Hypoglycemic Drug Interactions

See also chart, Page 2

1. What drugs should not be used in combination with oral hypoglycemics?

Despite numerous interactions affecting hypoglycemics, few are of major significance. These agents can be used relatively safely with almost all other medications with a couple notable exceptions:

Phenylbutazone – **can cause severe hypoglycemia when given together with oral sulfonylureas**, due to displacement of these agents from plasma protein binding sites and inhibition of their metabolic clearance. **Tolbutamide is affected the most**. One of the earliest NSAIDs, phenylbutazone is seldom prescribed but is occasionally found in Mexican drug products touted as antiarthritics. Phenylbutazone should be avoided and an alternate NSAID used. High-dose ASA (aspirin) and other salicylates can cause similar effects but to a lesser degree. (Low-dose ASA is usually indicated in persons with diabetes to reduce the risk of coronary artery disease.)

Alcohol – **can cause a disulfiram-like reaction when taken in combination with oral sulfonylureas, particularly chlorpropamide.** Persons experience flushing, sensations of warmth, dizziness, nausea and tachycardia. Alcohol is best avoided since the amount consumed does not necessarily correlate with occurrence or severity of the reaction. Diabetics not prescribed sulfonylureas are also wise to abstain or limit alcohol consumption as it has adverse effects on glycemic control with a tendency towards hypoglycemia. Pre-existing hypoglycemia can be potentiated. Acute and chronic alcohol consumption can also affect metabolic clearance of some hypoglycemics, further contributing to loss of glycemic control.

2. Since many diabetics have or develop concurrent cardiovascular disease, what effect do cardiac medications have on hypoglycemic efficacy?

Although there are numerous interactions between hypoglycemics and some of the major classes of cardiac drugs, the majority **are of moderate clinical significance. Most can be managed with more frequent blood sugar monitoring and dose adjustments** if use of alternate agents is not readily convenient. These include:

- **Antihypertensives:**

  Thiazide diuretics and furosemide – tend to cause hyperglycemia

  Calcium channel blockers (1st generation particularly nifedipine) – can cause hyperglycemia

  Beta blockers – can mask signs and symptoms of hypoglycemia (except sweating); also some inhibition of glycogenolysis and insulin secretion; cardioselective agents such as acebutolol *MONITAN, SECTRAL*, atenolol *TENORMIN*, bisoprolol *MONOCOR*, or metoprolol *LOPRESOR,BETALOC* may be safer.

- **Antihyperlipidemics:**

  Fibrate antihyperlipidemics and some beta blockers – can displace sulfonylureas and repaglinide *GLUCONORM* from plasma protein binding thereby potentiating their effects & possibly causing hypoglycemia

  Cholestyramine – increases the hypoglycemic effect of acarbose

  Nicotinic acid – worsens glycemic control & possibly increases insulin resistance

- **Hypoglycemics**

  Acarbose and Miglitol - can reduce the absorption of digoxin and propranolol

  Metformin - renal clearance can be delayed by digoxin, quinidine, procainamide, amiloride and triamterene (found in K+ sparing diuretic combos).

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Hypoglycemic Agents: Drug Interactions [1,2,3]

Drug	Effects Increased by: (Potential for Hypoglycemia)	Effects Decreased by: (Potential for Hyperglycemia)		Other Interactions:
Chlorpropamide (SU-1) **Gliclazide** *DIAMICRON* (SU-2) **Glyburide** *DIABETA* • highly PPB • cytochrome P450 substrate (CYP 3A3/4) (SU-2) **Tolbutamide** (SU-1) • cytochrome P450 substrate (CYP 2C8/9/18) and inhibitor (CYP 2C19)	***Displacement from PlasmaProteinBinding (PPB)*** : **Phenylbutazone,** Fibrates Fluoroquinolones (with Glyburide) Oral anticoagulants Phenytoin Salicylates Sulfonamides ***↓ Renal clearance***: Fibrates Salicylates Sulfonamides ***↓ Metabolism***: Azole antifungals (Tolbutamide) Chloramphenicol (with chlorpropamide & tolbutamide) Cimetidine (with Glyburide, Gliclazide & Tolbutamide) Sulfonamides ***Drugs potentiating hypoglycemia***: **Alcohol** *Beta Blockers MAOIs Tricyclic antidepressants	***↑ metabolism***: Alcohol-chronic use Rifampin	***Drugs causing hyperglycemia***: Beta Blockers Calcium Channel Blockers, some Corticosteroids, some Estrogens/ oral contraceptives Furosemide Isoniazid Phenothiazines Phenytoin Nicotinic Acid Sympathomimetics (e.g. decongestants) Thiazides Thyroid hormones	**Alcohol:** disulfiram-like rx • flushing, warmth, dizziness, nausea, tachycardia • .>>>chlorpropamide but also reported with other SUs Oral anticoagulants: may be affected due to PPB displacement and altered metabolism • initially = ↑ effect • chronically = ↓ effect H2 Antagonists, Proton Pump inhibitors & Antacids: can ↑ absorption; also ↑ effect of glyburide & gliclazide
Metformin *GLUCOPHAGE* •negligible PPB	***↓ Renal clearance*** (Cationic drugs): Amiloride Cimetidine Digoxin Morphine Procainamide Triamterene Quinine & Quinidine Trimethoprim Vancomycin			Alcohol: may potentiate metformin's effect on lactate metabolism
Acarbose *PRANDASE* **Miglitol** *GLYSET*	Cholestyramine	***↓ Absorption***: Amylase Charcoal Pancreatin		↓ absorption & effect of: Digoxin Propranolol Ranitidine
Pioglitazone *ACTOS* **Rosiglitazone** *AVANDIA*	Cytochrome P450 substrates so potential for some DIs as yet unknown			Oral contraceptives: pioglitazone may ↑ their metabolism and ↓ efficacy
Repaglinide *GLUCONORM* •Cytochrome P450 substrate (CYP3A4) •highly protein bound	***Displacement***: Beta Blockers, some Chloramphenicol MAOIs Phenylbutazone Phenytoin Salicylates Sulfomamides ***↓ Metabolism***: Azole antifungals Erythromycin	***↑ Metabolism***: Barbiturates Carbamazepine Rifampin		

Bolded drugs = major interactions. Avoid combination and use alternate agents.
All other drugs = moderate to mild interactions. More frequent blood glucose monitoring and dose adjustments may be required.
***** Beta Blockers mask signs and symptoms of hypoglycemia (e.g. tachycardia, tremor, blurred vision, hunger & headache) except sweating; also impair insulin release and glycogenolysis; cardioselective agents maybe safer (acebutolol, atenolol, bisoprolol, metoprolol).
DIs = drug interactions **MAOIs** = monoamine oxidase inhibitors **PPB** = plasma protein binding
SUs = sulfonylureas **SU-1** = first generation SU **SU-2** = 2nd generation SU.