

Chapter

6

DRUG THERAPY

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Five major classes of oral antihyperglycemic drugs and a wide variety of insulins are available for the management of patients with type 2 diabetes. Oral agents are characterized in Tables 6-1 to 6-5. These agents fall into two broad categories based on mechanism of action: (1) “secretagogues,” or drugs that augment insulin supply (sulfonylureas, non-sulfonylurea secretagogues, and insulin); and (2) “sensitizers,” or drugs that assist insulin action (biguanides, α -glucosidase inhibitors, and thiazolidinediones). Their use as monotherapy or in combination to achieve optimal glucose control are discussed in Chapter 8. These drugs differ significantly not only in their mechanisms of action, but in their advantages and disadvantages, dosage regimens, potential for adverse effects, costs, and other features, all of which may influence drug choice.

SULFONYLUREAS

Characteristics of sulfonylureas include:

- ▶ *Primary antihyperglycemic action:* Enhance insulin secretion by interacting with sulfonylurea receptors on β -cells, thereby closing ATP-sensitive potassium channels
- ▶ *Predominant impact on glucose:* Reduce fasting plasma glucose (FPG)
- ▶ *As monotherapy:* Reduce A1C 1.5% to 2.0% when initial A1C is 8% to 9%
- ▶ *Contraindications:* Known hypersensitivity to drug; type 1 diabetes; diabetic ketoacidosis; sulfa allergy

- ▲ *Advantages:* Well-established; rapidly reduce FPG; convenient daily dosing; neutral effect on plasma lipid levels; relatively inexpensive
- ▲ *Disadvantages:* Hypoglycemia, especially with longer-acting sulfonylureas and in the elderly with declining renal function; weight gain

Table 6-1 lists the “second-generation” sulfonylureas, which are the most commonly used. When initiating sulfonylureas, the clinician should consider the starting A1C level and the reduction needed to achieve goal. Titrate to desired effect at 1- to 2-week intervals based on patient FPG levels. The maximal antihyperglycemic effect usually occurs with one-half the maximal recommended dose. If no effect is observed at that dose, further dose increases are unlikely to have a clinically significant antihyperglycemic effect.¹⁻¹³

Less commonly used “first-generation” sulfonylureas include acetohexamide (Dymelor), chlorpropamide (Diabinese), tolbutamide (Orinase), and tolazamide (Tolinase).

NON-SULFONYLUREA SECRETAGOGUES

Characteristics of the non-sulfonylurea secretagogues include:

- ▲ *Primary antihyperglycemic action:* Enhance insulin secretion similar to sulfonylureas but effect a rapid and shortened stimulation of the β -cell
- ▲ *Predominant impact on glucose:* Reduce postprandial plasma glucose (PPG)
- ▲ *Contraindications:* Known hypersensitivity to drug; type 1 diabetes; diabetic ketoacidosis with or without coma
- ▲ *As monotherapy:* Repaglinide reduces A1C comparable to sulfonylureas, whereas nateglinide reduces A1C on average 0.5% to 1.0%
- ▲ *Advantages:* Target primarily PPG; possibly less hypo-

Table 6-1
Commonly Used Sulfonylureas

Drug and Available Strengths	Daily Dose (mg) ^c	Doses/Day	Maximum Daily Dose (mg)	Duration of Action (h)	Most Common Adverse Effects
Glimepiride ^a (Amaryl) 1, 2, 4 mg	1-8	1	8	16-24	Hypoglycemia, dizziness, nausea
Glipizide ^b (Glucotrol) 5, 10 mg	2.5-40	1-2	40	12-18	Hypoglycemia, nausea, diarrhea, weight gain
Glipizide-GITS ^a (Glucotrol XL) 2.5, 5, 10 mg	2.5-20	1	20	24	Hypoglycemia, headache, dizziness, diarrhea, flatulence, weight gain
Glyburide ^b (Micronase, DiaBeta) 1.25, 2.5, 5 mg	2.5-20	1-2	20	12-24	Hypoglycemia, nausea, heartburn, diarrhea, weight gain

(table continues)

Table 6-1
(continued)

Drug and Available Strengths	Daily Dose (mg) ^c	Doses/Day	Maximum Daily Dose (mg)	Duration of Action (h)	Most Common Adverse Effects
Glyburide ^b (Glynase) 3, 6 mg	3-12	1-2	12	12-24	Hypoglycemia, nausea, heartburn, diarrhea, weight gain
Glyburide/metformin combination ^a (Glucovance ^d) 1.25/250 mg 2.5/500 mg 5.0/500 mg	2.5/500	1-4	20/2000	12	Hypoglycemia, diarrhea, nausea, dizziness

Glipizide/metformin combination ^a (Metaglip)	2.5/250- 20/2000	1-2	20/2000	6-18	Diarrhea, abdominal pain, dizziness, hypoglycemia, lactic acidosis
2.5/250 mg					
2.5/500 mg					
5.0/500 mg					

Sources: AACE, 2002¹; Berelowitz, 1994²; Campbell, 1998³; Cefalu, 2001⁴; DeFronzo, 1999⁵; Goldberg, 1996⁶; Inzucchi, 2002⁷; Lebowitz, 1998,⁸ 2001⁹; Luna and Feinglos, 2001¹⁰; Riddle, 1999¹¹; Rosenstock, 1996¹²; Simonson, 1997.¹³
GITS, gastrointestinal therapeutic system (controlled release); XL, extended release.

^aGeneric formulation not available.

^bGeneric formulation available.

^cBrand name dose range; range for generic formulation, if available, may differ.

^dGlucovance information: www.familypractice.com.

glycemia and weight gain than with sulfonylureas; meal-adjusted dosing

- ▲ *Disadvantages:* More complex dosing (3 times daily [tid]); hypoglycemia; weight gain; no long-term data; relatively expensive

The available nonsulfonylurea secretagogues are listed in Table 6-2.^{1,4,5,7,8-11,14-15}

BIGUANIDES

Characteristics of biguanides include:

- ▲ *Primary antihyperglycemic action:* Direct action on liver to decrease glucose production; improves insulin action on liver and muscle
- ▲ *Predominant impact on glucose:* Reduce FPG
- ▲ *Contraindications:* Metabolic acidosis or hypoxic states, including renal disease or dysfunction (serum creatinine ≥ 1.5 mg/dL), liver failure, congestive heart failure requiring drug intervention, diabetic ketoacidosis, major surgery, dye procedures with iodinated contrast agents, sepsis, alcoholism, hypersensitivity to drug, patient age >80 years
- ▲ *As monotherapy:* Equally efficacious as sulfonylureas in reducing A1C
- ▲ *Advantages:* Well-established; weight loss (or no weight gain); no hypoglycemia; decrease micro- and macrovascular risk factors
- ▲ *Disadvantages:* Adverse gastrointestinal (GI) effects; many contraindications

Table 6-3 lists the biguanides currently available. Begin with 500 or 850 mg once a day and titrate weekly based on FPGs. Maximal effectiveness is usually seen at 2,000 mg/day. Initial dosing and titration should be conservative in the elderly.^{1,4-5,7,9-11,16}

Table 6-2
Non-Sulfonylurea Secretagogues

Drug and Available Strengths	Daily Dose (mg)	Doses/Day	Maximum Daily Dose (mg)	Duration of Action (h)	Most Common Adverse Effects
Repaglinide ^a (Prandin) 0.5, 1, 2 mg	0.5–16 ^b	2–4	16	2–6	Hypoglycemia, headache, weight gain
Nateglinide ^a (Starlix) 60, 120 mg	180–360 ^b	2–4	540	1–3	Hypoglycemia, diarrhea, dizziness

Sources: AACF, 2002¹; Cefalu, 2001⁴; DeFronzo, 1999⁵; Inzucchi, 2002⁷; Lebowitz, 1998,⁸ 2001⁹; Luna and Feinglos, 2001¹⁰; Riddle, 1999¹¹; Horton, 2000¹⁴; Jovanovic, 2000.¹⁵

^aGeneric formulation not available.

^bBased on number of meals; dose taken 15 minutes before meals.

Table 6-3
Biguanides

Drug and Available Strengths	Daily Dose (mg)	Doses/Day	Maximum Daily Dose (mg)	Duration of Action (h)	Most Common Adverse Effects
Metformin (Glucophage, Glucophage XR) 500, 850, 1000 mg	500–2550	2–3	2550	6–12	Diarrhea, nausea, vomiting, abdominal bloating, flatulence, anorexia, lactic acidosis (rare)
Rosiglitazone + metformin (Avandamet) 1/500, 2/500, 4/500, 2/1000, 4/1000 mg	2/500–8/2000	2	8/2000	>3–4 weeks	Edema, weight gain, dilutional anemia, diarrhea, nausea, vomiting, abdominal bloating, flatulence, anorexia, lactic acidosis (rare)

Sources: AACE, 2002¹; Cefalu, 2001⁴; DeFronzo, 1995,¹⁶ 1999⁵; Inzucchi, 2002⁷; Lebovitz, 1998,^{8,17} 2001⁹; Luna and Feinglos, 2001¹⁰; Riddle, 1999.¹¹
XR, extended release.

α -GLUCOSIDASE INHIBITORS

Characteristics of the α -glucosidase inhibitors include:

- ▲ *Primary antihyperglycemic action:* Slow digestion of carbohydrates to delay glucose absorption from gut
- ▲ *Predominant impact on glucose:* Reduce PPG
- ▲ *Contraindications:* Major GI disorders, including inflammatory bowel disease, chronic ulceration, malabsorption, or partial intestinal obstruction; hypersensitivity to drug; diabetic ketoacidosis
- ▲ *As monotherapy:* Reduce A1C about 0.5% to 1.0%
- ▲ *Advantages:* Target PPG; no hypoglycemia; can be used in patients with liver or heart disease
- ▲ *Disadvantages:* More complex dosing (3 times daily); weak effect on A1C; adverse GI effects; no long-term data; relatively expensive

α -Glucosidase inhibitor drugs are listed in Table 6-4. Begin with the lowest daily dose and titrate at 2- to 4-week intervals as needed to the maximal daily dose. Acarbose is not recommended for patients with serum creatinine >2.0 mg/dL. Miglitol is not recommended for patients with renal dysfunction.^{1,4-5,7-11,17-18}

THIAZOLIDINEDIONES

Characteristics of the thiazolidinediones (TZDs; also known as glitazones) include:

- ▲ *Primary antihyperglycemic action:* Enhance insulin action in liver and peripheral tissues via peroxisome proliferator-activated receptors (PPARs)
- ▲ *Predominant impact on glucose:* Decrease FPG
- ▲ *Contraindications:* Known hypersensitivity to drug; congestive heart failure because of volume expansion; evidence of

Table 6-4
 α -Glucosidase Inhibitors

Drug and Available Strengths	Daily Dose (mg)	Doses/Day	Maximum Daily Dose (mg)	Duration of Action (h)	Most Common Adverse Effects
Acarbose ^a (Precose) 50, 100 mg	75–300 ^b	3	300	<4	GI symptoms (may subside over time) including diarrhea, abdominal pain, and flatulence
Miglitol ^a (Glyset) 25, 50, 100 mg	75–300 ^b	3	300	<4	Abdominal pain, diarrhea, flatulence, skin rash, low serum iron

Sources: AACE, 2002¹; Cefalu, 2001⁴; DeFronzo, 1999⁵; Inzucchi, 2002⁷; Lebovitz, 1998,^{8,17} 2001⁹; Luna and Feinglos, 2001¹⁰; Riddle, 1999¹¹; Coniff, 1995.¹⁸

^aGeneric formulation not available.

^bBased on 3 meals; dose taken with first bite of each meal.

Table 6-5
Thiazolidinediones

Drug and Available Strengths	Daily Dose (mg)	Doses/Day	Maximum Daily Dose (mg)	Duration of Action (h)	Most Common Adverse Effects
Rosiglitazone ^a (Avandia) 2, 4, 8 mg	2-8 ^b	1 or 2	16	>3-4 weeks	Edema, weight gain, dilutional anemia
Pioglitazone ^a (Actos) 15, 30 mg	15-45 ^c	1	45	>3-4 weeks	Edema, weight gain, dilutional anemia

Sources: AACE, 2002¹; Cefalu, 2001⁴; DeFronzo, 1999⁵; Inzucchi, 2002⁷; Lebovitz, 1998,⁸ 2001⁹; Luna and Feinglos, 2001¹⁰; Riddle, 1999,¹¹

^aGeneric formulation not available.

^bStart therapy at 4 mg/day.

^cStart therapy at 30 mg/day.

Table 6-6 Optimal Patient Phenotypes for Antihyperglycemic Drugs

Major Patient Phenotype	Preferred Drug Class
Very symptomatic, FPG >300 mg/dL and/or A1C >11	Long-acting insulin plus secretagogue (if lean) or sensitizer (if obese)
Symptomatic, FPG 200-300 mg/dL, A1C >9 and <11, recent diagnosis of type 2 diabetes	Sulfonylurea and sensitizer
Minimally symptomatic, FPG <200 mg/dL or A1C <9, recent diagnosis of type 2 diabetes, elevated PPG	Sulfonylurea or sensitizer
Elevated FPG >140 mg/dL and <200 mg/dL and A1C >8	Sulfonylurea (if lean) or sensitizer (if obese)
FPG <140 mg/dL and A1C <7.5	Alpha-glucosidase inhibitor or meglitinide secretagogue
Very symptomatic, severe hyperglycemia, ketosis, unrecognized type 1 diabetes, or pregnancy	Basal-bolus insulin regimen
FPG, fasting plasma glucose.	

active liver disease (ALT >2.5 times upper limit of normal [ULN])

- ▲ *As monotherapy*: Reduce A1C 1.0% to 1.5%
- ▲ *Advantages*: No hypoglycemia; convenient daily dosing; increase high-density lipoprotein (HDL) cholesterol; may improve hemostasis and endothelial function
- ▲ *Disadvantages*: Monitoring of liver function required; slow onset of action; edema; weight gain; increase low-density lipoprotein (LDL) cholesterol; no long-term data; relatively expensive

Two thiazolidinediones are currently available, as listed in Table 6-5.^{1,4-5,7-11}

It is important to monitor liver function every 2 months for the first 12 months of therapy and periodically thereafter. Discontinue if ALT is >2× ULN on two samples. Use of insulin with rosiglitazone is not recommended because of the increased risk of heart problems.^{1,4-5,7-11,19,20}

PHENOTYPES AND DRUG CLASSES

A reasonable approach to choosing the most appropriate drug for a specific patient is to consider the patient's phenotype, based on the severity of symptoms and hyperglycemia. Table 6-6 lists major patient phenotypes and preferred drug classes. (See Chapters 8 and 9 for additional information on optimal antihyperglycemic therapy.)

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