

Beware cytochrome P450 inducers

Prescribing tips to prevent drug-drug interactions

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Hepatic enzyme induction—triggered by medications, smoking, or alcohol—can erode the effectiveness of most psychotropics. Here’s how to beat the system.

Psychiatrists know that common psychotropic medications can inhibit the liver’s cytochrome P450 enzyme system, increasing both plasma levels and the toxicity of co-administered drugs. Less well-known, perhaps, is that the opposite process—hepatic enzyme induction—can accelerate the liver’s metabolism of co-administered drugs, resulting in abnormally low plasma levels.

Hepatic enzyme-inducing agents may appear in a patient’s regimen by prescription or self-administration (e.g., cigarette smoking, use of St. John’s wort, etc.) (Table 1). Most psychotropics are metabolized by the liver, and co-administering them with a hepatic enzyme inducer may cause pharmacokinetic consequences, including lowered plasma levels of the parent compound and elevated plasma levels of its metabolites. These plasma level changes may result in:

- *reduced* efficacy (e.g., if the parent drug alone is responsible for clinical benefit)
- *greater* efficacy (e.g., with the prodrug codeine, where the analgesic effect may be amplified by accelerated metabolism into its active drug, morphine)
- or *no change* in clinical effect (e.g., if the metabolite of the parent drug is active and its increased plasma level sufficiently compensates for the decreased plasma level of the parent compound).

This article offers an overview of common inducers and



Table 1

COMMON AGENTS ASSOCIATED WITH HEPATIC ENZYME INDUCTION

Prescription	Nonprescription
Carbamazepine	Chronic cigarette smoking
Dexamethasone	Chronic ethanol use
Isoniazid	Chronic marijuana smoking
Modafinil	St. John's wort
Omeprazole	
Oxcarbazepine	
Phenobarbital	
Phenytoin	
Prednisone	
Primidone	
Rifampin	

the drugs they affect, as well as five principles that can help you anticipate and manage potential drug-drug interactions.

Carbamazepine

Carbamazepine is the best-known and most-thoroughly documented agent that can induce hepatic enzymes and lower plasma levels of co-administered drugs, both psychiatric and nonpsychiatric. This anticonvulsant also shows evidence of autoinduction, the unusual property of inducing its own accelerated hepatic metabolism.¹

Carbamazepine is a powerful inducer of CYP3A, the most abundant family of cytochrome P450 enzymes.² With initial carbamazepine therapy, hepatic enzyme induction begins within 3 to 5 days and is complete within 21 to 28 days.³ Because any co-administered drug requires some (often unknown) minimum plasma concentration for efficacy—and sometimes requires a “therapeutic window” level⁴—an inducing agent such as carbamazepine may compromise the other drug’s effectiveness.

Effect on neuroleptics. Drugs and classes of psychotropics whose levels and/or efficacies may be reduced in the presence of enzyme-inducing agents are listed in *Table 2*. For example, when carbamazepine and haloperidol are co-administered, haloperidol plasma levels may be reduced by 60%.⁵ The liter-

ature also shows a 50% reduction in fluphenazine levels⁶ and substantially reduced levels of valproic acid,⁷ clozapine,⁸ and perphenazine⁹ when co-administered with carbamazepine. Data on how these changes alter the drugs’ clinical effects are mixed: some patients have improved, and some have worsened.

It is unclear whether carbamazepine’s presence may lower drug levels into or below a neuroleptic plasma “therapeutic window,” or whether some observed patient improvement might occur as an independent augmenting effect of carbamazepine. Clearly, however, the presence or addition of the inducing agent—carbamazepine—substantially lowers neuroleptic plasma levels.

Effect on antidepressants. Carbamazepine has similar plasma level-reducing effects on antidepressants:

- amitriptyline and nortriptyline levels have been shown to be reduced by 40%¹⁰
- bupropion peak levels are decreased by 87%¹¹
- levels of clomipramine,¹² imipramine,¹³ and doxepin show marked reductions.¹⁰

No data have been reported regarding levels of selective serotonin reuptake inhibitors (SSRIs) when co-administered with carbamazepine. Perhaps this is because serotonergic antidepressant plasma levels are not generally measured in clinical practice, as SSRIs are not associated with the risks and toxicities that may occur with high plasma levels of tricyclic antidepressants.⁴ The clinician, however, may extrapolate from carbamazepine’s plasma-lowering effect on other agents and apply the same caution when co-administering serotonergic antidepressants.

Effect on other medications. Carbamazepine’s hepatic enzyme induction also may lower alprazolam levels by more

Table 2

PSYCHOTROPICS AFFECTED* BY HEPATIC ENZYME INDUCERS

- Antidepressants (tricyclics and potentially SSRIs)
- Antipsychotics (neuroleptics and atypicals)
- Benzodiazepines
- Bupropion
- Valproate

* Exhibit reduced plasma levels and/or impaired efficacy when co-administered

than 50%,¹⁴ risking sedative-hypnotic withdrawal in the dependent patient. Valproate levels have been reduced by more than 60% when co-administered with carbamazepine. Carbamazepine can also reduce the levels and efficacy of common nonpsychiatric medications, including warfarin and oral contraceptives.¹⁵

Other anticonvulsants

For unclear reasons, anticonvulsants are often hepatic enzyme inducers. Phenobarbital, primidone, and phenytoin have been associated with reduced plasma levels of numerous drugs.¹⁶ For example, phenytoin has been reported to increase clearance of the atypical antipsychotic quetiapine. In one report, phenytoin cessation resulted in a 24-fold increase in plasma quetiapine levels. Similarly, carbamazepine cessation increased quetiapine plasma levels 14-fold.¹⁷

Oxcarbazepine. Oxcarbazepine is a newer anticonvulsant—a keto-analogue of carbamazepine—that offers improved safety in overdose, no cardiotoxic effect, and no known risk of agranulocytosis. Like older anticonvulsants, oxcarbazepine is being used to treat mood disorders.

Oxcarbazepine has been described as exhibiting “mild induction” of hepatic enzymes.¹⁸ The drug’s manufacturer reports that the agent can induce the 3A4 hepatic enzyme, reduce levels of oral contraceptives by 50%, and decrease calcium channel blocker levels by 28%.¹⁶ In two patients recently treated by the author:

- adding oxcarbazepine, 600 mg bid, to the regimen of a male patient, age 46, with schizophrenia and obsessive-compulsive disorder resulted in a 100% reduction in the plasma level of clomipramine.
- adding oxcarbazepine, 600 mg in the morning and 900 mg at bedtime, to the regimen of a woman, age 44, with bipolar disorder led to a 71% decrease in the plasma level of valproate.

Both patients exhibited some worsening of psychiatric symptoms after the inducing agent was added. More widespread use of oxcarbazepine for epilepsy, mood disorders, and perhaps other indications will define its hepatic enzyme-inducing effect more clearly.

Topiramate. Topiramate—which is used as an antiepileptic and to treat mood disorders—has been shown to decrease

digoxin levels by 11% and the estrogenic component of oral contraceptives by 30%. Topiramate may both induce and inhibit hepatic enzyme metabolism and has been associated with a 25% increase in phenytoin levels in some patients.

Other known inducers

Lesser-known hepatic enzyme inducers include chronic cigarette smoking,¹⁹ marijuana smoking,²⁰ chronic ethanol use,²¹ modafinil,²² St. John’s wort,²³ prednisone,¹⁶ dexamethasone,¹⁶ omeprazole,¹⁶ rifampin,¹⁶ and isoniazid.¹⁶ Unfortunately, the doses and duration required for induction are undocumented. The effect of these agents can only be detected by the astute clinician or perhaps by measuring plasma levels of co-prescribed drugs.

Among more than 20 known CYP450 isoenzymes, the

Assume that any inducing agent may alter the efficacy of co-administered drugs that are also metabolized by the liver

six that metabolize most clinically useful medications are 1A2, 2C9, 2C19, 2D6, 2E1, and the 3A family. The 3A isoenzymes metabolize the widest range of drugs, so any agent that induces them is likely to have many interactions.

Inducing agents affect numerous specific enzymes (Table 3). For example:

- cigarette smoking induces at least 1A2
- carbamazepine and other anticonvulsants induce at least 3A4, 1A2, 2C9, 2C19, and 2D6
- alcohol induces at least 3A4 and 2E1.

These agents may induce other enzymes, but the effect has not yet been demonstrated in vivo or in vitro.

The catalogue of hepatic enzymes, inducers, and specific enzymes and substrates (affected drugs) is poorly documented, inadequately studied, and difficult to commit to memory. It is much simpler to assume that any inducing agent in a patient’s regimen may lower plasma levels and alter the efficacy of co-administered drugs that are also metabolized by the liver.

Compensating for induction

A careful patient history and monitoring of clinical effect and plasma levels can compensate for the effects of hepatic enzyme inducers.⁴ Dosages of affected drugs may need to be adjusted to achieve desired therapeutic levels.

continued

Table 3

HEPATIC INDUCERS¹, AFFECTED ISOENZYMES², AND SOME AFFECTED MEDICATIONS³

Hepatic enzyme inducer	CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP3A family	CYP2E1
Carbamazepine	Clozapine ⁴ Amitriptyline Fluoxetine Haloperidol	Citalopram Diazepam Imipramine Fluoxetine	Warfarin	Risperidone Paroxetine Amphetamine Perphenazine	OCP ⁵ Alprazolam Quetiapine	
Oxcarbazepine	Clomipramine			Clomipramine Risperidone	OCP	
Phenytoin	Clozapine	Diazepam			OCP Quetiapine	
Phenobarbital				Haloperidol Paroxetine Fluvoxamine		
Topiramate⁶					OCP	
Omeprazole	Clozapine	Phenytoin				
Rifampin		Phenytoin	Fluoxetine			
Prednisone					OCP	
Dexamethasone				Paroxetine	OCP	
Hypericum (St. John's wort)					OCP Cyclosporine ⁷ Haloperidol Pimozide	
Ethanol (chronic)				Tricyclics Neuroleptics	Alprazolam Trazodone Zaleplon	Ethanol Acetaminophen ⁸
Cigarette smoking	Haloperidol Clozapine					

OCP: Oral contraceptives

¹ Only clinically relevant inducing agents listed

² Cited by manufacturer or in literature

³ Examples of drugs known to be affected

⁴ Induction effect known, concomitant use not advisable due to possible addictive agranulocytosis risk

⁵ Among numerous medications metabolized by 3A isoenzymes

⁶ Acts as an inducer but also inhibits isoenzyme 2C19

⁷ St. John's wort use has been associated with reduced cyclosporine levels and acute transplant rejection.

⁸ Chronic alcohol intake has been associated with accelerated acetaminophen metabolism and toxic metabolite levels.

For example, a patient of the author was receiving two inducing agents, carbamazepine and phenytoin, for comorbid medical disorders. He required daily oral doses of 80 mg of haloperidol to achieve a plasma level of 8 ng/ml (therapeutic range in psychosis believed to be 4 to 16 ng/ml).⁴ By comparison, haloperidol given at 10 mg/d yielded a plasma level of 7 ng/ml in a comparably aged patient receiving no enzyme-inducing agents.

When an inducing agent is halted during psychotropic treatment, expect higher plasma levels, side effects, or even toxicity related to the psychotropic. This medication effect is likely as the inducing agent is tapered, discontinued, and cleared from the body (across approximately 5.5 times its half-life), and the induction process is gradually reversed.

Cessation of inducing agents has amplified the effects of clozapine⁸ and tricyclic antidepressants.¹⁰ Anecdotally, the taper and cessation of oxcarbazepine in the author's bipolar patient resulted in a 40% increase in plasma risperidone level and an 118% increase in valproic acid level, without any increase in the dosage of either psychotropic. At baseline, the patient's risperidone plasma level was 58 ng/ml (all parent compound). After oxcarbazepine was tapered and discontinued across 1 month, a repeat measurement of risperidone yielded a higher total plasma level (76 ng/ml) but an altered parent drug-to-metabolite ratio (risperidone 68 ng/ml, metabolite 8 ng/ml). This suggests that induction reversal was incomplete 2 weeks after oxcarbazepine was discontinued.

The literature offers little data on timelines for the onset and reversal of hepatic enzyme induction. Induction probably begins and becomes complete within days or weeks after drug therapy is initiated and steady-state levels are achieved. Similarly, the reversal likely occurs within days or weeks after clearance of the inducer.

How plasma levels correlate with clinical findings is the key, of course, and one must account for other possible influences, such as the presence of other hepatic enzyme inducers and inhibitors, dosage adjustments, cigarette smoking, chronic alcohol abuse, and other factors.

Box

MANAGING HEPATIC ENZYME INDUCTION: FIVE PRINCIPLES

- Prescription or nonprescription agents (e.g., cigarette smoking, St. John's wort) may induce hepatic enzymes.
- Inducing agents can lower plasma levels of co-administered medications that are also metabolized by the liver.
- Most psychotropics are metabolized by the liver, and their therapeutic effect requires a minimum plasma concentration.
- Hepatic enzyme induction can result in subtherapeutic plasma levels and inadequate drug trials of prescribed psychotropics.
- Assume that any inducing agent may lower plasma levels and alter the efficacy of co-administered drugs that are also metabolized by the liver. Observe carefully, monitor plasma levels, and use incremental dosing to assess and compensate for induction effects.

Five principles

When prescribing psychotropics, careful attention to five principles for managing the effects of hepatic enzyme induction (*Box*) can result in:

- fewer patients with refractory symptoms
- less polypharmacy
- fewer sequelae of undertreated serious psychiatric illness
- improved therapy of comorbid medical conditions whose therapeutic agents may be metabolized by the liver and are therefore vulnerable to the effects of hepatic enzyme induction.


Hepatic enzyme inducers can accelerate the liver's metabolism of psychotropic drugs, yielding low plasma levels. The catalogue of hepatic enzymes, inducers, and substrates is poorly documented and difficult to remember. Therefore, assume that any inducing agent may alter the efficacy of any co-administered drugs that are also metabolized by the liver.

BottomLine

continued

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 Related resources

- ▶ Flockhart D. Indiana University Department of Medicine. Cytochrome P450 drug interaction table. <http://www.Drug-Interactions.com>
- ▶ DiPiro JT, Talbert RL, Yee, GC, et al (eds). *Pharmacotherapy: A pathophysiologic approach*. New York: McGraw-Hill, 2002.
- ▶ Bernstein JG. *Handbook of drug therapy in psychiatry*. New York: Mosby-Year Book, 1995.

DRUG BRAND NAMES

- | | |
|--------------------------|---------------------------|
| Alprazolam • Xanax | Modafinil • Provigil |
| Amitriptyline • Elavil | Nortriptyline • Pamelor |
| Bupropion • Wellbutrin | Omeprazole • Prilosec |
| Carbamazepine • Tegretol | Oxcarbazepine • Trileptal |
| Clomipramine • Anafranil | Paroxetine • Paxil |
| Citalopram • Celexa | Perphenazine • Trilafon |
| Clozapine • Clozaril | Phenytoin • Dilantin |
| Diazepam • Valium | Pimozide • Orap |
| Doxepin • Sinequan | Primidone • Mysoline |
| Dexamethasone • Decadron | Quetiapine • Seroquel |
| Fluphenazine • Prolixin | Rifampin • Rifadin |
| Fluoxetine • Prozac | Risperidone • Risperdal |
| Fluvoxamine • Luvox | Trazodone • Desyrel |
| Haloperidol • Haldol | Valproate • Depakote |
| Imipramine • Tofranil | Warfarin • Coumadin |
| Isoniazid • Rifamate | Zaleplon • Sonata |

DISCLOSURE

Dr. Baird reports that he has served as a consultant to Eli Lilly and Co.

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