

Loss of enzyme induction: Ups and downs of a hidden drug-drug interaction

Patients on antipsychotics are at risk for adverse events when an inducer is removed

Mr. P, age 35 with schizophrenia and seizure disorder, has been maintained on risperidone, 6 mg qhs, and phenytoin, 300 mg qhs. For clinical reasons, the treating neurologist changes the anticonvulsant to divalproex. One week later, Mr. P presents to the emergency room complaining of jaw and neck stiffness.

Ms. K, age 43 with a history of schizoaffective disorder, bipolar type, and erratic medication adherence, is being treated with quetiapine, 600 mg at bedtime, and carbamazepine, 1,000 mg/d. Between appointments she stops taking carbamazepine, believing it is causing her to hear voices from her television. Two weeks later, the manager of Ms. K's independent living facility tells the psychiatrist that the patient appears excessively sedated and has fallen twice in the past few days.

Mrs. T, a 39-year-old state hospital resident with schizoaffective disorder, bipolar type, has been treated with clozapine, 250 mg bid for 6 months; her most recent trough serum level was 492 ng/mL. She smokes 15 cigarettes/d. Two weeks after the hospital institutes a no-smoking policy, Mrs. T complains of excessive drooling and lightheadedness. Her trough clozapine level is now 875 ng/mL.

Discontinuing a medication that has enzyme-inducing effects presents a hidden problem for patients receiving antipsychotic pharmacotherapy. Certain hepatic enzymes responsible for antipsychotic metabolism—as well those involved in intercellular drug transport—are induced by medication or environmental exposures.^{1,2}

continued



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Enzyme induction

Clinical Point

The workhorse of CYP metabolism is 3A4, which comprises 30% of hepatic activity and 70% of gut cytochrome activity

Box

Drug interactions: A common cause of nonadherence

Drug-drug interactions (DDIs) are a common and often preventable cause of morbidity and mortality. National surveillance data showed 700,000 emergency room visits related to adverse drug reactions (ADRs) in the 2 years from January 2004 through 2005.³ ADRs are particularly concerning for psychiatrists managing polypharmacy regimens for patients with severe mental disorders such as schizophrenia.

Literature on DDIs with antipsychotics focuses primarily on kinetic interactions that generate supratherapeutic drug levels.^{4,5} Because development of side effects is associated with reduced adherence, these kinetic interactions may increase the risk of adverse effects and lead to patients stopping the antipsychotic treatment.^{6,7}

Adding a medication that induces these enzymes to the regimen of a patient receiving antipsychotic therapy can result in markedly reduced serum antipsychotic levels, and discontinuing an inducing agent can result in increased antipsychotic levels.

Drug-drug interactions (DDIs) are a substantial contributor to adverse drug reactions (*Box*).³⁻⁷ Antipsychotic prescribing information highlights potential DDIs from the use of enzyme inhibitors and inducers but identifies only effects caused by adding a second agent. The prescriber remains the sole line of defense for monitoring for DDIs when discontinuing a medication that has inducing or inhibiting effects.

Most psychiatrists are aware that certain medications have clinically significant effects on cytochrome P450 (CYP) activity and of the potential for CYP inhibitors to generate DDIs. Clinicians often are aware of antidepressant medications' CYP-inhibiting effects, know that levels of other medications will change when discontinuing a potent P450 inhibitor, and understand the need to increase dosages of medications influenced by such agents.⁸

However, few studies have evaluated the effects of enzyme induction on antipsychotic drug levels,^{9,10} and the literature

rarely discusses changes in serum drug levels after loss of enzyme or drug transport induction.¹¹ If unrecognized, these changes may have significant clinical consequences.

Two induction pathways

The primary mechanism underlying clinically significant DDIs occurs during CYP-mediated phase I metabolism. Molecules undergo oxidative conversion into metabolites that can be conjugated by phase II enzymes, generating more soluble forms that facilitate excretion.

The workhorse of human CYP metabolism is 3A4 (*Table 1*),^{12,13} which comprises 30% of hepatic activity and 70% of gut cytochrome activity.¹⁴ CYP 1A2 is responsible for 10% to 15% of CYP activity.

Both CYP 3A4 and 1A2 are inducible. A wide variety of medications induce 3A4 activity. The list of 1A2 inducers is shorter; the most common are aryl hydrocarbons from cigarette smoke and proton pump inhibitors.

CYP 2D6 accounts for 20% of hepatic cytochrome activity but is not inducible. CYP 2D6 is well known to psychiatrists because some selective serotonin reuptake inhibitors (SSRIs) and the non-SSRI antidepressant bupropion are potent inhibitors of this enzyme.^{15,16}

P-glycoprotein (PGP) induction. Transmembrane shuttles such as P-glycoprotein (PGP) are an important component of drug disposition. PGP belongs to the family of ATP binding cassette (ABC) transporters that bring molecules across cellular barriers.^{17,18} It was first described in cancer cells that developed multiple drug resistance (MDR) and is often referred to as MDR1.¹⁹ PGP is encoded on human chromosome 7 and expressed in normal tissues, particularly in areas where cells seek to limit drug influx, such as those lining the luminal surface of the small and large intestine and those lining the blood-brain barrier and blood-testis barrier. The expression of PGP in hepatic cells promotes drug clearance by enhancing biliary drug excretion.

PGP is encoded on the same chromosome as CYP 3A4, and these 2 proteins

Table 1

What induces CYP 1A2 and 3A4?

Enzyme	Description	Inducers*
CYP 1A2	<ul style="list-style-type: none"> Responsible for 10% to 15% of all CYP P450 activity Located on chromosome 15 Low affinity/high capacity enzyme Located only in the liver Prevalence of genetic polymorphisms conferring poor metabolizer status: 12% to 13% 	Aryl hydrocarbons (smoking), proton-pump inhibitors (omeprazole > lansoprazole > pantoprazole), modafinil, St. John's wort, chargrilled meat, cruciferous vegetables such as broccoli and cabbage, flavones, protein supplements
CYP 3A4	<ul style="list-style-type: none"> Responsible for 30% of hepatic CYP 450 activity, 70% of gut cytochrome activity Located on chromosome 7 (same as PGP) Low affinity/high capacity enzyme Little evidence for significant functional polymorphisms 	Carbamazepine, phenytoin, phenobarbital, rifampin, oxcarbazepine, efavirenz, glucocorticoids, modafinil, nevirapine, pioglitazone, St. John's wort

* Listed in order from strongest to weakest induction
 CYP: cytochrome P450; PGP: P-glycoprotein
 Source: References 12,13

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Drug levels decreased by CYP induction will reach their peak 1 to 2 weeks after the inducer is discontinued

frequently are expressed in the same cells, particularly in the intestinal lining and liver. Moreover, PGP is inducible, and there is substantial overlap between medications that are substrates for—or inducers of—PGP and CYP 3A4 activity. This makes it challenging to determine whether the ki-

netic effects of a second medication are the result of interference of 3A4, PGP, or both.

Polymorphisms in PGP activity may influence the penetration of psychotropic medications into the CNS. Studies indicate an association between certain PGP polymorphisms and treatment outcomes.^{17,18}

continued

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Enzyme induction

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A slow taper of the antipsychotic to the target dose should compensate for the loss of enzyme or PGP induction

Table 2

Effects of CYP/PGP induction on atypical antipsychotics

Antipsychotic	Metabolic pathways	Effect of induction
Aripiprazole	2D6 and 3A4 convert aripiprazole to active metabolite dehydro-aripiprazole	3A4 induction decreases maximum concentration of aripiprazole and metabolite by 70%
Clozapine	Multiple enzymes convert clozapine to N-desmethylozapine; mean contributions of CYP 1A2, 2C19, 3A4, 2C9, and 2D6 are 30%, 24%, 22%, 12%, and 6%, respectively, with CYP 1A2 predominantly involved at low concentrations	Loss of smoking-related 1A2 induction results in 50% increase in serum levels
Olanzapine	Direct glucuronidation or 1A2-mediated oxidation to N-desmethylolanzapine	Carbamazepine use increases clearance by 50%. Olanzapine concentration:dose ratio is about 5-fold lower in smokers (7.9 +/- 2.6) than in nonsmokers (1.56 +/- 1.1; <i>P</i> < .0001)
Paliperidone	59% excreted unchanged in urine; phase I metabolism accounts for ≤10% of drug clearance	Unlikely to significantly impact levels, but impact of PGP induction is unknown
Quetiapine	3A4-mediated sulfoxidation to inactive metabolite is primary pathway, but numerous metabolites noted, with 1 active metabolite (norquetiapine)	Phenytoin increases clearance 5-fold
Risperidone	2D6 converts risperidone to active metabolite 9-OH risperidone	In a drug interaction study of risperidone, 6 mg/d for 3 weeks, followed by 3 weeks of carbamazepine, active moiety concentration was decreased by about 50%
Ziprasidone	3A4 (~1/3); aldehyde oxidase (~2/3)	Approximately 35% decrease in ziprasidone exposure by carbamazepine

CYP: cytochrome P450; PGP: P-glycoprotein
 Source: Reference 21

Stopping an inducer

In general, inducers of CYP enzymes stimulate gene transcription within hours of exposure; maximum transcriptional activity occurs after 10 to 12 hours of exposure. As transcription increases, the concentration of the CYP mRNA transcript steadily accumulates, as does concentration of CYP protein.

After an inducer is discontinued, transcription returns to basal levels within 18 hours; however, the degradation of CYP proteins is a first-order process, with a half-life of 8 to 30 hours. As a result, the decrease in cellular CYP concentration—and the level of activity—lags behind the decreased synthesis from reduced mRNA levels.

As with other first-order kinetic processes, the expected decrease in CYP activity will require 5 half-lives to reach the new steady state (ie, back to baseline CYP activity). This suggests that drug levels previously decreased by CYP induction will reach their peak on average 1 to 2 weeks after the inducer is discontinued.²⁰

Interactions with antipsychotics

Effects on serum antipsychotic levels caused by discontinuing a CYP or PGP inducer can be predicted from data on decreases in antipsychotic levels following inducer exposure. Except for ziprasidone and pali-

peridone, most atypical antipsychotics are prone to substantial decreases during concomitant inducer use (Table 2).²¹

The effect of enzyme inducers on risperidone is particularly interesting. Conversion of risperidone to its active metabolite 9-OH risperidone (paliperidone) occurs primarily via 2D6,²² yet concurrent use of carbamazepine—a potent CYP 3A4 inducer—results in a 50% decrease in the concentration of the active moiety (risperidone plus 9-OH risperidone). This finding and other early investigations suggested that CYP 3A had a role in risperidone metabolism,^{23,24} but these early studies and case series often involved molecules that had activity at both 3A4 and PGP. Further research clarified that effects on PGP—and not 3A4—are responsible for the changes in risperidone metabolism observed with the use of carbamazepine and other medications.^{25,26}

Induction in case patients: Follow-up. Regardless of whether induction is mediated by ≥ 1 metabolic pathways, the loss of the inducer will result in serum antipsychotic increases that are proportional to the initial decrease.²⁰ For example, with risperidone, the expected decrease is 50%. Therefore, after Mr. P stopped taking phenytoin, his serum risperidone level would be expected to double, which resulted in extrapyramidal side effects.

Quetiapine clearance is increased 5-fold by inducer exposure, so a clinician treating Ms. K would expect a marked increase in somnolence—and possibly orthostasis—as serum quetiapine levels peak 1 to 2 weeks following carbamazepine discontinuation.

The effects of smoking cessation on serum clozapine levels have been well-documented.^{1,27} Clinicians should anticipate median increases in serum clozapine levels of 55% after a patient discontinues smoking (aryl hydrocarbon exposure), but changes vary substantially among individuals. Mrs. T's serum clozapine increased approximately 78%.

Careful clinical monitoring and slow downward adjustment of antipsychotic doses could have prevented the adverse effects these 3 patients experienced after loss of CYP/PGP induction and the consequences those side effects present for future medication adherence. When loss of induction is unplanned—as when Ms. K stopped taking carbamazepine but continued quetiapine—clinicians need to be alert to the fact that the patient was prescribed an inducer and include the loss of induction as a hypothesis for the patient's somnolence.

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Know the extent of induction by common inducers such as carbamazepine and phenytoin

Clinical considerations

In the absence of detailed data on antipsychotic metabolism, clinicians can make intelligent decisions regarding potential DDIs by:

- knowing the extent of induction by common offenders (such as carbamazepine or phenytoin) documented in the medication's prescribing information or demonstrated through convincing case reports or case series
- memorizing the list of CYP 1A2 and CYP 3A4/PGP inducers.

Although the list of CYP 1A2 and CYP 3A4/PGP inducers is short, it is essential for clinicians to consult a readily available source of this information that is periodically updated to account for newer medications, such as the online table maintained by Flockhart (see *Related Resources*).²⁸

Patients who may be susceptible to effects from loss of enzyme induction (including smokers receiving olanzapine or clozapine or others taking 3A4/PGP

inducers) must be identified, and plans made for dosage adjustments if inducing agents are discontinued for a sufficient time (≥ 1 week) to result in downregulation of CYP or PGP activity. A slow taper of the antipsychotic over 1 to 2 weeks to the new target dose should compensate for loss of enzyme or PGP induction.

For newer antipsychotic medications with limited data, the proposed discontinuation of an inducer should, at the minimum, prompt a discussion between the psychiatrist and patient regarding the expected increase in serum antipsychotic levels and potential adverse effects that may result. Clinicians also must make every attempt to stay apprised of a patient's current medications, bearing in mind that another provider may prescribe an inducer. Patients with schizophrenia always should be educated to contact the psychiatrist following any change in medication regimen, placing particular emphasis on the 1 or 2 medications that are known to be impli-



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cated in DDIs with the patient's current antipsychotic.

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Bottom Line

Discontinuing a drug that induces enzymes responsible for antipsychotic metabolism—particularly CYP 3A4 and 1A2—can increase serum antipsychotic levels proportional to the initial decrease seen when the inducer was started. Be aware of which medications induce which enzymes, and slowly reduce antipsychotic dosages over 1 to 2 weeks to compensate for a planned inducer discontinuation.

Related Resources

- Flockhart DA. Drug interactions: Cytochrome P450 drug interaction table. Indiana University School of Medicine. 2007. <http://medicine.iupui.edu/flockhart/table.htm>.
- Cozza KL, Armstrong SC, Oesterheld JR. Concise guide to drug interaction principles for medical practice: Cytochrome P450s, UGTs, p-glycoproteins. Washington, DC: American Psychiatric Press, Inc; 2003.

Drug Brand Names

Aripiprazole • Abilify	Oxcarbazepine • Trileptal
Bupropion • Wellbutrin	Paliperidone • Invega
Carbamazepine • Carbatrol, Tegretol	Pantoprazole • Protonix
Clozapine • Clozaril	Phenobarbital • Barbita, Luminal, others
Divalproex • Depakote	Phenytoin • Dilantin
Efavirenz • Sustiva	Pioglitazone • Actos
Lansoprazole • Prevacid	Quetiapine • Seroquel
Modafinil • Provigil	Rifampin • Rifadin, Rimactane
Nevirapine • Viramune	Risperidone • Risperdal
Olanzapine • Zyprexa	Ziprasidone • Geodon
Omeprazole • Prilosec	

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Clinical Point

Stay apprised of a patient's medications, and bear in mind that another provider may prescribe an inducer