

# Drug Interactions of Medications Commonly Used in Diabetes

Curtis Triplitt, PharmD, CDE

When patients are diagnosed with diabetes, a large number of medications become appropriate therapy. These include medications for dyslipidemia, hypertension, antiplatelet therapy, and glycemic control. So many medications can be overwhelming, and it is imperative that patients are thoroughly educated about their drug regimen.

Patients have many concerns when multiple medications are started, including prescribing errors, the cost of medications, and possible adverse effects. Significantly, 58% of patients worry that they will be given medications that have drug interactions that will adversely affect their health.<sup>1</sup> These worries are not unfounded given that several highly publicized drugs have been withdrawn from the U.S. market in the past several years because of adverse effects from drug interactions. Terfenadine, mibefradil, and cisapride have all been withdrawn from the market specifically because of drug-drug interactions. When terfenadine or cisapride were given with a strong inhibitor of their metabolism, torsades de pointes, a life-threatening drug-induced ventricular arrhythmia associated with QT prolongation, could occur.<sup>2</sup> Cisapride, for gastroparesis or gastrointestinal reflux disease, and mibefradil, for hypertension, were prescribed for many patients with diabetes.

An adverse drug interaction is defined as an interaction between one or more coadministered medications that results in the alteration of the effectiveness or toxicity of any of the coadministered medications. Drug interactions can be caused by prescription and over-the-counter medications, herbal products or vitamins, foods, diseases, and genetics (family history). The true incidence of drug

interactions is unknown because many are not reported, do not result in significant harm to patients, or do not require admission to a hospital. When a hospitalization does occur, it is usually not documented as a drug interaction, but rather as an adverse drug reaction because the drug interaction may only be one component of the reason for admission.<sup>3,4</sup> Although drug interactions for a select few drugs are well known, we often ignore the substantial evidence that potential interactions exist in many of the medications prescribed today.

Minimizing the risk for drug interactions should be a goal in drug therapy because interactions can result in significant morbidity and mortality. Health care providers should take responsibility for the safe prescribing of medications, but we often discuss potential adverse drug reactions—not drug interactions—with patients. We may overlook this responsibility because there are rarely quick, easily accessible, and comprehensive resources that cover drug interactions. Even when available, comprehensive resources often list all drug interactions and do not emphasize those that are most important.

In addition, many diabetes educators are confused by drug interaction terminology and rely heavily on pharmacists and prescribers to properly screen for drug interactions. Causes and terminology common to drug interactions, common interactions with medications used in people with diabetes, and tools that busy diabetes educators can use will be provided in this article. Not all drug interactions will be covered, and drug-herbal<sup>5,6</sup> and drug-nutrient<sup>6,7</sup> interaction information can be found elsewhere, as

well as non-diabetes-related drug-drug interactions.<sup>7</sup>

## DRUG-DRUG INTERACTIONS

Drug interactions are often categorized as pharmacodynamic or pharmacokinetic in nature. A pharmacodynamic drug interaction is related to the drug's effect on the body. An example is the combination of alcohol with medications that cause sedation. A pharmacokinetic drug interaction is related to the body's effect on the drug. An example is an increase in the systemic concentration of a renally eliminated drug because of renal insufficiency. A pharmacokinetic drug interaction can be caused by an alteration in absorption, distribution, metabolism, or elimination of a drug.<sup>8</sup>

## Pharmacodynamic Interactions

Pharmacodynamic drug interactions can be either beneficial or detrimental to patients. A beneficial example is the additive blood pressure-lowering effect when an ACE inhibitor is added to a calcium channel blocker (CCB). Likewise, synergistic blood pressure lowering may be seen if a diuretic is added to an ACE inhibitor. The pharmacodynamic drug interaction can also be detrimental. When alcohol and a medication that causes sedation are combined, additive unwanted sedation may occur. Antagonistic effects may also be encountered, as with the combination of an acetylcholinesterase inhibitor for myasthenia gravis or Alzheimer's disease with amitriptyline for painful diabetic peripheral neuropathy. The acetylcholinesterase inhibitor increases acetylcholine levels, whereas amitriptyline has antagonistic anticholinergic effects.<sup>8</sup>

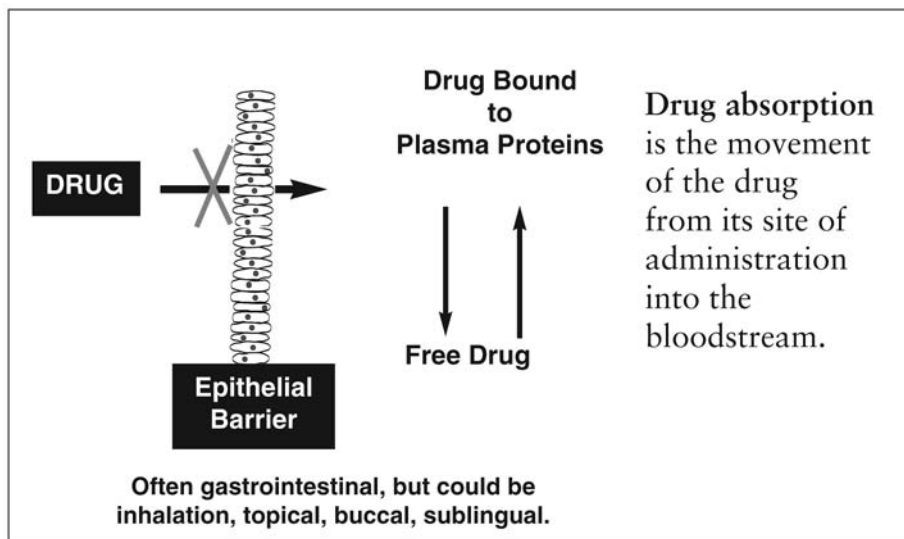
## Pharmacokinetic Interactions

**Absorption interactions.** Drug absorption is the movement of the drug from its site of administration into the bloodstream (Figure 1). Absorption interactions are changes in a drug's effects caused by food, drink, or medications taken concurrently.

Classically, we think of the oral administration of a medication and absorption from the gastrointestinal system, but it applies to all routes of administration, including injection, inhalation, topical, buccal, sublingual, and others.

Drug-food interactions can affect the total amount of drug absorbed (bioavailability), but most often they only slow absorption. For example, the hypoglycemic effect of glipizide may be delayed slightly if taken with a meal versus 30–60 minutes before a meal, although hemoglobin A<sub>1c</sub> (A1C) values are unaffected.<sup>9,10</sup> Alteration of gastrointestinal motility, as is the case with exenatide (Table 1), or pH may also affect absorption. In addition, components of food may interact. For example, vitamin K intake from green leafy vegetables interacts with warfarin. Similarly, several medications may complex or chelate with coadministered medications, significantly reducing their absorption.<sup>6</sup> For example, levothyroxine absorption is reduced when coadministered with ferrous sulfate or antacids and should be moved either 1 hour earlier or at least 2 hours after administration of these drugs.<sup>7,11</sup> It is best not to administer other medications with antacids because they can reduce the absorption of many medications.

**Distribution interactions.** Distribution is the movement of the absorbed drug through the bloodstream and its transport throughout extracellular or intracellular compartments to the site of action (Figure 2). Many medications extensively bind to plasma proteins such as albumin in the bloodstream. When a drug is bound to these plasma proteins, it is not actively distributed to the site of action, and only the “free” drug is available to cause an effect. One drug can displace another from the binding sites on the plasma proteins if its binding is stronger. This increases the amount of



**Figure 1.** Graphic depiction of a theoretical drug absorption interaction.

“free” drug available to cause an effect.

In the past, many protein-displacing interactions were documented in vitro, with in vivo consequences assumed. The majority of protein-displacing interactions have since been documented to be test-tube phenomena and are not clinically important.<sup>12</sup> Most of the suspected distribution interactions have now been reclassified as metabolism interactions. Distribution interactions can be significant for drugs that have extremely rapid distribution, narrow safety margins, and possibly nonlinear kinetics.<sup>12</sup> No significant distribution interactions are pertinent for oral medications commonly used for diabetes.<sup>12</sup>

**Metabolism interactions.** Drug metabolism is the modification or degradation of drugs. Metabolism can make drugs more or less toxic, active or inactive, or more easily eliminated from the body.<sup>13</sup> The primary organ involved in metabolism is the liver, although metabolism has been documented in the kidneys, lungs, gastrointestinal system, blood, and other tissues.<sup>6</sup> The most extensively studied family of isoenzymes found in the liver and gastrointestinal tract is the cytochrome P450 (CYP) system. The name “cytochrome P450” comes from the experimental techniques used to identify the isoenzymes and is not clinically relevant.<sup>14</sup> CYP2D6, for example, includes “2,” the genetic family; “D,” the genetic subfamily; and “6,” the specific gene member.

The nomenclature used to classify different subsets of the CYP system has no functional implications but clinically allows us to classify metabolism interactions.

Drugs can inhibit (decrease) metabolism, induce (increase) metabolism, or have no effect on each CYP450 isoenzyme subset. Thus, inhibition of metabolism will likely increase the affected drug's systemic concentrations, whereas induction of metabolism often reduces systemic concentrations. Not all isoenzymes are inducible, and only CYP2C9 and CYP3A4 induction is clinically relevant to people with diabetes. A drug may also be a substrate for (metabolized by) one or more of these enzyme subsets, and clinically, if an inhibitor or inducer affects that isoenzyme, it could affect the efficacy of the drug.

Drugs can have a complex profile, being a substrate for or an inhibitor or inducer of multiple subsets. For example, quinidine is a potent inhibitor of CYP2D6, but it is primarily metabolized by CYP3A4. More than 50% of all drugs are metabolized at least in part by CYP3A4 or CYP2D6, and several important diabetes drugs are metabolized by these pathways.<sup>15</sup> Phase 2 metabolism (glucuronidation, acylation, sulfation, and so forth) includes attachment of a water-soluble molecule to aid elimination and detoxification of a drug. Phase 2 metabolism need not but often does occur after metabolism by the CYP450 system. Research in this area is expanding, and glucuronidation is the basis of

**Table 1. Common Diabetes, Hypertension, and Lipid Drug Interactions**

MEDICATION	DRUG-DRUG INTERACTIONS	DRUG-NUTRIENT INTERACTIONS	DRUG-DISEASE INTERACTIONS
<b>Glucose Lowering</b>			
Sulfonylureas	Inhibitors/inducers of CYP2C9 (see Table 2)	Alcohol: first-generation sulfonylureas may cause flushing reaction, if severe nausea/vomiting	Metabolized: liver/kidney Caution if dysfunction ADR: loss of efficacy or hypoglycemia
Meglitinides	Nateglinide: none Repaglinide: -gemfibrozil: ↑ effect -other inducers/inhibitors of 2C8	None	Liver dysfunction: caution with both agents ADR: loss of efficacy or hypoglycemia
Metformin	Cimetidine may compete with metformin for renal elimination, which may increase levels of metformin	Vitamin B12 depletion; periodic monitoring if at risk	Lactic acidosis: renal insufficiency and hypoxic states (congestive heart failure, surgery, shock, or liver disease, including alcohol intake) ADR: hospitalization/death
TZDs	Strong inducers/inhibitors of CYP2C8 (see Table 2) Clinical effect of interaction: unknown	None	Fluid retention ADR: peripheral edema, heart failure, pulmonary edema ALT ≥ 3 × upper normal limit: do not start therapy; stop if taking
α-Glucosidase inhibitors	May decrease digoxin absorption May increase effect of warfarin Action: space administration	None	None
Exenatide	May slow absorption of medications: caution if rapid adsorption needed (e.g. acetaminophen, pain meds)	None	Renal insufficiency: potential for increased nausea/vomiting Gastroparesis: may worsen symptoms
<b>Hypertension</b>			
ACE inhibitors, ARBs	Captopril: see CYP2D6 Enalapril: see CYP3A4 (See Table 2) Aspirin, NSAIDs: may reduce antihypertensive effects of ACE inhibitor Lithium: levels may increase	Caution with potassium supplements with moexipril, captopril, and valsartan. Take 1 hour before or 2 hours after meals	Renal insufficiency, pregnancy
CCBs	CYP3A4 inducers/inhibitors (see Table 2)	Grapefruit juice may increase antihypertensive effects	Verapamil, diltiazem: caution—heart failure and cardiac conduction problems/heart block Dihydropyridine: peripheral edema
Diuretics	NSAIDs and phenytoin may reduce effectiveness of loop diuretics Thiazides may affect lithium levels	Thiazide and loop diuretics may cause hypokalemia. Potassium sparing diuretics may cause hyperkalemia	Caution in hyperuricemia or gout; may exacerbate attack May exacerbate lupus May worsen or cause severe photosensitivity reactions
<b>Lipid-Lowering</b>			
HMG-CoA reductase inhibitors (statins)	Lovastatin, simvastatin, atorvastatin: 3A4 (see Table 2) Fluvastatin: CYP2C9 (see Table 2) Pravachol: sulfated, but still cases of rhabdomyolysis reported	Lovastatin: food increases absorption Lovastatin extended-release: food decreases absorption  Lovastatin: food increases absorption	Watch for myopathy and rhabdomyolysis
Fibric acids	Gemfibrozil: inhibitor of 3A4, 2C8, (See Table 2) Increase ezetimibe levels Fenofibrate: 3A4, less risk of interaction (See Table 2)	None	Do not use if active cholecystitis

ADR, adverse drug reaction

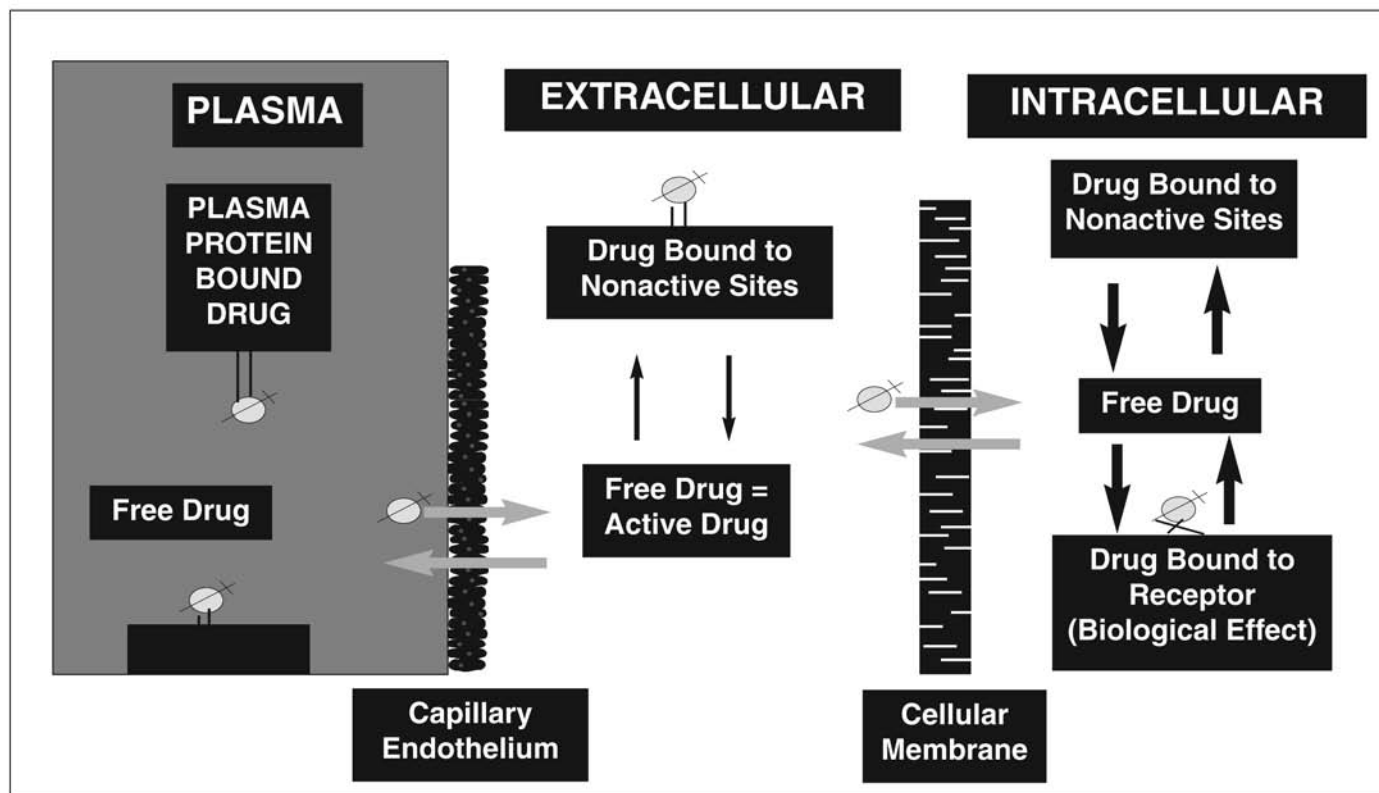


Figure 2. Graphic depiction of a theoretical drug distribution interaction.

one important drug-drug interaction involving gemfibrozil and several hydroxymethylglutaryl (HMG) CoA reductase inhibitors (statins).

High-risk groups for drug interactions include neonates, infants, the elderly, and those with significant organ disease (i.e., renal or hepatic disease) warranting increased screening vigilance. Neonates, infants, and the elderly will often metabolize drugs slower than healthy adults, and lifestyle choices such as smoking (induces metabolism) and alcohol use (may induce or inhibit metabolism) can alter metabolism. Metabolism patterns can also be altered by genetically determined variations. For example, ~ 5–10% of Caucasians, but only 0–1% of Asians, have little CYP2D6 enzyme activity, making them “CYP2D6 poor metabolizers,” the consequences of this are dependent on the drug and alternative pathways available for metabolism.<sup>16</sup>

**Elimination interactions.** Drug elimination is the removal of a drug from the body. The major organs involved in elimination are the kidneys and liver, although other bodily processes, including saliva, sweat, or exhaled air, may be pathways for elimination.

Elimination through the liver is primarily through bile. There are not many true drug-drug interactions through bile elimination, but drug-disease interactions, as described below, can be important when bile elimination is affected, as with severe biliary or liver disease. Renal drug-drug interactions are dependent on the pH of the urine and the pH of the drug or on competition for the same pathway of elimination. If the pH of the urine and the drug are the same, renal reabsorption of the drug will be increased. When two drugs compete for elimination through a single route, one drug may competitively inhibit the elimination of the other.<sup>8</sup> Metformin and cimetidine, both cationic (positively charged) drugs, can compete for elimination through kidneys by renal tubular secretion, resulting in higher metformin concentrations in the plasma.<sup>17</sup>

#### DRUG-DISEASE INTERACTIONS

Many comorbid diseases can affect metabolism in people with diabetes. Patients with diabetes have higher rates of cardiovascular, renal, gastrointestinal, neurological, and thyroid diseases and ophthalmological complications compared with individuals without diabetes. All may

increase the chance of having drug-disease interactions. Metformin and impaired renal function is a well-documented drug-disease interaction. Serum creatinine  $\geq 1.4$  mg/dl in women or  $\geq 1.5$  mg/dl in men warrants discontinuation of metformin because systemic concentrations can be elevated, increasing the risk of lactic acidosis.<sup>18</sup> Drug-disease interactions for specific medications used in people with diabetes will be covered below.

#### Diabetes Drug Interactions

**Sulfonylurea drugs.** Several drug-drug interactions occur with sulfonylureas. First-generation sulfonylureas, especially chlorpropamide, may cause a facial flushing reaction when alcohol is ingested. This may be similar to that caused by disulfiram, which blocks aldehyde dehydrogenase, resulting in increased levels of acetaldehyde. Acetaldehyde can result in flushing and possibly nausea or vomiting at higher levels.<sup>7,19</sup> A switch to a second-generation sulfonylurea would be advised (Table 1).

Sulfonylureas are commonly listed as having protein-binding drug interactions, and the first-generation sul-

fonylureas (acetohexamide, chlorpropamide, tolazamide, and tolbutamide), which bond ionically to plasma proteins, are thought to have a higher risk of protein-binding drug interactions.<sup>20</sup> If they do occur, they should occur shortly after the second medication is added to the sulfonylurea by displacing the sulfonylurea and increasing the active drug available. This would result in a reduction of plasma glucose and possibly hypoglycemia, if the plasma glucose was near normal. As stated previously, most of these have now been restated as interactions resulting from the CYP450 isoenzyme system.<sup>12</sup>

Sulfonylureas are a substrate of CYP2C9. Thus, inducers and inhibitors of CYP2C9 can affect the metabolism of sulfonylureas. Common medications that may interact with sulfonylureas are listed in Table 2. Sulfonylureas have two significant drug-disease interactions. Most are metabolized in the liver to active or inactive metabolites. When significant impairment in liver function is present, sulfonylurea metabolism may be altered. Active or inactive metabolites of sulfonylureas are eliminated by the kidneys, and renal insufficiency may reduce elimination (Table 3).

**Short-acting secretagogues.** Nateglinide, which is metabolized by CYP2C9 (70%) and CYP3A4 (30%), could be affected by strong inhibitors/inducers of CYP2C9, but significant drug-drug interactions have not been reported. Repaglinide is metabolized by the CYP3A4 and CYP2C8 isozyme systems and then extensively glucuronidated. A serious drug-drug interaction may occur with gemfibrozil, which is used for triglyceride lowering. This is likely caused by gemfibrozil's inhibition of CYP2C8 and glucuronidation. In vivo, gemfibrozil increases the total exposure of repaglinide eightfold.<sup>21</sup> Several reports of severe, prolonged hypoglycemia have been documented with the combination.<sup>22</sup> Strong inhibitors of CYP3A4, such as azole antifungal agents and erythromycin derivatives, may also enhance the hypoglycemic effect of repaglinide. Drugs that are inducers of CYP2C8/3A4 may reduce the effica-

cy of repaglinide, and a higher dose of repaglinide may be necessary<sup>23</sup> (Table 2).

The main drug-disease interaction of concern is impaired liver function, and the risk of hypoglycemia in this popu-

**Table 2. Common Inducers, Inhibitors, and Substrates of Select CYP450 Isozymes**

2C8	2C9	2D6	3A4
<b>Substrates (Metabolized By)</b>			
Repaglinide	Sulfonylureas	Captopril	Repaglinide
Pioglitazone	Nateglinide	Metoprolol	CCBs
Rosiglitazone	Losartan	Carvedilol	Enalapril
Cavedilol	Irbesartan		Losartan
	Warfarin		Irbesartan
	Zafirlukast		
<b>Inhibitors (↑ Drug Levels of Substrates)</b>			
Gemfibrozil	Fluconazole	Amiodarone	Clarithromycin
Fluconazole	Trimethoprim	Cimetidine	Erythromycin
Nicardipine	Amiodarone	Fluoxetine	(NOT Azithromycin)
Delavirdine	Zafirlukast	Paroxetine	Verapamil
Ketoconazole		Delavirdine	Diltiazem
		Ritonavir	Itraconazole
		Ropinirole	Ketoconazole
			Fluoxetine
			Fluvoxamine
			HIV protease inhibitors
			Delavirdine
<b>Inducers (↓ Drug Levels of Substrates)</b>			
Rifampin	Rifampin	None	Carbamazepine
Phenobarbital	Phenobarbital		Rifampin
Primidone			Rifabutin
			Phenobarbital
			Phenytoin
			St. John's Wort

**Table 3. Metabolism and Elimination of Sulfonylureas**

DRUG	METABOLISM	ELIMINATION
<b>First generation</b>		
Acetohexamide	Metabolized in liver; metabolite potency equal parent compound	Renal
Chlorpropamide	Metabolized in liver	Also renally eliminated unchanged
Tolazamide	Metabolized in liver; metabolite less active than parent compound	Renal
Tolbutamide	Metabolized in liver to inactive metabolites	Renal
<b>Second generation</b>		
Glipizide	Metabolized in liver to inactive metabolites	Renal
Glyburide	Metabolized in liver to inactive metabolites: elimination	50% renal, 50% feces
Glimepiride	Metabolized in liver; one metabolite one-third activity of glimepiride—unclear contribution to effects	60% urine, 40% feces

lation may be increased. No adjustment in dosing is needed in renal impairment until the patient has end-stage renal disease. When low-dose sulfonylureas cause hypoglycemia in renally impaired type 2 diabetic patients, repaglinide or nateglinide may be a good therapeutic alternative. Neither has significant drug-food interactions, but both should be taken preprandially to better match pancreatic insulin release with a meal (Table 1).

**Metformin.** Although not because of a drug interaction, metformin should be taken with a meal to limit gastrointestinal side effects. Metformin may cause malabsorption of vitamin B12, which may result in B12 deficiency and subsequent anemia. The mechanism by which metformin causes malabsorption of B12 is not clearly defined, although oral or injected B12 (cyanocobalamin) or calcium supplementation may be effective for correction<sup>24,25</sup> (Table 1).

Metformin does not undergo metabolism and is eliminated renally by tubular secretion and glomerular filtration. Metformin is a cationic (positively charged) molecule and may compete with other cationic drugs for renal secretion through organic cation transporters in the kidneys.<sup>17</sup> Procainamide, digoxin, quinidine, trimethoprim, and vancomycin are all cationic drugs that have the potential to interact with metformin, but only cimetidine, which is available over the counter for heartburn, has been implicated in one case of metformin-associated lactic acidosis (MALA)<sup>26,27</sup> (Table 1).

Metformin has many drug-disease interactions that can increase the risk of MALA. Metformin may increase lactic acid production from the splanchnic tissues slightly, but MALA occurs in the setting of comorbid diseases that increase systemic levels of lactic acid or reduce elimination of metformin. Any disease that may increase lactic acid production or decrease lactic acid metabolism may predispose to lactic acidosis. Tissue hypoperfusion from congestive heart failure, hypoxic states, shock, or septicemia can increase lactic acid production, and alcohol or severe liver disease can reduce removal of lactic acid in the liver, increasing the risk of lactic acidosis.

Metformin use in renal insufficiency, defined as a serum creatinine  $\geq 1.4$  mg/dl in women and  $\geq 1.5$  mg/dl in men, is contraindicated because it is renally eliminated. Elderly patients, who often have reduced muscle mass, should have their creatinine clearance rate estimated before use. If the creatinine clearance rate is  $< 70$ – $80$  ml/min, metformin should not be given. Because of the risk of acute renal failure during intravenous dye procedures, metformin should be withheld starting the day of the procedure and resumed in 2–3 days, when normal renal function has been documented.

Clinical presentation of lactic acidosis is often nonspecific flu-like symptoms and may include altered consciousness, heavy, deep (Kussmaul) breathing, and abdominal pain and thirst. Thus, the diagnosis is usually made by laboratory confirmation.<sup>18,28</sup>

**Thiazolidinediones.** Pioglitazone and rosiglitazone can both be taken without regard to meals. Rosiglitazone is a substrate for the CYP2C8 and to a lesser extent CYP2C9 pathways, and pioglitazone is a substrate for CYP2C8 (39%) and CYP3A4 (17%), as well as several other CYP450 pathways.<sup>29,30</sup> Rosiglitazone and pioglitazone metabolism in vivo can be affected by inhibitors or inducers of CYP2C8, but no significant drug-drug interactions have been reported to date<sup>30,31</sup> (Table 2). Neither drug has significant elimination drug-drug interactions.

However, both thiazolidinediones (TZDs) have significant drug-disease interactions. Both can cause fluid retention that may result in peripheral edema or, rarely, pulmonary edema and/or heart failure. Mechanistically, this may relate to increased renal reabsorption of sodium, a reduction of systemic vascular resistance, or other mechanisms.<sup>32,33</sup> Unlike troglitazone, no data link pioglitazone or rosiglitazone to drug-induced hepatotoxicity.<sup>34,35</sup> Nevertheless, it is recommended that drug therapy not be started if the alanine aminotransferase (ALT) is  $> 2.5$  times the upper limit of normal and stopped if the ALT is  $> 3$  times the upper limit of normal (Table 1). Prudent clinical judgment is needed for TZD drug-disease interactions,

but a full discussion is beyond the scope of this review.<sup>36,37</sup>

**$\alpha$ -Glucosidase inhibitors.** Because neither acarbose nor miglitol is extensively metabolized, neither has significant metabolism interactions. Several case reports have documented a reduction in absorption of digoxin and an increase in absorption of warfarin.<sup>38,39</sup> It is recommended that any drug with a very small dose and a narrow safety margin be administered apart from acarbose or miglitol. Drug-disease interactions are related to  $\alpha$ -glucosidase inhibitor-induced gastrointestinal side effects (gas, diarrhea, and abdominal gas pain), which could harm patients with certain gastrointestinal diseases (e.g., short bowel syndrome, Crohn's disease, or ulcerative colitis).

### Hypertension- and Lipid-Reducing Medications

**Antihypertensive drugs.** Many different classes of antihypertensive medications may be used for blood pressure control in diabetes, but the four most common include ACE inhibitors, angiotensin-II type 1 receptor blockers (ARBs), thiazide diuretics, and CCBs. CCBs can be further subdivided into dihydropyridine CCBs, so called for their chemical structure, and the nondihydropyridine CCBs, diltiazem and verapamil, which are pharmacodynamically linked because of their effect on the heart. Drug interactions may be present for some but not all medications within an antihypertensive class.

#### ACE inhibitors and ARBs

Drug-food interactions are important for two ACE inhibitors, moexipril and captopril, which should be administered 1 hour before or at least 2 hours after a meal.<sup>7</sup> A 40–50% decrease in systemic levels may be seen when valsartan, an ARB, is taken with food.<sup>40</sup> Because both classes may increase serum potassium levels, caution should be taken when potassium supplements or a high-potassium diet are consumed with either class (Table 1).

ACE inhibitors and ARBs have several interactions of importance. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) may

blunt the antihypertensive effect of an ACE inhibitor, presumably through inhibition of ACE inhibitor-induced prostaglandin synthesis. Clinically, the interaction does not appear to affect the ACE inhibitor's ability to prevent adverse cardiovascular or renal outcomes.<sup>41</sup> ACE inhibitors may increase hypersensitivity reactions, such as flu-like symptoms and skin rash, with allopurinol, although the exact mechanism is not known.<sup>7</sup> ACE inhibitors and ARBs may increase lithium levels, and concurrent use warrants close monitoring of lithium levels.<sup>7</sup>

Captopril, a CYP2D6 substrate, and enalapril, a CYP3A4 substrate, may be affected by strong inhibitors or inducers of these pathways<sup>7</sup> (Table 2). Concentration changes resulting from these interactions should be monitored by following the ambulatory blood pressure. Losartan is the only ARB with significant interactions with CYP3A4, although losartan and irbesartan are substrates of CYP2C9. Strong inhibitors or inducers of these pathways would likely increase or decrease the antihypertensive effectiveness of losartan (Table 2).

Despite potential interactions, very few clinically significant drug interactions have been documented with ARBs. Caution should be taken when either class is started in renal insufficiency because both can worsen renal function or even cause acute renal failure in patients with renal artery stenosis. Neither class is recommended in pregnancy because severe birth defects to neonatal kidneys can occur.

**Calcium channel blockers.** Most CCBs are metabolized by CYP3A4 and will be affected by strong inhibitors and inducers of CYP3A4 (Table 2). Grapefruit juice in sufficient quantities can block intestinal CYP3A4, which can lead to an enhancement of the effects of CCBs. This could affect the blood pressure response for all CCBs and further lower the pulse rate when diltiazem and verapamil are used. Studies that have explored the effect of grapefruit juice on diltiazem and verapamil have not reported changes in blood pressure or heart rate, despite increases in systemic drug concentrations.<sup>42-44</sup> Alcohol ingestion appears to have variable effects on the antihyperten-

sive effects of CCBs, and intake should be limited. In addition, diltiazem and verapamil are weak inhibitors of CYP3A4, and drug interactions with HMG-CoA inhibitors, which will be discussed later, have been documented.

The risk of cardiac conduction abnormalities with diltiazem or verapamil is the main drug-disease interaction to monitor. Diltiazem or verapamil given in combination with a  $\beta$ -blocker can further lower the pulse rate, increasing the risk for heart block. Dihydropyridine CCBs do not cause heart conduction drug-disease interactions, but they may cause peripheral edema, which may worsen preexisting edema present from heart failure, venous insufficiency, or other causes.

Nicardipine is an inhibitor of CYP3D6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4, and alcohol ingestion may enhance its antihypertensive effects.<sup>45</sup> Nicardipine is not recommended because other medications within the class have fewer drug interactions (Tables 1 and 2).

#### Diuretics

Thiazide diuretics are the most commonly used diuretics for blood pressure control in people with diabetes. No significant drug-food interactions exist for diuretics, but bile acid sequestrants, used rarely to reduce cholesterol, may cause a significant reduction in absorption, and thus dosing should be separated by several hours.<sup>7</sup> Loop and thiazide diuretics may deplete potassium and magnesium; adequate intake of these minerals is essential. Hypokalemia may greatly increase the toxicity of some concurrent medications (e.g., digoxin and antiarrhythmics).<sup>7</sup> Potassium-sparing diuretics (triamterene, amiloride, and spironolactone) may cause hyperkalemia. Monitoring of serum potassium is recommended for all diuretics on initiation and periodically thereafter. Thiazide diuretics decrease lithium excretion, and monitoring of lithium levels in conjunction with a reduction in dose is recommended. NSAIDs and phenytoin may decrease the effectiveness of loop diuretics.<sup>7</sup> Diuretics may also exacerbate several diseases, including hyperuricemia or gout and systemic lupus erythematosus, and cause photosensitivity reactions<sup>46</sup> (Table 1).

#### Lipid-lowering medications

##### *Fibric acid derivatives*

Both gemfibrozil and fenofibrate should be taken with food to reduce gastrointestinal upset. Bile acid sequestrants may interfere with absorption of fibric acid derivatives and should be separated from each other by at least 2 hours.<sup>7</sup> Gemfibrozil can significantly block CYP2C8/9/19, glucuronidation, and possibly human organic anion transporting polypeptide-2 (OATP2).<sup>47,48</sup> Several medications commonly used in the treatment of patients with diabetes are metabolized by these pathways, including sulfonylureas, repaglinide, sertraline, fluoxetine, and carvedilol. These medications may need dose reductions or close monitoring when combined with gemfibrozil<sup>7</sup> (Table 2).

The interaction of gemfibrozil with statins may be caused by a glucuronidated metabolite of gemfibrozil competing for metabolism after the OATP2 allows it into hepatocytes. Details can be further explored in a recent review article.<sup>48</sup> Further information on this important interaction can be found in the statins section.

When gemfibrozil is added to ezetimibe (Zetia), it likely blocks glucuronidation of ezetimibe, increasing systemic levels, but the clinical relevance of this interaction has yet to be documented.<sup>49</sup> Fenofibrate, which appears to have less potential to interact with the aforementioned drugs, also has a questionable ability to lower cardiovascular events in people with type 2 diabetes.<sup>50</sup>

##### *Statins*

Drug interactions that inhibit metabolism of statins increase systemic exposure, which may predispose to a greater risk of myopathy. The exact pathophysiological mechanism leading to myopathy is unknown, but direct effects of statins on the myocyte have been hypothesized.<sup>51</sup>

Although most myopathy cases occur as a result of drug-drug interactions, statins in monotherapy have also caused myopathy.<sup>51</sup> Patients often present with muscle aches with or without creatinine phosphokinase elevations, which are indicative of muscle destruction. If the myopathy is allowed to progress, it may lead to

rhabdomyolysis, with proximal weakness in the arms or legs. Myoglobinuria, characterized by brown or black urine, may also develop and is associated with acute renal failure. The risk of rhabdomyolysis is

low, but the majority of cases occur in patients with potential drug-drug interactions.<sup>52</sup> Proper education to stop the medication and report symptoms to their health care provider is essential to minimize risk to patients.

Caution should be taken when strong inhibitors of CYP3A4 are given with lovastatin, simvastatin, or atorvastatin. Strong inhibitors of CYP2C9 may increase fluvastatin and rosuvastatin levels (Table 2). Common classes

Name: \_\_\_\_\_ Provider/Diabetes Educator: \_\_\_\_\_  
 Date: \_\_\_\_\_ Email address \_\_\_\_\_ Phone number: \_\_\_\_\_  
 Diagnoses: \_\_\_ Diabetes \_\_\_ Hypertension \_\_\_ Hyperlipidemia \_\_\_ Other: \_\_\_\_\_  
 Allergies: \_\_\_\_\_  
 Diet/Vitamin Supplements: \_\_\_\_\_ Herbal Supplements: \_\_\_\_\_  
 Over-the Counter: \_\_\_\_\_

MEDICINE NAME/DOSE	INSTRUCTIONS	DRUG/ DRUG Interactions	DRUG/ FOOD Interactions	DRUG/ DISEASE Interactions

Inducers 3A4/2C9	3A4 Inhibitors		2C9 Inhibitors	Binders	Metformin
Rifampin	Fluconazole	Itraconazole	Bactrim	Antacids	Cimetidine
Carbamazepine	Erythromycin	Clarithromycin	Fluconazole	Bile acid sequestrants	
Rifabutin	Fluoxetine	Fluvoxamine	Amiodarone	Action: do not administer drugs at same time as above	
Phenytoin	Verapamil*	Diltiazem*	Cimetidine		
Phenobarbital	Cimetidine	Cyclosporine	Bactrim ointment		
St. John's wort	HIV protease inhibitors				
	Grapefruit juice in large amounts				
Drugs that may be affected	Drugs that may be affected		Drugs that may be affected	Drugs that may be affected	Cimetidine will renally compete for elimination and may increase metformin levels.
All drugs listed here	Statins†	CCBs	Sulfonylureas	All	
			Fluvastatin		
			Warfarin		

\* Not pravastatin, fluvastatin (CYP2C9), or rosuvastatin  
 † Weak inhibitors: caution with lovastatin or simvastatin  
 CCB, calcium channel blockers

Figure 3: Medication documentation/drug-drug interaction tool for diabetes educators.



of drugs that are strong inhibitors of CYP3A4 include azole antifungals, macrolide antibiotics (except azithromycin), protease inhibitors used for HIV, amiodarone, diltiazem, and verapamil<sup>52</sup> (Table 2).

Gemfibrozil and the immunosuppressant cyclosporine appear to increase the risk of myopathy with all statins.

To minimize the risk of myopathy and rhabdomyolysis, the maximum recommended dose of immediate-release lovastatin is 20 mg/day with cyclosporine, niacin (> 1 g/day), and fibric acid derivatives and 40 mg with verapamil or amiodarone. If the lovastatin sustained-release dosage form is used, the maximum recommended dose is one-half of the above-stated lovastatin doses.<sup>53</sup> The maximum recommended dose of simvastatin is 10 mg with cyclosporine, niacin (> 1 g/day), and fibric acid derivatives and 20 mg with verapamil or amiodarone.<sup>53,54</sup>

Other potential inducer/inhibitor drug-drug interactions of significance can be found in Table 2. Food may increase the absorption of immediate-release lovastatin but decrease the absorption of extended-release lovastatin.

## DRUG INTERACTIONS AND DIABETES EDUCATORS

It is nearly impossible to memorize the plethora of possible interactions currently affecting drug therapy in diabetes. Because of this complexity, it is essential that drug-drug interaction tools be used. This responsibility is usually shouldered by prescribers and pharmacists, but only diabetes educators may have a complete and up-to-date list of medications, and they should not assume that someone else will cover these topics. Strive to keep the conversation succinct and patient specific (only cover possible problems with drugs they are currently taking) when discussing possible drug interactions. Often, this involves not discussing the interaction itself, but rather the possible adverse consequences of the interaction.

Tools to list medications and evaluate potential drug interactions may help. Resources such as drug product inserts, websites for a specific drug, reference books, and printed primary literature review articles are often dia-

betes educators' best resources for evaluating the potential for drug interactions. It is important to involve a patient's health care team, and a pharmacist can be especially helpful when it is unclear whether drugs may interact. Pharmacists receive specialized training in drug interactions, often have software or reference books that specifically address drug interactions, and have additional background that can aid with an educated recommendation if no data are available.

Abbreviated forms to help busy diabetes educators keep a current medication list and ascertain whether patients with diabetes may be at risk for possible drug interactions can be found in Figure 3.

## CONCLUSIONS

Detecting potential drug interactions need not be burdensome, but it must not be ignored. Drug interactions resulting from absorption, distribution, metabolism, or elimination, as well as pharmacodynamic factors, are present for many common medications given to people with diabetes. The team approach is best, and it should not be assumed that prescribers and pharmacists are the only team members responsible for detecting and resolving drug interactions. Diabetes educators can and should be active team members in screening, educating, and following up on suspected drug interactions. This will likely lead to a lower risk of adverse effects and an improved quality of life for people with diabetes.

## Acknowledgments

The author thanks Magda Ortiz, RN, who was involved in the development, formatting, and editing of Figure 3 and several tables.

## References

- American Society of Health-System Pharmacists: ASHP national concerns research report [article online]. Available from <http://www.ashp.org/pr/survey.cfm>
- Zhou S, Chan SU, Goh BC, Eli C, Wei D, Min H, McLeod HL: Mechanism-based inhibition of cytochrome P450 3A4 by therapeutic drugs. *Clin Pharmacokinet* 44:279–304, 2005
- Yu DT, Peterson JF, Seger DL, Gerth WC, Bates DW: Frequency of potential azole drug-drug

interactions and consequences of potential fluconazole drug interactions. *Pharmacoepidemiol Drug Saf* 14:755–767, 2005

<sup>4</sup>Malone DC, Hutchins DS, Hauptert H, Hansten P, Duncan B, Van Bergen RC, Solomon SL, Lipton RB: Assessment of potential drug-drug interactions with a prescription claims database. *Am J Health Syst Pharm* 62:1983–1991, 2005

<sup>5</sup>Hu Z, Yang X, Ho PCL, Chan SY Chan, Hen PWS, Chan E, Wei D, Koh HL, Zhou S: Herb-drug interactions: a literature review. *Drugs* 65:1239–1282, 2005

<sup>6</sup>Sorenson JM: Herb-drug, food-drug, nutrient-drug, and drug-drug interactions: mechanisms involved and their medical implications. *J Altern Complement Med* 8:293–308, 2002

<sup>7</sup>Lexi-comp's Clinical Reference Library Online: Lexi-Interact [article online]. Available from <http://online.lexi.com/crlsql/servlet/crlonline>

<sup>8</sup>Rowland M, Tozer T: *Clinical Pharmacokinetics: Concepts and Applications*. 3rd ed. Baltimore, Md., Williams & Wilkins, 1995

<sup>9</sup>Wahlin-Boll E, Melander A, Sartor G, Schersten B: Influence of food intake on the absorption and effect of glipizide in diabetics and in healthy controls. *Eur J Clin Pharmacol* 18:279–283, 1980

<sup>10</sup>Berelowitz M, Fischette C, Cefalu W, Schade DS, Sutfin T, Kourides IA: Comparative efficacy of a once-daily controlled-release formulation of glipizide and immediate-release glipizide in patients with NIDDM. *Diabetes Care* 17:1460–1464, 1994

<sup>11</sup>Campbell NRC, Hasinoff BB, Stalts H, Rao B, Wong NCW: Ferrous sulfate reduces thyroxine efficacy in patients with hypothyroidism. *Ann Intern Med* 117:1010–1013, 1992

<sup>12</sup>Benet L, Hoener B: Changes in plasma protein binding have little clinical relevance. *Clin Pharmacol Ther* 71:115–121, 2002

<sup>13</sup>Sikka R, Magauran B, Ulrich A, Shannon M: Bench to bedside: pharmacogenomics, adverse drug interactions, and the cytochrome P450 system. *Acad Emerg Med* 12:1227–1235, 2005

<sup>14</sup>Estabrook RW: The remarkable P450s: a historical overview of these versatile hemoprotein catalysts. *FASEB J* 10:202–204, 1996

<sup>15</sup>Guengerich FP, Hosea NA, Parikh A, Bell-Parikh LC, Johnson WW, Gillam EMJ, Shimada T: Twenty years of biochemistry of human P450s: purification, expression, mechanism and relevance to drugs. *Drug Metab Dispos* 26:1175–1178, 1998

<sup>16</sup>Hasler JA, Estabrook R, Murray M, Pikuleva I, Waterman M, Capdevila J, Holla V, Helvig C, Falck JR, Farrell G, Kaminsky LS, Spivack SD, Boitier E, Beaune P: Human cytochromes P450. *Mol Aspects Med* 20:1–137, 1999

<sup>17</sup>Somogyi A, Stockley C, Keal J, Rolan P, Bochner F: Reduction of metformin renal tubular secretion by cimetidine in man. *Br J Clin Pharmacol* 23:545–551, 1987

<sup>18</sup>Bristol Myers Squibb: Glucophage (metformin HCl): prescribing information [article online]. Available from <http://www.glucophage.com>

- <sup>19</sup>Groop L, Eriksson CJ, Huupponen R, Ylikahri R, Pelkonen R: Roles of chlorpropamide, alcohol and acetaldehyde in determining the chlorpropamide-alcohol flush. *Diabetologia* 26:34–38, 1984
- <sup>20</sup>White JR, Campbell RK: Dangerous and common drug interaction in patients with diabetes mellitus. *Endocrinol Metab Clin North Am* 29:789–802, 2000
- <sup>21</sup>Niemi M, Backman JT, Neuvonen M, Neuvonen PJ: Effects of gemfibrozil, itraconazole, and their combination on the pharmacokinetics and pharmacodynamics of repaglinide: potentially hazardous interaction between gemfibrozil and repaglinide. *Diabetologia* 46:347–351, 2003
- <sup>22</sup>Novo Nordisk: Prandin (repaglinide): prescribing information [article online]. Available from <http://www.prandin.com>
- <sup>23</sup>Hatorp V, Hansen KT, Thomsen MS: Influence of drugs interacting with CYP3A4 on the pharmacokinetics, pharmacodynamics, and safety of the prandial glucose regulator repaglinide. *J Clin Pharmacol* 43:649–660, 2003
- <sup>24</sup>Bauman WA, Shaw S, Jayatilleke E, Spungen AM, Herbert V: Increased intake of calcium reverses vitamin B12 malabsorption induced by metformin. *Diabetes Care* 23:1227–1231, 2000
- <sup>25</sup>Gilligan MA: Metformin and vitamin B12 deficiency. *Arch Int Med* 162:484–485, 2002
- <sup>26</sup>Kimura N, Okuda M, Inui K: Metformin transport by renal basolateral organic cation transporter hOCT2. *Pharm Res* 22:255–259, 2005
- <sup>27</sup>Dawson D, Conlon C: Case study: metformin-associated lactic acidosis: Could orlistat be relevant? *Diabetes Care* 26:2471–2472, 2003
- <sup>28</sup>Triplitt C, Reasner C, Isley W: Diabetes mellitus. In *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. Dipiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, Eds. New York, McGraw-Hill. p. 1333–1367
- <sup>29</sup>Baldwin SJ, Clark SE, Chenery RJ: Characterization of the cytochrome P450 enzymes involved in the in vitro metabolism of rosiglitazone. *Br J Clin Pharmacol* 55:53–56, 1999
- <sup>30</sup>Niemi M, Backman JT, Neuvonen PJ: Effects of trimethoprim and rifampin on the pharmacokinetics of the cytochrome P450 2C8 substrate rosiglitazone. *Clin Pharmacol Ther* 76:239–249, 2004
- <sup>31</sup>Jaakkola T, Backman JT, Neuvonen M, Neuvonen PJ: Effects of gemfibrozil, itraconazole, and their combination on the pharmacokinetics of pioglitazone. *Clin Pharmacol Ther* 77:404–414, 2005
- <sup>32</sup>Zanchi A, Chiolero A, Maillard M, Nussberger J, Brunner HR, Burnier M: Effects of the peroxisomal proliferator-activated receptor-gamma agonist pioglitazone on renal and hormonal responses to salt in healthy men. *J Clin Endocrinol Metab* 89:1140–1145, 2004
- <sup>33</sup>Nesto RW, Bell D, Bonow RO, Fonseca V, Grundy SM, Horton ES, Le Winter M, Porte D, Semenkovich CF, Smith S, Young LH, Kahn R: Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and the American Diabetes Association. *Diabetes Care* 27:256–263, 2004
- <sup>34</sup>Lebovitz HE, Kreider M, Freed MI: Evaluation of liver function in type 2 diabetic patients during clinical trials: evidence that rosiglitazone does not cause hepatic dysfunction. *Diabetes Care* 25:815–821, 2002
- <sup>35</sup>Isley WL: Hepatotoxicity of thiazolidinediones. *Expert Opin Drug Saf* 2:581–586, 2003
- <sup>36</sup>Takeda Pharmaceuticals and Eli Lilly: Actos (pioglitazone): prescribing information [article online]. Available from <http://www.actos.com>
- <sup>37</sup>GlaxoSmithKline: Avandia (rosiglitazone): prescribing information [article online]. Available from <http://www.avandia.com>
- <sup>38</sup>Ben-Ami H, Krivoy N, Nagachandran P, Roguin A, Edoute Y: An interaction between digoxin and acarbose. *Diabetes Care* 2:860–861, 1999
- <sup>39</sup>Morreale AP, Janetzky K: Probable interaction of warfarin and acarbose. *Am J Health Syst Pharm* 54:1551–1552, 1997
- <sup>40</sup>Unger T, Kaschina E: Drug interactions with angiotensin-receptor blockers: comparison with other antihypertensives. *Drug Saf* 26:707–720, 2003
- <sup>41</sup>Teo KK, Yusuf S, Pfeffer M, Kober L, Hall A, Pogue J, Latini R, Collins R: Effects of long-term treatment with angiotensin-converting-enzyme inhibitors in the presence of absence of aspirin: a systematic review. *Lancet* 360:1037–1043, 2002
- <sup>42</sup>Fuhr U, Muller-Peltzer H, Kern R, Lopez-Rojas P, Jünemann M, Harder S, Staib HA: Effects of grapefruit juice and smoking on verapamil concentrations in steady state. *Eur J Clin Pharmacol* 58:45–53, 2002
- <sup>43</sup>Ho PC, Ghose K, Saville D, Wanwimolruk S: Effect of grapefruit juice on pharmacokinetics and pharmacodynamics of verapamil enantiomers in healthy volunteers. *Eur J Clin Pharmacol* 56:693–698, 2000
- <sup>44</sup>Christensen H, Asberg A, Holmboe AB, Berg KJ: Coadministration of grapefruit juice increases systemic exposure of diltiazem in healthy volunteers. *Eur J Clin Pharmacol* 58:515–520, 2002
- <sup>45</sup>Nakamura K, Ariyoshi N, Iwatsubo T, Fukunaga Y, Higuchi S, Itoh K, Shimada N, Nagashima K, Yokoi T, Yamamoto K, Horiuchi R, Kamataki T: Inhibitory effects of nicardipine to cytochrome P450 (CYP) in human liver microsomes. *Biol Pharm Bull* 28:882–885, 2005
- <sup>46</sup>Kaplan NM: *Kaplan's Clinical Hypertension*. 8th ed. Baltimore, Md., Williams & Wilkins, 2002
- <sup>47</sup>Ogilvie BW, Zhang D, Li W, Rodrigues AD, Gipson AE, Holsapple J, Toren P, Parkinson A: Glucuronidation converts gemfibrozil to a potent, metabolism-dependent inhibitor of CYP2C8: implications for drug-drug interactions. *Drug Metab Dispos* 34:191–197, 2006
- <sup>48</sup>Shitara Y, Hirano M, Sato H, Sugiyama Y: Gemfibrozil and its glucuronide inhibit the organic anion transporting polypeptide 2-mediated hepatic uptake and CYP2C8-mediated metabolism of cerivastatin: analysis of the mechanism of the clinically relevant drug-drug interaction between cerivastatin and gemfibrozil. *J Pharmacol Exp Ther* 311:228–236, 2004
- <sup>49</sup>Kosoglou T, Statkevich P, Johnson-Levonas AO, Paolini JF, Bergman AJ, Alton KB: Ezetimibe: a review of its metabolism, pharmacokinetics and drug interactions. *Clin Pharmacokinet* 44:467–494, 2005
- <sup>50</sup>FIELD Study Investigators: Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 366:1849–1861, 2005
- <sup>51</sup>Bellosta S, Paoletti R, Corsini A: Safety of statins: focus on clinical pharmacokinetics and drug interactions. *Circulation* 109:III50–III57, 2004
- <sup>52</sup>Thompson PD, Clarkson P, Karas RH: Statin-associated myopathy. *JAMA* 289:1681–1690, 2003
- <sup>53</sup>Lexi-comp's Clinical Reference Library Online: Lexi-drugs [article online]. [Accessed 17 February 2005] Available at: <http://online.lexi.com/crlsql/Servlet/crlonline>
- <sup>54</sup>Merck: Zocor (simvastatin): prescribing information [article online]. Available from <http://www.zocor.com>

*Curtis Triplitt, PharmD, CDE, is a clinical assistant professor in the Department of Medicine, Division of Diabetes, and Clinical Pharmacy Programs of the University of Texas Health Science Center and the Texas Diabetes Institute in San Antonio.*