

Background for Health Care Provider:

Carbamazepine is variably absorbed from the small intestine and has bioavailability in the range of 75-85% depending on the dosage form. In vitro testing indicates carbamazepine is approximately 75% protein bound in serum, suggesting little potential for clinically relevant protein binding displacement interactions. Carbamazepine is almost entirely metabolized by the CYP450 enzyme system in the liver to multiple metabolites of various pharmacologic activities, the most relevant of which is the 10,11 epoxide metabolite. This metabolite is pharmacologically active and is thought to be partially responsible for carbamazepine mediated adverse effects. Carbamazepine induces cytochrome P450 isozymes as well as UDP-glucuronyltransferase. Carbamazepine may also inhibit CYP 2C19. Carbamazepine undergoes autoinduction (via CYP 3A4), which is both time and dose dependent. The renal excretion of carbamazepine is minimal and is often clinically insignificant.

Effect of Other Drugs on Carbamazepine Serum Levels:

Decrease Carbamazepine Serum Levels

- Felbamate
- Oxcarbazepine
- Phenytoin
- Phenobarbital
- Primidone
- St. John's Wort

Increase Carbamazepine Serum Levels

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| • Cimetidine | • Metoclopramide |
| • Danazol | • Metronidazole |
| • Diltiazem | • Propoxyphene |
| • Erythromycin | • Rifampin |
| • Fluconazole | • Ritonavir |
| • Fluoxetine | • Ticlopidine |
| • Isoniazid | • Verapamil |
| • Ketoconazole | • Valproic acid (increases carbamazepine epoxide) |
| • Loxapine | |

Effect of Carbamazepine on Other Drugs' Serum Levels:

Increase Other Serum Drug Levels

- Phenytoin

Decrease Other Serum Drug Levels

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| • Alprazolam | • Midazolam |
| • Amitriptyline | • Nifedipine |
| • Aripiprazole | • Nimodipine |
| • Bupropion | • Olanzapine |
| • Caspofungin | • Oral Contraceptives |
| • Clomipramine | • Phenobarbital |
| • Clonazepam | • Phenytoin |
| • Clozapine | • Primidone |
| • Cyclosporin | • Quetiapine |
| • Diazepam | • Rifampin |
| • Ethosuximide | • Risperidone |
| • Felbamate | • Tacrolimus |
| • Fentanyl | • Tiagabine |
| • Haloperidol | • Topiramate |
| • Imipramine | • Trazodone |
| • Indinavir | • Valproic Acid |
| • Itraconazole | • Warfarin |
| • Lamotrigine | • Zonisamide |

Ryan F. Miller
 Doctor of Pharmacy Candidate 2007
 University of Wisconsin School of Pharmacy

On July 10, 2008, an advisory panel was convened by the Food and Drug Administration (FDA) to review data that the FDA had previously collected from drug studies showing an association between many of the antiepileptic drugs (AEDs) and suicidal ideation and behavior, which together are called suicidality. According to the FDA's Alert, among the patients with epilepsy in these drug studies, 1 out of 1000 people taking the placebo (inactive substance) showed suicidality compared to approximately 3.5 out of 1000 people who took an AED. The FDA advisory panel voted to accept the FDA's data at its meeting on July 10.

The FDA has provided the following information for patients, family members, and caregivers at www.fda.gov/cder/drug/InfoSheets/HCP/antiepilepticsHCP.htm):

- Taking antiepileptic medicines may increase the risk of having suicidal thoughts or actions;
- Do not make any changes to the medication regimen without first talking with the responsible healthcare professional;
- Pay close attention to any day-to-day changes in mood, behavior and actions. These changes can happen very quickly so it is important to be mindful of any sudden differences.

- Be aware of common warning signs that might be a signal for risk of suicide. Some of these are:
 - Talking or thinking about wanting to hurt yourself or end your life
 - Withdrawing from friends and family
 - Becoming depressed or having your depression get worse
 - Becoming preoccupied with death and dying
 - Giving away prized possessions

We again urge patients and families to contact their doctor before stopping an epilepsy medication because this may possibly lead to seizures and worsening of mood.