Drug Interactions with Carbamazepine

Carbamazepine (CBZ) is an anticonvulsant medication used for the treatment of seizure disorders, bipolar disorders and other affective disorders, and the treatment of pain. CBZ is implicated in many drug interactions because it induces the metabolism of itself as well as multiple other drugs metabolized through the cytochrome P450 system. These drug interactions may manifest at initiation, during dose changes, or after discontinuation of carbamazepine or the interacting drug. CBZ toxicity may present as dizziness, ataxia, drowsiness, nausea, vomiting, tremor, agitation, nystagmus, urinary retention, dysrhythmias, or coma. The table below contains a partial listing of drug interactions involving CBZ. For complete and updated interaction information, consult drug interaction resources or the Department of Pharmacy at your facility.

Medication(s)	Actions on CBZ	CBZ's Actions on Drug	Mechanism	Action to be Taken
Antipsychotics:				
Atypicals: risperidone, clozapine, olanzapine, quetiapine, ziprasidone, aripiprazole, asenapine, paliperdione, lurasidone iloperidone, cariprazine, brexpiprazole	None	⇓ plasma levels of the antipsychotic agent	Induction of antipsychotic metabolism by CBZ	Observe for deterioration of psychiatric status- some patients may require an ⇑ in antipsychotic dosage. *Cariprazine is converted to active metabolite via CYP 3A4. Not recommended for coadministration with CBZ (per manufacturer's recommendations). ***Clozapine & CBZ should not be used concurrently due to risk of agranulocytosis/aplastic anemia (per Maryland State P&T guidelines).**
Typicals: haloperidol, fluphenazine, thioridazine, loxapine, chlorpromazine	CBZ suspension is incompatible with chlorpromazine solution & thioridazine liquid	⇓ plasma levels of the antipsychotic agent	Induction of antipsychotic metabolism by CBZ	Observe for deterioration of psychiatric status- some patients may require an ⇑ in antipsychotic dosage. Schedule CBZ suspension at least 1-2 hours apart from other liquids.
Antidepressants:				
Bupropion	None	Serum levels of bupropion metabolites may ⇓ or ⇑	CBZ ⇑ metabolism of bupropion	Observe clinical response; if interaction is suspected adjust therapy. Bupropion metabolites contribute to therpeutic & toxic effects of the antidepressant- monitor for ⇓ in seizure threshold.
Fluoxetine Fluvoxamine Sertraline	CBZ & CBZ metabolite levels may ⇑	Exacerbation of hyponatremia (syndrome of inappropriate antidiuretic hormone secretion- SIADH)	Unknown, but may be due to inhibition of metabolism of CBZ by the SSRI	Monitor CBZ levels. May be necessary to alter dose when starting or stopping SSRI. Monitor for s/sx of neurotoxicity when SSRI is added to CBZ. Monitor serum sodium concentrations & for clinical signs of hyponatremia.
Mirtazapine	None	CBZ may ⇓ plasma levels of mirtazapine	Induction of mirtazapine metabolism through CYP3A4	Higher doses of mirtazapine may be required in patients receiving CBZ.
Selegiline	None	⇑ plasma levels of selegiline = hyperpyrexia, excitation, seizure	Unknown	The concurrent administration of CBZ and MAOIs is contraindicated. Selegiline should be discontinued for a minimum of 14 days before CBZ therapy is initiated.
Trazodone Nefazodone	Serum CBZ levels may ⇑ (~20%)	Plasma levels may be ⇓ by 60-75% for trazodone & ~90% for nefazodone	Induction of antidepressant metabolism by CBZ; nefazodone & trazodone may inhibit hepatic metabolism of CBZ.	Monitor clinical response (antidepressant effect of trazodone). Monitor serum CBZ levels and observe patient for signs of neurotoxicity. Co-administration of nefazodone and CBZ is contraindicated.
Tricyclic Antidepressants (TCAs)	May ⇑ plasma levels of CBZ	⇓ plasma levels of TCAs	Unknown, but TCA may compete with CBZ for hepatic metabolism, & CBZ may induce metabolism of TCA	Observe for signs of toxicity or loss of therapeutic effect when either drug is added or discontinued, monitor levels and adjust when needed. Higher doses of the TCAs may be needed in patients receiving CBZ.

Anticonvulsants:					
	Lamotrigine	Plasma levels of active epoxide metabolite of CBZ may be ⇑	⇓ in lamotrigine plasma levels	CBZ ⇑ the clearance of lamotrigine through induction of glucuronidation	Start lamotrigine therapy at higher initial dose of 50 mg/day, with a maximum recommended dosage of lamotrigine at 400 mg/day. Adjust dose of lamotrigine if CBZ is discontinued during treatment.
	Phenobarbital Primidone	CBZ plasma levels may ⇓ by 20 – 50%	None	Induction of CBZ metabolism by phenobarbital/primidone	An ⇑ in CBZ dose may be necessary. Dose based on clinical response.
	Phenytoin Fosphenytoin	CBZ levels may be ⇓ by phenytoin	Phenytoin plasma levels may ⇑ or ⇓ (highly variable & unpredictable)	Induction of CYP2C9/19 & inhibition of CYP2C19	Closely monitor plasma levels and clinical response of both drugs. Phenytoin plasma levels may initially ⇑ due to inhibition reaction, then ⇓ in a few weeks after induction develops.
	Tiagabine	None	⇓ in tiagabine plasma levels	CBZ ⇑ the clearance of tiagabine through induction of CYP3A4	Doses of tiagabine may need to be ⇑ by 2-4 times the normal recommended dosage.
	Topiramate	None	⇓ in topiramate plasma levels by 40-50%	CBZ ⇑ the clearance of topiramate though induction of topiramate metabolism	No modification of topiramate dose necessary when initiating therapy in patients receiving CBZ, however ⇓ in topiramate dose may be required if ongoing CBZ dose is lowered or discontinued.
	Valproic Acid	⇑ in plasma levels of carbamazepine epoxide may occur	Serum levels may be ⇓ by CBZ	VPA inhibition of epoxide hydrolase	Monitor serum levels and observe for seizure activity and toxicity for at least 1 month after starting/stopping either drug. Dosage adjustments should be guided by clinical response.
	Zonisamide	None	CBZ may ⇓ zonisamide plasma levels by 40-50%	CBZ ⇑ the clearance of zonisamide by 30-40%, through induction of zonisamide metabolism	Monitor clinical response; a ⇓ in zonisamide dose may be required if the CBZ dose is lowered or discontinued.
Estrogen Products (oral contraceptives)		None	⇓ in estrogen & progestin plasma levels by 40%	CBZ may ⇑ hepatic metabolism of OCs	⇓ OC efficacy, possibly leading to unintended pregnancy. Use alternate method of contraception & ⇑ the ethinyl estradiol component to at least 50 mcg/day with subsequent ⇑ up to 80-100 mcg if breakthrough bleeding occurs. Also consider use of depot medroxyprogesterone, which is not affected by inducing anticonvulsants.
Antibiotics / Antifungals:					
	Antituberculosis Agents: Isoniazid	May ⇑ plasma levels of CBZ	CBZ may ⇑ hepatic toxicity of INH	Unknown but suspected to be due to metabolic interaction	Monitor CBZ levels and monitor liver function, consider discontinuing isoniazid if hepatotoxicity occurs. Monitor for CBZ neurological toxicity.
	Azole Antifungals: ketoconazole, itraconazole, miconazole, voriconazole isavuconazonium	29% ⇑ in CBZ plasma levels with ketoconazole therapy	CBZ may ⇓ plasma levels of azole antifungals	Induction of CYP3A4-mediated metabolism by CBZ	Monitor for antifungal treatment failure and/or CBZ toxicity.
	Doxycycline	None	Chronic CBZ therapy may ⇓ the t½ of doxycycline by 50%	Induction of doxycycline metabolism by CBZ	Dose of doxycycline may need to be ⇑ during CBZ coadministration.

	Macrolide Antibiotics: clarithromycin, erythromycin	May ⇑ CBZ plasma levels by 2-4 fold	CBZ may ⇑ the clearance & ⇓ the effectiveness of antibiotic	Inhibition of CYP3A4 hepatic metabolism of CBZ by macrolide antibiotic and induction of CYP3A4 by CBZ	Avoid concomitant use; if agents must be given together, monitor closely and ⇓ in dosage of CBZ (by ~ 25%) if necessary. Use of azithromycin is preferable, as it lacks any interaction with CBZ.
	Metronidazole	CBZ plasma levels may ⇑	None	Possible inhibition of CBZ metabolism by metronidazole	When metronidazole & CBZ are coadministered, monitor CBZ plasma levels & observe for signs & symptoms of CBZ toxicity (nausea, dizziness, diplopia). Doses of carbamazepine may need to be adjusted when metronidazole is added to or withdrawn from therapy.
Benzodiazepines:					
	Alprazolam **Clonazepam** **Clobazam**	None	⇓ plasma levels of BZD	Induction of BZD metabolism by CBZ	Observe for loss of BZD clinical effectiveness. Concurrent use of CBZ & alprazolam/clonazepam may require higher doses of the BZD.
Antihypertensives / Antilipemics / Anticoagulants:					
	Non-dihydropyridine Calcium Channel Blockers (CCB's): diltiazem, verapamil	Plasma CBZ levels may ⇑ by 40-60%	None	CCB inhibition of metabolic degradation of CBZ	Monitor serum CBZ levels and observe patient if CCB is added or discontinued. CBZ dose may need to be ⇓ 40-60% when administered with verapamil or diltiazem.
	Dihydropyridine CCB's: e.g. nifedipine, amlodipine	None	CBZ may decrease antihypertensive activity of CCB	Induction of CCB metabolism by CBZ	Monitor blood pressure if CBZ is introduced or titrated during coadministration with CCB
	Diuretics: furosemide, HCTZ	Exacerbation of hyponatremia	Exacerbation of hyponatremia	Fluid & sodium loss through diuresis	Serum sodium concentrations and clinical signs of hyponatremia should be monitored.
	Statins: simvastatin, atorvastatin, lovastatin	None	⇓ plasma levels of statins (68% ⇓ in simvastatin plasma levels with concomitant use)	Induction of CYP3A4 metabolism by CBZ	Monitor of ⇓ in cholesterol-lowering effect of simvastatin, atorvastatin, or lovastatin. May need to ⇑ statin dose or switch to a different statin (e.g. pravastatin, fluvastatin, rosuvastatin, pitavastatin) without this documented interaction.
	Warfarin	None	CBZ may ⇓ anticoagulant effects of warfarin by up to 2- fold	Induction of hepatic metabolism of anticoagulants by CBZ	Monitor prothrombin times & INR more frequently for at least 3-4 weeks when beginning or stopping CBZ therapy in patients receiving warfarin. Warfarin dose may need to be adjusted.
	Direct Acting Oral Anticoagulants: apixiban, dabigatran, edoxaban, rivaroxaban	None	CBZ may reduce anticoagulant effectiveness of DOACs	CBZ-induced induction of P-glycoprotein and CYP enzymes	Concomitant therapy with CBZ and DOACs should be avoided.
Mood Stabilizers:					
	Lithium	⇑ neurotoxicity without change in plasma drug levels	⇑ neurotoxicity without change in plasma drug levels	Unknown	Monitor patient for signs of neurotoxicity. Monitor for the development of adverse CNS effects, lethargy, muscular weakness, ataxia, tremor, hyperreflexia (may occur despite therapeutic levels of both medications).
Stimulants:					
	Methylphenidate	None	Concurrent use of CBZ may ⇓ the therapeutic effect of methylphenidate	Induction of CYP3A4 metabolism of methylphenidate by CBZ	Monitor for ⇓ effect of stimulant. Doses of methylphenidate may need to be ⇑ to maintain efficacy.
Methylxanthines:					
	Theophylline **Aminophylline**	CBZ levels may ⇓	⇓ in theophylline plasma levels by 30-50%	⇑ in theophylline clearance through induction of CYP1A2	Monitor theophylline & CBZ levels, adjust doses as necessary. With concomitant therapy, patients may need higher & more frequent theophylline doses.

Antivirals / Antiretrovirals:					
	NNRTIs: efavirenz	27% ⇓ in CBZ AUC	36% ⇓ Efavirenz AUC	Induction of CYP3A4 metabolism by CBZ & efavirenz	Consider alternative agent OR monitor CBZ levels and virologic responses
	NNRTIs: etravirine and rilpirivine	Etravirine may ⇓ CBZ levels	⇓ in etravirine and rilpirivine levels	Induction of NNRTI metabolism by CBZ	**Do not co-administer etravirine or rilpirivine with CBZ.**
	NNRTI: nevirapine	CBZ levels may ⇓	⇓ nevirapine plasma levels	Induction of NNRTI metabolism by CBZ	Monitor CBZ levels and virologic responses
	NRTIs: ONLY zidovudine	None	⇓ zidovudine plasma levels	Induction of zidovudine metabolism through glucuronosyltransferase	Coadministration with other NRTIs (didanosine, lamivudine, and zalcitabine) will not produce the same interaction.
	Protease Inhibitors (PIs): amprevavir, atazanavir, darunavir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir, tipranavir	⇑ CBZ plasma levels (up to 2-3 fold ⇑)	⇓ PI plasma levels	Induction of CYP3A4 metabolism by CBZ & inhibition of metabolism by PIs	Caution with concomitant use, as it may result in PI treatment failure. Monitor for development of neurotoxicity (especially with ritonavir use- potent inhibitor of CYP3A4) & ⇓ CBZ dose if necessary.
	Integrase Inhibitors: Dolutegravir Elvitegravir	None	⇓ antiviral plasma levels	Induction of CYP3A4 metabolism by CBZ	Combined use of dolutegravir or elvitegravir with carbamazepine is generally not recommended as concurrent use may result in loss of antiretroviral efficacy and development of resistance.
	CCR5 Antagonist: Maraviroc	None	⇓ maraviroc plasma levels	Induction of CYP3A4 metabolism by CBZ	Use 600 mg BID dose with carbamazepine EXCEPT when given concurrently with potent CYP3A4 inhibitors (e.g.: PIs, delaviridine, ketoconazole, itraconazole, clarithromycin, nefazodone). Use 150 mg BID dose with CYP3A4 inhibitors.
	Cytochrome P-450 Inhibitor: Cobicistat	CBZ levels may ⇑	⇓ cobicistat plasma levels, diminished efficacy	Induction of CYP3A4 metabolism by CBZ. Inhibition of CYP3A4 metabolism by cobicistat.	This combination is **contrainidicated** due to potential reduction of cobicistat efficacy and development of viral resistance.
	Hepatitis C Antivirals: Daclatasvir Elbasvir/Grazoprevir	None	⇓ antiviral plasma levels, diminished efficacy	Induction of CYP3A4 metabolism by CBZ.	Concurrent use with CBZ is **contraindicated** due to decreased antiviral efficacy.
Pain Medications:					
	Tramadol	None	⇓ tramadol plasma levels & ⇑ risk for seizure	Induction of CYP3A4 metabolism of tramadol by CBZ	Due to the seizure risk involved with tramadol, concomitant administration of tramadol and CBZ is not recommended. If used together, monitor for break-thru pain.
Food Interactions:					
	Grapefruit Juice	May ⇑ plasma levels of CBZ by ~40%	None	Inhibition of CBZ metabolism	Monitor CBZ levels in individuals who consume ~300 ml or more of grapefruit juice regularly and adjust CBZ dosage if needed.
	Caffeine	May ⇓ bioavailability of CBZ.	None	Induction of CBZ metabolism	Avoid excessive caffeine intake while on CBZ therapy.

References:
- Fischer, JH. Drug Interactions with Antiepileptic Agents, 2005.
- Facts and Comparisons® online, accessed 2010
- UpToDate® online, accessed 2007
- Micromedex® online, accessed 2010, 2012, 2018 • Package inserts

K. Gable, Pharm.D. 2007 *; M.Thomas, PharmD, 2010; J. Noel, PharmD, 2012, 2015, 2018*