



# Indiana Medicaid Drug Utilization Review Board Newsletter

Volume 10 Issue 1

February 2007

Indiana Medicaid DUR Board  
Room W382  
Indiana State Government  
Center, South  
402 West Washington Street  
Indianapolis, Indiana 46204

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## Primer on Drug-Drug Interactions

The frequency of drug interactions reported in the literature ranges from 2.2 to 70.3%, and though the contribution of drug-drug interactions to the total occurrence of adverse drug reactions (ADRs) is unknown, an estimated 25% of ADRs are attributed to drug interactions.<sup>1,2</sup> Given the incidence and potential for harm, a review of the basic principles of drug interactions is warranted.

Common clinical mistakes of evaluating drug interactions and their significance include the following: relying on personal clinical experience to assess the importance of an interaction, failure to consider the effects of dose or sequence of administration on the outcome of the interaction, failure to anticipate the time course of the interaction, assumption that all members of a medication class will interact in a like manner, assumption that the patient will manifest the same degree of interaction as in the literature, assumption that other health care providers will consider potential interactions before prescribing medications, and failure to appreciate that the discontinuation of a precipitant drug may result in an adverse interaction.<sup>3-5</sup>

A drug-drug interaction is the phenomenon that occurs when the effects or pharmacokinetics of a medication are altered by prior or concomitant administration of a second medication.<sup>6,7</sup> The object (index) drug is the one whose action is altered by the interaction, and the precipitant (interacting) drug is that which causes the altered action of the object drug.<sup>4,6</sup> Drug-drug interactions are often classified as ei-

ther pharmacodynamic or pharmacokinetic in nature.<sup>3,5,6</sup> However, interactions may also be pharmaceutical in origin, a result of physical or chemical incompatibility.

An interaction is pharmacodynamic when one drug induces a change in the patient's response to a drug without altering the pharmacokinetics of the object drug and may be additive, synergistic, antagonistic, or the result of disturbances in fluid and electrolyte balance.<sup>1,3,5,6</sup> An additive interaction occurs when medications with similar pharmacological effects are given in combination.<sup>2,4</sup> For example, the concomitant administration of aspirin (various) and warfarin (Coumadin®) may result in increased bleeding. Synergistic interactions occur when the combination of medications produces more than the expected effects from the addition of the second medication. The addition of furosemide (Lasix®) to an aminoglycoside antibiotic results in an increased risk of ototoxicity and nephrotoxicity. In contrast, when medications with opposite actions are given in combination, the effects of one counteract the other, resulting in an antagonistic interaction. For example, when vitamin K is administered with warfarin, the anticoagulant effects of warfarin are offset. Finally, disturbances in fluid and electrolyte balance may result in a pharmacodynamic drug interaction. Consider that a patient taking digoxin (Lanoxin®) may experience toxicity if they are hypokalemic, since a decrease in plasma potassium concentrations may result in myocardium sensitivity to digoxin.

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## Primer on Drug-Drug Interactions

drug-drug interaction occurs when one drug alters the rate or extent of absorption, distribution, metabolism, or excretion of another drug.<sup>3,5,6</sup> The small intestines is the primary site of absorption for most orally administered medications; therefore, altered gut motility, pH, drug solubility, metabolism, or mucosa may result in an interaction.<sup>4,5</sup> Protein and receptor binding contribute to interactions from altered distribution.<sup>3,6</sup> Serum proteins (eg, albumin, alpha<sub>1</sub>-acid glycoprotein) act as a transport for medications, carrying them either to the site of action or to an organ of elimination. The binding of drugs to these proteins can change as a result of concomitant drug administration. The potential for drug-drug interactions should be examined for orally administered medications that exhibit high protein binding (>95%), have a narrow therapeutic index, occupy most of the available binding sites at clinically relevant concentrations, have a small volume of distribution, or have a long half-life. The change in the metabolism of one drug by another is considered the cause of more clinically important drug interactions than any other mechanism.<sup>4,5</sup> The cytochrome P450 (CYP450) enzyme system consists of nearly 30 different enzymes and is responsible for the metabolism of many medications.<sup>4,6</sup> Since drugs must be lipid-soluble to cross the lipid plasma membrane to reach receptor sites and produce their systemic effects, the role of drug-metabolizing enzymes is to transform lipid-soluble drugs into more water-soluble metabolites, which facilitates their excretion in the urine and bile. Some medications are capable of increasing these enzymes (induction) and others inhibit the action of the enzymes (inhibition). Enzyme induction results in the acceleration of me-

tabolism and decrease in the duration and magnitude of the pharmacologic response of the object drug. Phenobarbital, phenytoin, and rifampin are common CYP450 inducers. Enzyme inhibition results in an increased plasma concentration and pharmacologic response of a medication. This effect increases the risk of toxicity and adverse effects of the object drug. Common CYP450 inhibitors include cimetidine, erythromycin, fluoxetine, azole antifungals, and grapefruit juice. Interactions may also result from altered excretion.<sup>3,6</sup> The kidney employs glomerular filtration, active tubular secretion, and passive tubular reabsorption to excrete medications and metabolites. The ability to predict which drugs will alter the excretion of other drugs is difficult; therefore, drug-drug interactions of this type are hard to predict.

Several variables may influence the risk of an interaction occurring. Elderly patients are less likely to manifest enzyme induction and are at an increased risk for interactions.<sup>2,4,6</sup> Additionally, they may have chronic diseases and/or decreased organ function. Regardless of age, patients with decreased organ function should be monitored closely in order to prevent drug interactions. Genetic influences are an important factor in the prevention of interactions. Approximately 5 to 10% of patients lack the CYP2C19 or CYP2D6 enzymes. Patients with multiple chronic disease states may have an altered response to various medications, since altered physiology can affect the outcome of the interaction. Alcohol consumption may affect drug metabolism as well, primarily through enzyme induction. Smoking increases the activity of enzymes in the liver, which stimulates metabolism of certain drugs (eg, theophyl-

line). Patients who smoke may require increased doses of these medications to maintain therapeutic serum concentrations. Finally, diet can have the following effects on pharmacokinetics: influence absorption (eg, milk and tetracycline), affect the action of the drug (eg, tyramine-containing foods and monoamine oxidase inhibitors), and affect elimination.

In addition to a careful and comprehensive medication history, the following are factors to consider when interpreting potential drug-drug interactions: time course of the interaction, dosage of the medications, whether the interaction is a class effect, whether the interaction is clinically significant, and the appropriate management of the interaction.<sup>3,4</sup> Several resources are available, which allow clinicians to check for interacting drug ingredients, resultant effects, and potential clinical significance (eg, Drug Interaction Facts™, Drug Interactions Analysis and Management, MICROMEDEX®, Lexi-Interact™).

### References

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## Top 20 Drugs for 4Q 2006

Top 20 Drugs 4 <sup>th</sup> Quarter 2006 Ranked by Total Amount Paid			
Drug	Total Paid	Total Claims	Avg Paid/Claim
Risperdal	\$3,619,300	13,783	\$263
Antihemophilic factor	\$3,176,412	109	\$29,141
Seroquel	\$2,936,042	12,088	\$243
Zyprexa	\$2,934,903	6,808	\$431
Abilify	\$2,716,039	7,446	\$365
Depakote	\$1,654,891	11,362	\$146
Insulin	\$1,461,258	12,881	\$113
Novoseven	\$1,447,623	7	\$206,803
Topamax	\$1,441,372	5,819	\$248
Lamictal	\$1,219,363	5,461	\$223
Fentanyl	\$1,079,472	3,631	\$297
Lipitor	\$1,050,549	10,808	\$97
Geodon	\$977,038	3,751	\$260
Sertraline	\$886,212	10,972	\$81
Advair	\$846,952	5,038	\$168
Trileptal	\$813,107	4,514	\$180
Amphetamine salts	\$760,485	8,221	\$93
Methylphenidate	\$759,115	9,094	\$83
Protonix	\$754,176	6,206	\$122
Oxycodone	\$753,310	4,930	\$153

Top 20 Drugs 4 <sup>th</sup> Quarter 2006 Ranked by Claims Paid		
Drug	Total Claims	Total Paid
Hydrocodone/APAP	43,244	\$357,533
Aspirin	39,943	\$27,987
Docusate	38,279	\$87,002
Acetaminophen	32,883	\$90,907
Alprazolam	32,770	\$315,574
Calcium/Vit D	31,184	\$98,110
Multivitamins	25,533	\$32,297
Loratadine	24,210	\$285,498
Lorazepam	21,553	\$131,549
Clonazepam	21,538	\$116,510
Multivitamins with Minerals	21,439	\$50,649
Albuterol	18,989	\$266,782
Prilosec OTC	17,059	\$463,545
Risperdal	13,783	\$3,619,300
Ferrous Sulfate	13,359	\$13,572
Insulin	12,881	\$1,461,258
Levothyroxine	12,182	\$133,991
Diazepam	12,137	\$225,790
Seroquel	12,088	\$2,936,042
Amoxicillin	11,655	\$90,260

### Program Assistance

All prior authorization requests or questions regarding the PDL should be directed to the ACS Clinical Call Center at 1-866-879-0106.

### PDL Listing

The fee-for-service PDL listing may be found at the following Web site:

<http://www.indianapbm.com/>