Psychopharmacologic management has become increasingly complex, and physicians run the risk of precipitating drug-drug interactions when certain drugs interact via the cytochrome P450 system. In addition, the P-glycoprotein transporter may play a role in certain drug-drug interactions. While physicians currently rely on Web sites and textbooks to avoid potentially morbid and lethal interactions, electronic medical records may play a crucial role in the future.

The psychopharmacologic management of our patients has become much more complex with time. The number of medications in our vast armamentarium continues to grow with every passing month. Our patients often carry significant medical comorbidities, which are frequently managed with a variety of nonpsychotropic medications. The range of these medications has increased as well. It is hard enough to remain familiar with their intended therapeutic actions and purported mechanisms, but even more daunting is the task of becoming familiar with the metabolic paths of each agent and their capabilities to affect the bioavailability and metabolism of other agents. At first glance, this sounds like an impossibly complex task to undertake. Yet, in order for psychiatrists to safely prescribe medications, we must somehow master these concerns. Otherwise we run the risk of wantonly precipitating drug-drug interactions.

One may argue that these concerns are overly academic, but the lives lost to cardiac arrhythmias induced by drug-drug interaction-generated terfenadine (Seldane), astemizole (Hismanal) and cisapride (Propulsid) toxicity suggest otherwise (Michalets and Williams, 2000; Yap and Camm, 2002). Hence the removal of these drugs from the U.S. market over the past seven years. It is further estimated that in patients who take medications, 2.8% of all hospital admissions are primarily attributable to drug-drug interactions (Grymonpre et al., 1988). There are numerous other studies that have documented the real cost in lives and dollars from drug-drug interactions. In the background of this evil of drug-drug interactions and the deep blue sea of available drugs is the evolving mode of standard psychiatric practice. Increasingly, we are expected to do more with less time and to do so safely. First, do no harm--this is much easier said than done. The range of possible drug combinations and their associated drug-drug interactions defies the limits of human recall. However, an appreciation for the organizing concepts that lie at the heart of drug-drug interactions may allow clinicians to anticipate and thus prevent what they might not be able to memorize.

**Cytochrome P450**

Our understanding of drug metabolism and the mechanisms that cause drug-drug interactions has grown over the years. In an ongoing manner, we are elucidating the essential role played by the cytochrome P450 system in the metabolism of most drugs and how perturbations in this system may lead to drug-drug interactions. The P450 system is a family of mostly hepatic enzymes that perform oxidative (phase I) metabolism. A list of common P450 substrates, inhibitors and inducers are shown in Table 1 and Table 2. Specific P450 enzymes are named by number-letter-number sequences that specify their precise identity, the main ones being 1A2, 2C9, 2C19, 2E1, 2D6 and 3A4. Substrates are those agents that are metabolized by particular P450 enzymes. Inhibitors impair the ability of specific P450 enzymes to metabolize their target substrates, thus producing increased blood levels of those substrates. Conversely, inducers cause an increase in the production of particular P450 enzymes, leading to increased metabolism of the substrates of that P450 enzyme.

We are learning more about two other systems that also exert an influence on possible drug interactions: phase II glucuronidation and the P-glycoprotein transporter. Phase II metabolism usually follows phase I oxidation, and it usually plays a relatively minor metabolic role. However, there are some medications whose metabolism is primarily governed by phase II metabolism, such as lamotrigine (Lamictal), morphine and lorazepam (Ativan). Phase II metabolism is catalyzed by specific enzymes, which are associated with specific substrates, inhibitors and inducers in a manner similar to phase I metabolism. The P-glycoprotein transporter, however, does not affect drug metabolism, but rather drug bioavailability. P-glycoprotein is an adenosine triphosphate-dependent
extruding transporter that lines the gut lumen and the blood-brain barrier. It removes P-glycoprotein substrates from the cytosol of enterocytes and returns them back into the gut lumen or from the capillaries of the blood-brain barrier back into the bloodstream. P-glycoprotein inhibitors antagonize this process and lead to retention of P-glycoprotein substrates. P-glycoprotein inducers increase the amount of active P-glycoprotein, thus leading to more extrusion of P-glycoprotein substrates.

A few cases may serve to clarify how an appreciation of these systems can help us understand and hopefully avoid drug-drug interactions.

Case 1. A 72-year-old female with type II diabetes mellitus and atrial fibrillation was receiving warfarin (Coumadin) 5 mg/day (INR=2.9) and amitriptyline (Elavil) 50 mg q hs for neuropathic pain. Fluoxetine (Prozac) 20 mg/day was added to her regimen for major depression. Over the following 10 days, she experienced increasing dizziness, dry mouth and inability to void. She eventually required transportation to the emergency department (ED), where a bladder catheterization yielded two liters of dark urine. Her INR was found to be 17.3.

Discussion. This is an example of an inhibitor added to two substrates, whose effects synergized to produce the complications described above. First, warfarin's metabolism mostly occurs at 2C9 for the more active S-isomer of warfarin (Heimark et al., 1987; Linder and Valdes, 1999). Fluoxetine (in concert with its active metabolite, norfluoxetine) is a strong 2D6 inhibitor and a moderate inhibitor of 2C9, 2C19 and 3A4 (Greenblatt et al., 1999; Stevens and Wrighton, 1993). Thus, the addition of the fluoxetine significantly impaired the ability of 2C9 to efficiently metabolize the warfarin, which led to an increase in the warfarin blood level. This drastically increased the anticoagulant effect of warfarin. Second, amitriptyline is a tertiary amine tricyclic antidepressant whose metabolism depends mostly on the intact functioning of 2D6, 3A4 and 2C19 (Venkatakrishnan et al., 1998). As above, the fluoxetine and norfluoxetine significantly impaired the ability of 2D6, 3A4 and 2C19 to contribute to the metabolism of amitriptyline, which led to an increase in the blood level of amitriptyline and nortriptyline. The resultant increase in anticholinergic tone led to the inability to void and subsequent bladder wall distension. These combined effects of a hypocoagulable state and anticholinergic-induced urinary retention led to spontaneous bleeding within the patient's distended bladder.

Case 2. A 29-year-old woman with rapid-cycling bipolar I disorder had responded well to lamotrigine monotherapy at a dosage of 250 mg/day. She unfortunately required hospitalization for a breakthrough manic episode. She had a history of poorly tolerating lithium (Eskalith, Lithobid) and antipsychotic medications (even atypical agents). Her psychiatrist decided to try oxcarbazepine (Trileptal), titrated to 600 mg bid, and lorazepam (Ativan) for control of agitation. The patient's manic symptoms gradually improved, and she was discharged after a 10-day hospital stay. However, three weeks later, the patient experienced an emergence of depressive symptoms. Her psychiatrist responded by gradually increasing the dosage of lamotrigine to 400 mg/day, which produced a remission of her depressive symptoms.

Discussion. This is an example of an inducer added to a substrate. Lamotrigine is primarily metabolized through phase II glucuronidation, specifically by the UDP-glucuronosyltransferase (UGT) 1A4 enzyme (Hiller et al., 1999). Oxcarbazepine is a moderately strong inducer of UGT 1A4 (May et al., 1999). This led to an increase in the amount of the enzyme that was available to metabolize the lamotrigine, resulting in a decrease in the blood level of lamotrigine. The addition of oxcarbazepine to lamotrigine can decrease lamotrigine blood levels by roughly 30% on average (May et al., 1999). Although this is not a huge effect, in this situation it accounted for lamotrigine's loss of mood-stabilizing efficacy (for the depressive pole) and the patient's mood instability following the addition of oxcarbazepine. The psychiatrist compensated for this effect by increasing the lamotrigine dosage to 400 mg/day.

Case 3. A 57-year-old man was receiving carbamazepine (Tegretol) 800 mg/day (blood level=10.7 mcg/mL) for the successful treatment of trigeminal neuralgia. He was also experiencing increased heartburn and obvious gastroesophageal reflux. He reported these symptoms to his internist, who prescribed omeprazole (Prilosec) 20 mg/day. One week later, the patient noted increasing fatigue, dizziness and diplopia. His wife informed him that his eyes were "fluttering" at times. Over the next four days, the patient became increasingly confused and even frankly stuporous at times. The patient's wife finally brought him to the local ED, where his carbamazepine level was found to be 19.5 mcg/mL (Dixit et al., 2001).

Discussion. This is an example of an inhibitor added to a substrate. Carbamazepine is a substrate of the P-glycoprotein transporter (Potschka et al., 2001), and omeprazole is an inhibitor of the activity of this transporter (Pauli-Magnus et al., 2001). Thus, the addition of omeprazole significantly impaired the ability of the P-glycoprotein transporter to extrude carbamazepine from enterocytes.
and return them back into the gut lumen. The resulting increase in the absorption of carbamazepine led to an increase in the carbamazepine blood level.

**On Avoiding Interactions**

So what is to be done? Ultimately, we will have to make extensive use of computers to master the problems posed by the universe of significant drug-drug interactions. I am hopeful that electronic medical records and order entry are the wave of the future, and that sophisticated computer programs will alert clinicians to drug-drug interactions before they can arise. The difficulty in creating such interactive programs currently lies in achieving a balance between a comprehensive database and the problem of constant alerts, which would obstruct physician workflow. Perhaps the programs of the future will provide graded magnitudes of alert status with multileveled options for learning more about a potential drug-drug interaction.

Until that day arrives, however, here are some drug-drug interaction survival tips:

1. Become familiar with the drug-drug interactions involving the drugs you prescribe most frequently.
2. Pay special attention to drug-drug interactions involving agents with a low therapeutic index (lithium, digoxin, TCAs and so on).
3. Refer frequently to tables, charts, references and computer programs you like and trust, and keep them handy. In my opinion, there is no program that can currently compare to the drug-drug interaction program of Jessica Oesterheld, M.D., and David Osser, M.D., which can be downloaded at [www.mhc.com/Cytochromes](http://www.mhc.com/Cytochromes). Also, the American Psychiatric Press has published two helpful books on this subject: *Concise Guide to Drug Interaction Principles for Medical Practice: Cytochrome P450s, UGTs, P-Glycoproteins* (Cozza et al., 2003) and *Drug Interactions Casebook: The Cytochrome P450 System and Beyond* (Sandson et al., 2003).
4. Encourage your patients to purchase all their medications at the same pharmacy and to enroll in that pharmacy's drug-drug interaction monitoring program. Patients should additionally be instructed to include all over-the-counter medications, herbal preparations and special foods in their pharmacy drug list.
5. Whenever possible, try to select agents with a low likelihood of producing drug-drug interactions within a given class of agents, such as citalopram (Celexa), escitalopram (Lexapro) and mirtazapine (Remeron) among the antidepressants, pravastatin (Pravachol) among the statins, and azithromycin (Zithromax) among the macrolides.

Hopefully, these prudent measures will provide reasonable protection from the worst that drug-drug interactions have to offer, until computer software programs evolve to the point where they can be both complete and useful.

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**References:**


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