamil, grapefruit juice, protease inhibitors, valproate.

CYP 3A4 inducers can increase the rate of carbamazepine metabolism:
- cisplatin, doxorubicin HCl, felbamate, rifampin, phenobarbital, phenytoin, primidone, methsuximide, theophylline.

CBZ is an enzyme inducer and accelerates the metabolism of many other antiepileptic drugs and drugs used to treat other conditions.

Although a clear pattern of drug potential interaction/potentiation has not emerged, use of CBZ with TCAs or antiarrhythmic agents that slow AV conduction should be used with caution – see next section.

**Important side effects**

FDA Black Box Warning.

Serious and sometimes fatal dermatologic reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis) have been reported, especially in patients with the inherited allelic variant HLA-B*1502, found almost exclusively in patients of Asian descent. Screen genetically-at-risk patients prior to receiving carbamazepine. Do not start carbamazepine in patients who test positive for the allele.

In the Caucasian population, the risk is 1 to 6 per 10,000 patients. But in the Asian population, the risk is 10-fold higher and tends to be associated with a specific allele HLA-B*1502. In MiChart, search in Facility list (F6) for "Carbamazepine Hypersensitivity (HLA-B*1502)" lab code LAB7597.

Aplastic anemia (2/MM) and agranulocytosis (6/MM) have been reported. Obtain pretreatment hematological testing and periodically monitor CBC. Consider drug discontinuation if significant bone marrow depression develops or if serious dermatologic reactions occur

- CBZ may worsen absences or myoclonic seizures, and may precipitate NCSE in these patients. Idiosyncratic reactions include serious hematological disorders-although regular lab monitoring is not considered justified in many other countries. Benign LFT elevations in 5-20%, but may cause acute hepatotoxicity. Decr thyroid and sex hormones, not usu. clinically important.

- Decreased vitamin D levels ?due to enzyme induction, and decrease in bone mineral density.
CBZ in low doses can increase the degree of AV conduction delay in a dose dependent fashion in subjects with a preexisting AV conduction defect, especially in older patients, causing varying degrees of heart block in these individuals. Bradycardia and AV block have also been described in patients without apparent AV conduction defects with high carbamazepine blood levels. For these reasons, the following seem reasonable -- see: Kasarskis EJ, Carbamazepine-induced cardiac dysfunction PMID 1728915

- In patients >50yo perform a baseline ECG before starting CBZ. If AV conduction block is present, use a different AED.
- In patients >50yo perform an ECG once at a therapeutic level of CBZ. If AV conduction block has developed, reduce the dose or stop CBZ.
- CBZ should be avoided in patients in whom conduction abnormalities are likely to occur (eg, patients with myotonic dystrophy).
- In epileptic patients treated with carbamazepine who subsequently experience syncopal episodes, carefully search for bradyarrhythmias or AV conduction delay.

- Hyponatremia. Dose-dependent, more common in elderly -- worse for OXC. No fatal cases of CBZ- or OXC-induced hyponatremia have been reported. If asymptomatic, NA 130 or higher is fine, if asymptomatic. If clinical sxs -- HA, nausea, fatigue, confusion -- then reduce the dose; other meds incl SSRIs may worsen this, as well. See Van Amelsvoort T, Hyponatremia associated with carbamazepine and oxcarbazepine therapy PMID 8112243

Contraindications

- bone marrow depression, or hx of.
- concomitant use of an MAOI, or use within 14 days of discontinuing an MAOI
- concomitant use of nonnucleoside reverse transcriptase inhibitors
- hypersensitivity to carbamazepine or to tricyclic compounds (amitriptyline, desipramine, imipramine, protriptyline, nortriptyline)