

# NEW PHARMACOTHERAPIES FOR TYPE 2 DIABETES



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## LEARNING OBJECTIVES

1. Compare and contrast the differences between the drug therapy recommendations of several of the latest and leading diabetes guidelines.
2. Assess the differences in incretin-based therapies for the treatment of type 2 diabetes mellitus (T2DM) and tell how they compare with other agents to treat hyperglycemia.
3. Delineate the role and place in therapy of bromocriptine and colesevelam in the treatment of T2DM.
4. Convert a patient with T2DM with significant hyperglycemia to an insulin-only drug regimen.
5. Evaluate the latest noncardiac precautions, contraindications, or warnings with agents used in the treatment of hyperglycemia.

## INTRODUCTION

The prevalence and incidence of type 2 diabetes mellitus (T2DM) continues to rise. It is estimated that 8.3% of U.S. adults have diabetes and that about 1.9 million adults were newly given diagnoses of diabetes in

2010 (CDC 2011). Regardless of the health care setting, today's clinical pharmacist is faced with many challenges and responsibilities to minimize the impact of this disease on patients and health care resources. New therapeutic agents, older drugs with new indications to treat hyperglycemia, changing therapeutic recommendations, safety of existing diabetes drugs, and patient education are just a few of these challenges and responsibilities for pharmacists. This chapter focuses on the treatment of hyperglycemia in patients with T2DM and how pharmacists can best develop and recommend safe and effective treatment options. The focus on hyperglycemia does not negate the critical need to optimize blood pressure and cholesterol control, the importance of lifestyle changes in diet and physical activity, or the treatment or prevention of disease complications.

## CLINICAL GUIDELINE UPDATES IN DRUG THERAPY MANAGEMENT

Given the volume of research and literature devoted to the management of hyperglycemia, it is very diffi-

### BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of the pathophysiology that leads to hyperglycemia in T2DM
- Fasting and postprandial glycemic goals defined by leading diabetes guidelines
- Drug knowledge of the oral pharmacologic agents used to treat T2DM
- Basic knowledge of the various parenteral diabetes agents used to treat hyperglycemia, including the onset and duration of insulin formulations as well as the dosing and insulin requirements of pramlintide therapy
- The consequences of poor glycemic control including microvascular and macrovascular complications

### ADDITIONAL READINGS

The following free resource is available for readers wishing additional background information on this topic. American Diabetes Association. Standards of medical care in diabetes – 2012. *Diabetes Care* 2012;35(suppl1): S11-S63.

## ABBREVIATIONS IN THIS CHAPTER

ADA	American Diabetes Association
BAS	Bile acid sequestrant
DPP-4	Dipeptidyl peptidase-4
GIP	Glucose-dependent insulinotropic peptide
GLP-1	Glucagon-like peptide 1
LDL	Low-density lipoprotein
PPAR	Peroxisome proliferator activated receptor
T2DM	Type 2 diabetes mellitus

cult for most clinicians to keep abreast of therapeutic options for T2DM. Hence, clinical guidelines or consensus recommendations provide useful tools and guidance to aid in T2DM management. There is a plethora of diabetes guidelines and recommendations, with some more recognized than others. Some are updated annually, whereas others are updated only after a sufficient volume of new literature supports changes in recommendations.

Optimizing physical activity and weight loss are goals of T2DM management. Diets should be low in fat, high in fiber, and not excessive in total daily caloric intake. Patients should be encouraged to exercise with a variety of activities at least 150 minutes/week (ADA 2012). For patients who are considerably overweight, bariatric surgery may be an option to significantly lose weight and has been associated with considerable improvements in hyperglycemia in patients with T2DM. The American Diabetes Association (ADA) recommends consideration of bariatric surgery in adults with T2DM and body mass indexes greater than 35 kg/m<sup>2</sup> (ADA 2012).

With respect to drug therapy management of hyperglycemia, metformin is the drug of choice to initiate in patients newly given a diagnosis with T2DM or in patients whose lifestyle modifications fail to attain glycemic control. This recommendation is in large part because of this agent's tolerability, low cost, effectiveness in hemoglobin A1C (A1C) reduction, low rate of hypoglycemia, potential for weight loss, cardiovascular benefit in obese patients, and ability to be combined with most other medications used to treat T2DM. Metformin continues to be the most widely used medication in T2DM, but with the emergence of other treatment options and provider or patient preferences, the drug remains underused in as many as 35% of patients (Desai 2012).

Although metformin monotherapy is effective in the average patient with T2DM, the disease is progressive,

and most patients will eventually require additional therapy. The recommended options—once metformin fails to adequately control hyperglycemia—vary between guidelines (Table 1-1; Figure 1-1).

### ADA/European Association for the Study of Diabetes

The ADA, in conjunction with the European Association for the Study of Diabetes, updated its drug therapy recommendations for T2DM in early 2012 (Inzucchi 2012). The ADA 2009 drug management recommendations used an algorithm and tiered approach to therapeutic options and response to therapy based on the quality and quantity of data at the time. These organizations now take a less prescriptive but more patient-centered approach to drug therapy recommendations. Metformin remains the initial treatment of choice (barring contraindications), though guidelines suggest if patients are highly motivated and their A1C is less than 7.5%, a 3- to 6-month trial of lifestyle modifications can be used before pharmacotherapy is initiated. The guidelines continue to recommend adding, rather than changing to, additional agents when metformin no longer provides adequate glycemic control or when A1C remains elevated after about a 3-month trial. Despite a failing metformin regimen, there may still be some clinical benefit with its continued use. If the baseline A1C is between 9.0% and 9.9%, the initial treatment regimen may contain an additional agent because metformin alone is unlikely to attain glycemic targets. Insulin therapy may be considered for initial therapy if a patient is symptomatic and/or has markedly elevated plasma glucose concentrations (i.e., greater than 300 mg/dL) or A1C (i.e., 10% or greater). If insulin is initiated early, other T2DM medications may be added when improved glycemic control is achieved, and daily insulin requirements can be lowered.

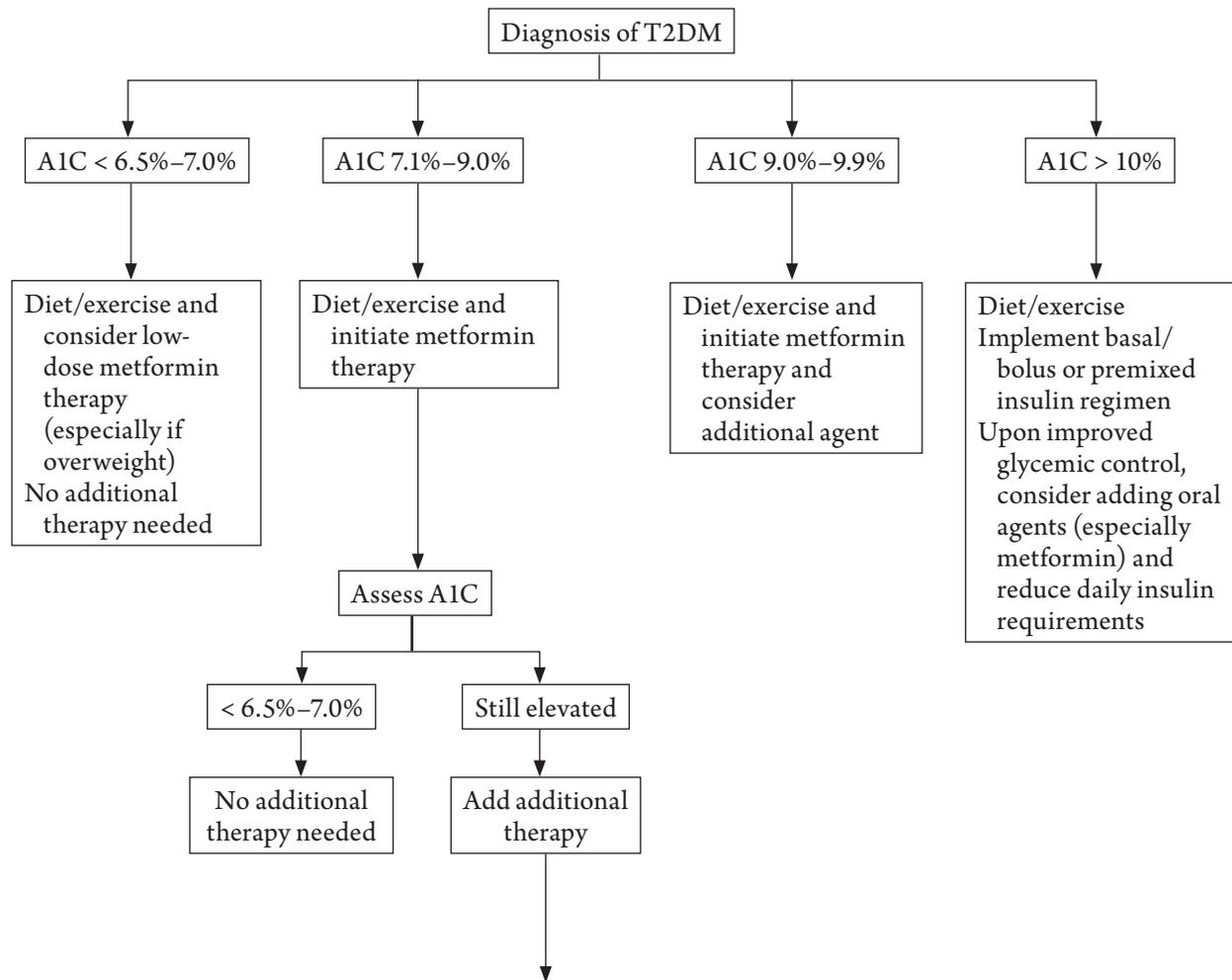
The choice of which agent(s) to add to metformin depends on the advantages and disadvantages of the other therapies such as cost; risk of hypoglycemia; degree of hyperglycemia; other comorbidities; adverse event profile, whether fasting, postprandial, or both are problematic; and patient injection preference. More importantly, patient preferences and values must be considered, and the patient should take part in the decision-making process. Another oral agent, basal insulin, or a glucagon-like peptide 1 (GLP-1) agonist is a potential option to add to metformin; however, the lack of long-term comparative studies limits any specific recommendation. If dual therapy after about 3 months fails to meet glycemic goals, a third agent may be added. The guidelines state that adding insulin, if not already implemented, is the most likely choice to attain therapeutic goals, especially if the A1C is 8.5% or greater.

**Table 1-1.** Comparison of T2DM Drug Therapy Recommendations

Guideline	ADA/EASD	ACCE/ACE	NICE	ACP
First-line monotherapy <sup>a</sup>	Metformin	Metformin	Metformin	Metformin
Dual therapy (options to add to metformin)	Other oral DM medication (e.g. sulfonylurea, thiazolidinedione, DPP-4 inhibitor) GLP-1 agonist Basal insulin	In order: GLP-1 agonist, DPP-4 inhibitor, thiazolidinedione, meglitinide, sulfonylurea	Sulfonylurea DPP-4 inhibitor or thiazolidinedione (if high risk for hypoglycemia) GLP-1 agonist (if BMI $\geq 35$ kg/m <sup>2</sup> )	No specific recommendations provided
Considerations based on:	Efficacy Adverse effect profile Cost Injection preference Glucose issue (fasting or prandial)	Degree of hyperglycemia based on A1C. Risk of hypoglycemia and effects on weight also considered	Risk of hypoglycemia Problems with weight gain	No specific recommendations provided
Triple therapy (options to add to metformin)	Same as for dual therapy Insulin most likely to obtain A1C goal Strongly consider if A1C $\geq 8.5\%$	GLP-1 agonist plus thiazolidinedione GLP-1 agonist plus meglitinide GLP-1 agonist plus sulfonylurea DPP-4 inhibitor plus thiazolidinedione DPP-4 inhibitor plus meglitinide DPP-4 inhibitor plus sulfonylurea	DPP-4 inhibitor or thiazolidinedione or GLP agonist or Insulin (with marked hyperglycemia)	Not addressed
When to initiate insulin	At diagnosis with symptoms and/or glucose $> 300$ mg/dL or A1C $\geq 10\%$	Symptomatic patients with A1C $> 9\%$	A1C remains $\geq 7.5\%$ despite other measures	Not addressed

<sup>a</sup>Assumes no contraindications to metformin use.

ACCE = American College of Clinical Endocrinologists; ACE = American College of Endocrinology; ACP = American College of Physicians; ADA = American Diabetes Association; BMI = body mass index; DPP-4 = dipeptidyl peptidase-4; EASD = European Association for the Study of Diabetes; NICE = National Institute for Health and Clinical Excellence; T2DM = type 2 diabetes mellitus. Information from: Inzucchi S, Bergenstal R, Buse J. Management of hyperglycemia in type 2 diabetes: a patient-centered approach. *Diabetes Care* 2012;35:1364-79; Rodbard H, Jellinger P, Davidson J, et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control. *Endocr Pract* 2009;15:540-59; Qaseem A, Humphrey L, Sweet D, et al. Oral pharmacologic treatment of type 2 diabetes mellitus: A clinical practice guideline from the American College of Physicians. *Ann Intern Med* 2012;156:218-31; and National Institute for Health and Clinical Excellence. The Management of Type 2 Diabetes, NICE Clinical Guideline 87, 2009. Available at [guidance.nice.org/CG87/NICEGuidance/pdf/English](http://guidance.nice.org/CG87/NICEGuidance/pdf/English). Accessed May 3, 2012.



Cost is significant issue	Primary glucose issue is prandial	Primary glucose issue is fasting	Both fasting and prandial problematic	Weight loss desired	No aversion to injections
Sulfonylurea NPH insulin	GLP-1 agonist DPP-4 inhibitor Meglitinide Glucosidase inhibitor Rapid-acting insulin Pramlintide <sup>a</sup>	Thiazolidinedione Basal insulin Sulfonylurea	Thiazolidinedione Sulfonylurea Once-weekly exenatide Bromocriptine Colesevelam	GLP-1 agonist	GLP-1 agonist Insulin

**Figure 1-1.** General approach to the management of type 2 diabetes mellitus.

<sup>a</sup>Pramlintide should only be used in patients currently receiving bolus/prandial insulin therapy.

A1C = hemoglobin A1C; DPP-4 = dipeptidyl peptidase -4; GLP-1 = glucagon-like peptide 1; NPH = neutral protamine Hagedorn; T2DM = type 2 diabetes mellitus.

Information from Inzucchi S, Bergenstal R, Buse J. Management of hyperglycemia in type 2 diabetes: a patient-centered approach. *Diabetes Care* 2012;35:1364-79; and Rodbard H, Jellinger P, Davidson J, et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control. *Endocr Pract* 2009;15:540-59.

### **American Association of Clinical Endocrinologists/ American College of Endocrinology**

The American Association of Clinical Endocrinologists/American College of Endocrinology recommendations and algorithm for managing hyperglycemia were last updated in 2009 (Rodbard 2009). Their 2011 guidelines for developing diabetes comprehensive care plans continue to follow the 2009 recommendations. The approach to therapy is similar to the ADA's newer recommendations; however, initial and subsequent treatment options are categorized more so by A1C and differ by A1C range (i.e., 6.5%–7.5%, 7.6%–9.0%, or greater than 9.0%). Their goal A1C is 6.5% or less, which is more stringent than the ADA goal of 7% or less. Monotherapy is recommended for those with an A1C of 7.5% or less; this advances to dual and perhaps triple therapy, with or without insulin, if the glycemic goal is not met after 2–3 months. Dual therapy is warranted early when the A1C is between 7.6% and 9.0%, again with progression to triple therapy or insulin as needed. If the patient presents with an A1C of greater than 9% and without symptoms, triple therapy may be initiated; if the patient has an A1C of greater than 9% with symptoms, insulin should be considered. Recommended agents to add to metformin are, in order, a GLP-1 agonist, a dipeptidyl peptidase-4 (DPP-4) inhibitor, thiazolidinedione, meglitinide, or sulfonylurea. This selection sequence is based on overall efficacy, risk of hypoglycemia, and effects on weight.

### **Practice Guideline from the American College of Physicians**

In early 2012, the American College of Physicians published a practice guideline specific to the oral pharmacologic treatment of T2DM (Qaseem 2012). Although the guideline is thorough in evaluating the existing clinical data in this area, it provides few specific recommendations. Metformin is recommended as initial monotherapy for patients who do not achieve glycemic control through diet, physical activity, and weight loss. The only additional recommendation regarding glycemic control is to add a second agent to metformin if persistent hyperglycemia continues; the guideline finds no proven superiority of one combination over another in reduced mortality, cardiovascular events, or microvascular complications. The place in therapy of GLP-1 agonists or insulin therapies is not addressed, which limits the use of this guideline in clinical practice.

### **National Institute for Health and Clinical Excellence**

The United Kingdom's National Institute for Health and Clinical Excellence (NICE) guidelines regarding the therapeutic management of T2DM were last updated in 2009 (NICE 2009). These guidelines are more prescriptive than current ADA guidelines. For patients not attaining adequate glycemic control despite metfor-

min monotherapy, sulfonylurea therapy is regarded as second-line therapy. If the patient is at significant risk of hypoglycemia and did not tolerate the sulfonylurea, or if the sulfonylurea is contraindicated, DPP-4 inhibitors or thiazolidinediones are considered alternatives. Adding a third agent depends on the choice of dual therapy, considering the consequences of further weight gain, existing obesity, insulin resistance, and level of hyperglycemia.

## **INCRETIN-BASED THERAPIES**

Decreased insulin sensitivity and progressive loss of pancreatic beta-cell insulin secretion remain hallmarks of the pathophysiology of T2DM. In addition, a significant amount of research has focused on the incretin system and its role in contributing to hyperglycemia. The two main incretin hormones thought to maintain euglycemia are GLP-1 and glucose-dependent insulinotropic peptide (GIP). Both hormones are secreted because of carbohydrate and fat consumption, and both result primarily in increased glucose-dependent insulin secretion and decreased glucagon secretion. Both hormones are rapidly metabolized in the circulation by DPP-4. In patients with T2DM, the action of DPP-4 is maintained and GLP-1 is minimized, and the activity of GIP is almost completely lost. Even if exogenous GIP is administered at supraphysiologic doses, GIP effects are negligible. Therefore, most research into incretin-based therapies has focused on preserving or enhancing the effects of GLP-1.

### **DDP-4 Inhibitors**

By competing for GLP-1 binding to DPP, DPP-4 inhibitors block the breakdown of naturally secreted GLP-1 and extend its duration of effect in the body. Five DPP-4 inhibitors are available on the international market: sitagliptin, saxagliptin, linagliptin, vildagliptin, and alogliptin. The first three are approved for use in the United States and are administered orally and once daily. Sitagliptin and saxagliptin require dosage adjustment with kidney impairment, whereas linagliptin does not (Table 1-2).

These agents appear to have a larger effect on reducing postprandial than fasting glucose concentrations. Many clinical studies of varying design are reported in the literature, and each agent has not been studied to the same degree, particularly with respect to comparisons with other T2DM drugs. Meta-analyses suggest that DPP-4 inhibitors, when used as monotherapy, do not provide the same degree of glycemic control as metformin (Karagiannis 2012). In combination therapy with metformin, DPP-4 inhibitors provide an A1C decrease slightly smaller than that with sulfonylureas, about the same as that with pioglitazone, and significantly less than that with GLP-1 agonists. From a safety

**Table 1-2. Comparison of Incretin-Based Therapies**

	Sitagliptin	Saxagliptin	Linagliptin	Twice-Daily Exenatide	Liraglutide	Once-Weekly Exenatide
Dosage	100 mg/day	2.5–5 mg/day	5 mg/day	5 mcg bid for 1 month; then 10 mcg bid if tolerated	0.6 mg/day; increase weekly as tolerated up to 1.8 mg/day	2 mg once weekly
Dosage adjustment with kidney impairment	CrCl ≥ 30–49: 50 mg/day CrCl < 30: 25 mg/day	CrCl ≤ 50: 2.5 mg/day	Adjustment not needed	Adjustment not needed, but use caution if CrCl is 30–50, and avoid if < 30	Adjustment not needed Use with caution in patients with kidney impairment	Same as for twice-daily formulation
Primary glycemic focus	Postprandial	Postprandial	Postprandial	Postprandial	Postprandial	Fasting and Postprandial
Adverse effect profile	Upper respiratory tract infection, urinary tract infection, headache, hypoglycemia (when taken with sulfonyleurea), angioedema (rare), case reports of acute kidney failure and pancreatitis			Nausea, vomiting, constipation, diarrhea, hypoglycemia, case reports of acute kidney failure and pancreatitis		Injection site pruritus, nausea, vomiting, diarrhea
Comparative efficacy <sup>a</sup>						
Monotherapy vs. placebo	-0.79%	-0.63 to 0.65%	-0.69%	-0.7% to 0.9%	-1.65%	NS
Monotherapy vs. metformin	0.14%–0.51%	0.24%–0.30%	NS	NS	NS	-0.05%
Monotherapy vs. pioglitazone	0.48%	NS	NS	NS	NS	0.10%
Monotherapy vs. GLP-1 agonist	0.38%	NS	NS	NA	NA	NA
Monotherapy vs. DPP-4 inhibitor	NA	NA	NA	NS	NS	-0.38%
Monotherapy vs. sulfonyleurea	NS	NS	NS	NS	-0.81%	NS
+ Metformin vs. placebo	-0.65%	-0.82%	-0.64% to 0.73%	-0.60% to 0.86%	-1.1%	NS
+ Metformin vs. sulfonyleurea	0.035%–0.07%	0.06%	NS	NS	0.0%	NS
+ Metformin vs. thiazolidinedione	0.06%	NS	NS	NS	NS	-0.3%
+ Metformin vs. DPP-4 inhibitor	NA	NA	NA	NS	-0.9%	-0.6%
+ Metformin vs. GLP-1 agonist	0.9%	NS	NS	NA	NA	NA

<sup>a</sup>Efficacy denoted as between group difference in A1C change from baseline (positive difference suggests the comparator medication more effective). bid = twice daily; CrCl = creatinine clearance (mL/minute); DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide 1; NA = not applicable; NS = not studied.

standpoint, DPP-4 inhibitors are very well tolerated. In one comparative study, the incidence of hypoglycemia with sitagliptin was low (4.9%), whereas that with the sulfonylurea glipizide was much higher (32%) (Nauck 2007). In contrast to sulfonylureas and pioglitazone, both of which are associated with weight gain, DPP-4 inhibitors appear to be weight neutral. A concern with this class upon postmarketing surveillance is case reports of pancreatitis. This is discussed in more detail below.

The DPP-4 inhibitors provide a novel mechanism of action that is a good complement when added to metformin. There are no data from long-term comparative studies on whether one agent within the class is either more effective or safer than another. The overall reduction in A1C is modest (0.6%–0.9%) and dependent on baseline A1C. Patients with high A1Cs are more likely to experience a greater reduction in A1C than those closer to goal. The DPP-4 inhibitors are a viable option in patients with mildly elevated A1C despite metformin therapy, especially when postprandial hyperglycemia is a predominant issue. The tolerability, route and frequency of administration, and weight neutrality of DPP-4 inhibitors make them an attractive option compared with other T2DM agents. Limitations of their use include cost and the inability to continually dose adjust to optimize glycemic control. If DPP-4 inhibitors are added to existing sulfonylurea therapy, consider decreasing the dose of sulfonylurea by one-half to reduce the risk of hypoglycemia. Linagliptin offers the advantage of not requiring a dose adjustment when used in patients with kidney impairment.

## GLP-1 Agonists

### Short-Acting GLP-1 Agonists

#### *Exenatide and Liraglutide*

Exenatide entered the world market in 2005 and was the first GLP-1 agonist to receive U.S. Food and Drug Administration (FDA) label approval. Liraglutide followed, with FDA approval in 2010. As GLP-1 analogs, these agents mimic endogenously secreted GLP-1 and increase pancreatic insulin secretion, reduce glucagon secretion, slow gastric emptying, and promote satiety during meals. Liraglutide is more homologous to human GLP-1 than exenatide. Administration of exenatide must be within 60 minutes of the morning and evening meals, whereas liraglutide can be administered once daily without regard to meals. Exenatide can be titrated from initial to maximal daily dosage after 1 month if tolerated (see Table 1-2). Liraglutide can be increased at weekly intervals as tolerated.

Exenatide significantly reduces A1C both as monotherapy and when added to existing treatments with a sulfonylurea, metformin, thiazolidinediones, the combination of sulfonylurea and metformin, and the combination of metformin and sitagliptin (see Table 1-2). Direct

comparisons of twice-daily exenatide with other oral T2DM medications are lacking. Exenatide in combination with basal insulin therapy provides additional benefit in reducing A1C over either agent as monotherapy.

Liraglutide monotherapy has been shown to reduce A1C significantly more than sulfonylurea monotherapy,  $-1.14\%$  and  $-0.51\%$ , respectively (Garber 2009). It also provided better improvements in fasting ( $-25.5$  vs.  $-5.2$  mg/dL) and postprandial glucose ( $-37.5$  vs.  $-24.5$  mg/dL) concentrations as well as a more favorable effect on weight and a lower risk of hypoglycemia (8% vs. 24%). For patients unable to respond adequately to metformin monotherapy, adding liraglutide shows efficacy similar to adding a sulfonylurea as well as a greater reduction in A1C compared with adding a DPP-4 inhibitor. Liraglutide also shows a favorable effect on glycemic control compared with placebo when added to the combination of metformin and thiazolidinedione. Liraglutide and exenatide have each shown either similar or greater reductions in A1C compared with insulin glargine when added to the regimen of patients taking metformin and a sulfonylurea ( $-1.11\%$  to  $1.33\%$  vs.  $1.09\%$  to  $1.11\%$ , respectively). However, because these studies showed a very low rate of attaining the a priori goal fasting glucose concentration in the basal insulin treatment arms, any direct comparison is difficult.

Data from head-to-head comparisons suggest liraglutide reduces A1C to a small ( $-0.33\%$ ) but greater degree than twice-daily exenatide in patients treated with metformin, a sulfonylurea, or both (Buse 2009). When switching from exenatide to liraglutide, an additional reduction ( $-0.32\%$ ) in A1C reduction can be seen (Buse 2010). Both agents show a beneficial, though modest, effect on blood pressure ( $-2.0$  to  $2.5$  mm Hg systolic,  $-1.0$  to  $2.0$  diastolic) and lipids ( $-15$  mg/dL to  $17$  mg/dL in low-density lipoprotein [LDL] cholesterol). However, no prospective studies have specifically evaluated any cardiovascular benefit of this class of agents. A substantial amount of research is addressing whether these agents preserve beta-cell function over time. Agents that stimulate insulin secretion (e.g., sulfonylureas) can hasten the loss of beta-cell insulin secretion. The GLP-1 agonists have shown improvements in beta-cell insulin secretion; exenatide studies with up to 3 years of follow-up show that insulin secretion does not significantly decrease and may actually increase (Klonoff 2008).

Overall, the incidence of serious adverse events is very low in clinical trials. The GLP-1 agonists show significant benefits in weight loss ( $-1.6\%$  to  $3.4\%$ ) compared with DPP-4 inhibitors, thiazolidinediones, sulfonylureas, and insulin. As previously mentioned, DPP-4 inhibitors are relatively weight neutral, whereas the latter three agents can increase patient weight. The incidence of hypoglycemia is lower than with sulfonylureas.

Dose-dependent nausea and vomiting are significant with either exenatide or liraglutide, but the persistence of these adverse effects appears to be less with liraglutide than with twice-daily exenatide (Buse 2009). These effects limit the use of these agents, although a tolerance to nausea and vomiting may develop over time in some patients. Weight loss, although markedly higher in patients who experience significant nausea or vomiting, is still seen in patients who do not experience these adverse effects.

Either exenatide or liraglutide should be considered in patients with a suboptimal response to metformin, those with moderate hyperglycemia, those willing to receive injections, or those seeking additional weight loss beyond what they might attain with metformin. In patients with significant gastroparesis, both agents should be avoided because they may aggravate this condition. Kidney function should be assessed before initiating either agent. If significant renal insufficiency (creatinine clearance less than 30 mL/minute) exists, exenatide should be avoided. The manufacturer of liraglutide states to use with caution but does not provide a specific clearance cutoff.

### **Long-Acting GLP-1 Agonists**

In June 2011, an extended-release formulation of exenatide allowing once-weekly administration was approved in Europe. Petitions for approval in the United States were rejected pending additional safety data; however, in early 2012, extended-release exenatide received FDA approval. Incorporating exenatide into microspheres allows the extended-dosage interval. Previous treatment with the twice-daily formulation is not a stipulation for initiation. The only available dosage is 2 mg by subcutaneous injection once weekly. In contrast to the twice-daily formulation, extended-release exenatide is administered without regard to meal ingestion, and it requires no dose titration to minimize adverse effects (see Table 1-2). It normally takes 6–10 weeks to see the maximal effect on plasma glucose concentrations. The drug is supplied as a kit with a powder vial that must be reconstituted by the patient immediately before injection. The supplied materials also include a prefilled syringe to deliver the diluent, a vial connector for the two, and a custom needle for the delivery system. A delivery pen that may lessen the administrative steps for patients is currently under development.

In clinical trials comparing the once-weekly and twice-daily formulations, the extended-release agent provided a greater and statistically significant A1C reduction (0.4%–0.7% between-group difference from baseline) and a more profound impact on fasting glucose concentrations (16–23 mg/dL between-group difference) (Blevins 2011; Drucker 2008). Switching from the twice-daily to the once-weekly formulation can

further lower the A1C to a small degree (–0.2%), but the clinical relevance of this has not been evaluated. A comparative study of drug-naive patients showed that once-weekly exenatide provides a reduction in A1C from baseline similar to that of metformin or pioglitazone but greater than that of sitagliptin (Table 1-3) (Russell-Jones 2012). When added to metformin, once-weekly exenatide showed reductions in A1C similar to those with pioglitazone and greater than those with sitagliptin. If patients are currently receiving and then switched from pioglitazone or sitagliptin to extended-release exenatide, A1C reductions are maintained in patients receiving pioglitazone and further decreased in those receiving sitagliptin (Wysham 2011). Studies comparing once-weekly exenatide with insulin glargine in patients not under optimal control with other oral T2DM agents suggest that exenatide reduces A1C to a slightly greater extent, is associated with weight loss versus weight gain, and has a lower incidence of hypoglycemia. However, the trial data must be considered with caution because the insulin glargine arm of the study attained prespecified fasting glucose targets in only about 20% of subjects, and the dropout rate was higher in those receiving exenatide (Diamant 2010). Unlike twice-daily exenatide, the extended-release formulation is not approved for use with insulin of any type because the combination has not been studied in clinical trials.

The adverse effect profile of the once-weekly exenatide formulation appears to be similar to that of the twice-daily formulation. No difference in weight loss between the two agents has been reported. The weight loss in drug-naive patients is similar between monotherapy with metformin and once-weekly exenatide and is more favorable than that observed with pioglitazone, sitagliptin, or insulin. The incidence of nausea and vomiting is lower with once-weekly exenatide, but injection site pruritus is much higher. In preclinical rodent studies, exenatide showed a potential risk of thyroid carcinoma similar to early studies with liraglutide. This has not been an issue with the twice-daily formulation. This topic is discussed in greater detail below.

As with insulin, use of once-weekly exenatide is limited because some patients may be averse to the parenteral route of administration. Nor does the agent allow dose titration if glycemic goals are not met. Patients should be monitored for improvement in glycemic control using A1C and both fasting and postprandial glucose concentrations. Weight loss and gastrointestinal tolerability should be monitored.

Because of the potential for severe adverse events, once-weekly exenatide should not be considered first-line therapy for patients with a contraindication to metformin until a better understanding of its overall risk can be assessed. The agent should be considered in patients who might benefit from a GLP-1 analog, in those

**Table 1-3.** Comparison of Therapies for T2DM Hyperglycemia Added to Metformin

Agent or Class	Primary Glycemic Effect	Benefits	Limitations/Precautions
Sulfonylurea	Fasting and prandial	Efficacy Cost	Weight gain Hypoglycemia risk Hastens beta-cell dysfunction
Meglitinide	Prandial	Prandial focus Use in kidney impairment	Hypoglycemia risk Weight gain Mealtime dosing
Pioglitazone	Fasting and prandial	Improves insulin sensitivity Low risk of hypoglycemia Possible cardiovascular benefit	Weight gain and edema Risk of heart failure Risk of osteoporosis Possible bladder cancer risk
α-Glucosidase inhibitor	Prandial	No systemic absorption Prandial focus	GI adverse effect profile Mealtime dosing
DPP-4 inhibitor	Prandial	Well tolerated Weight neutral	Possible pancreatitis risk Modest A1C effect Cost
GLP-1 agonist	Fasting and prandial (once-weekly exenatide greater fasting effect)	Greater effect on prandial glucose Weight loss Efficacy	Nausea/vomiting Injection site effects Questionable pancreatitis or thyroid cancer risk Cost
Colesevelam	Prandial	Lipid benefits No systemic absorption	Large pill size/burden GI adverse effect profile Small decrease in A1C Avoid with high triglycerides
Bromocriptine	Fasting and prandial	Low risk of hypoglycemia	Small decrease in A1C CNS adverse effects
Amylin agonist	Prandial	Modest weight loss Efficacy on postprandial glucose	High risk of hypoglycemia Must be taken with insulin Frequent injections Injection site effects GI adverse effects
Insulin	Basal – fasting Bolus – prandial	Significant A1C reduction Flexibility in dosing strategies and titration	Hypoglycemia Weight gain Injection site effects

CNS = central nervous system; DPP-4 = dipeptidyl peptidase-4; GI = gastrointestinal; GLP = glucagon-like peptide.

Information from: Inzucchi S, Bergenstal R, Buse J. Management of hyperglycemia in type 2 diabetes: a patient-centered approach. *Diabetes Care* 2012;35:1364-79; and Rodbard H, Jellinger P, Davidson J, et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control. *Endocr Pract* 2009;15:540-59.

willing and able to reconstitute the dry powder, and in those for whom once-weekly administration could improve adherence.

## OTHER AGENTS NOW APPROVED FOR T2DM HYPERGLYCEMIA

### Bromocriptine

The dopamine (D<sub>2</sub>) receptor agonist bromocriptine has been used for Parkinson disease and various endocrinologic disorders since its approval in the late 1970s. Bromocriptine mesylate quick release was approved in 2009 for use in T2DM to control hyperglycemia. How bromocriptine lowers glucose concentrations is unknown. The mechanism is thought to include resetting the body's circadian clock by increasing dopaminergic and sympathetic tone within the central nervous system to a time of day it normally peaks in healthy subjects. This increased tone has been linked to an increase in glucose tolerance and improved insulin sensitivity and may affect lipid metabolism (DeFronzo 2011). In addition, bromocriptine has  $\alpha_2$ -agonist,  $\alpha_1$ -antagonist, prolactin, and serotonin-like properties.

The dosing strategy and formulation used for the treatment of T2DM differ from those employed for other disorders. The usual starting dose is 0.8 mg once daily, taken with food to improve bioavailability and within 2 hours of awakening. The dose can be increased at weekly intervals as tolerated and to glycemic effect by 0.8 mg/day to an effective dose of 1.6–4.8 mg/day. Bromocriptine affects both fasting glucose (0–27 mg/dL) and postprandial glucose (37 mg/dL) concentrations. Clinical efficacy data are limited to small, short-term studies of up to 24 weeks, and no comparisons with other diabetes drugs have been published. When added to other oral agents or insulin, bromocriptine lowers A1C from baseline by 0.1%–0.6%.

Compared with placebo, the formulation of bromocriptine used for T2DM causes an increase in nausea, vomiting, dizziness, headache, and diarrhea; it also produces a lower rate of hypoglycemia and cardiovascular events and is weight neutral (Gaziano 2010). Bromocriptine should not be used during pregnancy or in patients with a history of syncopal migraines. Caution is warranted in patients with orthostatic hypotension or psychosis because bromocriptine may exacerbate these conditions or limit the effectiveness of agents used in their treatment.

Because there are no data comparing bromocriptine with other agents used to treat hyperglycemia, it is difficult to determine the role of this agent in the treatment of T2DM. In patients with mild hyperglycemia who have both fasting and postprandial glycemic problems, bromocriptine may be considered in addition to other oral agents or insulin therapy.

### Colesevelam

Bile acid sequestrants (BASs) have been used in the treatment of dyslipidemia for decades. In addition to their ability to lower LDL cholesterol, they have been shown to improve glycemic control in patients with T2DM. Colesevelam was approved for dyslipidemia in 2000; in 2008, it was approved to control hyperglycemia in adults with T2DM. Colesevelam remains the only BAS approved for such use in the United States, even though colestimide is approved in Japan for the same indication.

The exact mechanism of how colesevelam improves glucose concentrations is unknown. It is proposed to have an effect on farnesoid X receptor, a bile acid receptor, and activity in the gut and possibly in the liver. This is thought to eventually lead to reduced hepatic gluconeogenesis and perhaps affects GLP-1 and GIP as well (Handelsman 2011). The standard total daily dosage is 3.75 g orally, given in one or two doses. Colesevelam is available as a pill or suspension.

This agent has not been studied as monotherapy in patients with T2DM, but it has been compared with placebo when added to metformin, sulfonylurea, and insulin therapy. The ability of colesevelam to lower A1C is limited, with reductions from baseline of –0.3% to –0.5% (Handelsman 2011; Goldfine 2010). Limited data exist to compare colesevelam with other diabetes agents in their ability to lower A1C. In a small (n=169), short (16 weeks) study, colesevelam 3.75 g/day was compared with rosiglitazone 4 mg/day and sitagliptin 100 mg/day (Rigby 2010). In each treatment group, A1C was significantly reduced from baseline; colesevelam reduced A1C by –0.3%, rosiglitazone by –0.6%, and sitagliptin by –0.4%. However, no statistical analysis was performed between treatment groups.

Colesevelam is well tolerated, showing no impact on weight and only a minimal risk of hypoglycemia. As with all BAS agents, constipation, dyspepsia, and nausea are the most common adverse effects. The agent should be used with caution in patients with gastroparesis and not used at all in patients with triglyceride concentrations greater than 500 mg/dL, a history of bowel obstruction, or previous hypertriglyceridemia-induced pancreatitis. According to the manufacturer's package insert, this agent should also not be administered within 4 hours of other drugs known to have reduced absorption or effect when coadministered with colesevelam (e.g., phenytoin, warfarin, cyclosporine, levothyroxine).

The precise place in therapy of colesevelam is unknown. Given its limited efficacy, the agent may be considered in patients with only mildly elevated A1C who are inadequately controlled with a sulfonylurea, metformin, or insulin therapy with or without mild elevations in LDL cholesterol. The individual pills are large, and six tablets are required to achieve the

recommended daily dose. Therefore, colesevelam may not be an appropriate alternative for patients who have difficulty swallowing; a suspension is available, which may be a better substitute in such patients.

## CONVERSION FROM ORAL DM AGENTS TO INSULIN-ONLY THERAPY

Some patients, because of significant hyperglycemia, adverse effects, or contraindications to other T2DM drugs, require an insulin-only regimen to control their hyperglycemia. Current ADA recommendations are to initiate insulin early in patients with significant baseline hyperglycemia (A1C of 10% or greater; glucose greater than 300 mg/dL) and in those with symptoms of hyperglycemia (e.g., polyuria, polydipsia, polyphagia) (Inzucchi 2012). Monotherapy with a long-acting basal insulin alone (e.g., glargine, detemir) in patients with T2DM will not provide control of hyperglycemic excursions after meals. Therefore, the most common insulin-only regimens include the use of twice-daily premixed insulin preparations or basal/bolus insulin therapy. The premixed option uses existing commercial insulin products containing more than one type of insulin (e.g., 70% neutral protamine Hagedorn, 30% regular insulin), or has the patient draw two types of insulin into the same syringe. Basal/bolus insulin therapy employs a long-acting insulin preparation either once or twice daily (basal therapy) and premeal injections with a rapid-acting insulin (bolus therapy). The intent of the basal therapy is to mimic the natural insulin secretion that occurs throughout the day and night even while fasting, whereas the bolus therapy controls for hyperglycemic excursions after meals.

Whether premixed or basal/bolus therapy is initiated, the first step in developing an insulin-only regimen is to estimate the patient's total daily insulin requirements. Initial estimates vary by clinician and are most commonly weight-based. Estimates of 0.4–0.6 unit/kg/day are common, and patients with T2DM often require considerably more insulin compared with patients with type 1 diabetes mellitus because of insulin resistance. Premixed insulin therapy administers two-thirds of the total daily insulin requirements before the morning meal and the remaining one-third before the evening meal. Administration time before meals depends on the specific short- or rapid-acting insulin selected. Alterations in basal insulin dosage can then be based on assessing glycemic control in the morning and before the evening meal.

With basal/bolus therapy, one-half of the total daily insulin requirement is provided as basal insulin, with the other half used for premeal bolus dosing. The daily bolus requirement is then equally divided for morning, midday, and evening meals. An alternative to the initial

bolus estimates is 0.1 unit/kg before the biggest carbohydrate meal of the day (referred to as basal plus), with subsequent increases in frequency to other mealtimes as needed (Ampudia-Blasco 2011). These initial bolus estimates assume a fixed carbohydrate intake; therefore, if the patient eats very little at one meal and significantly more at another, hypoglycemia or hyperglycemia can occur. Eventually, it is best to provide a specific amount of bolus insulin based on total carbohydrate ingestion at each meal. This latter technique requires considerable patient education to estimate the carbohydrate quantity of meals but has the advantage of providing adequate mealtime insulin based on the patient's specific diet.

Advantages of using premixed insulin therapy include fewer injections per day, less calculation by the patient, lower costs with older insulin formulations, and ease of use in patients incapable of or unwilling to determine and manage their daily insulin needs. The primary disadvantage of this therapy option is that dosage adjustment alters both administered insulins, and patients may not have issues with both fasting and postprandial glucose control. The risk of hypoglycemia using older, less expensive insulin options is higher than with newer insulin analogs. Patients also need to make sure they are consistent in their food intake because increases in dosage are not as flexible.

Advantages of basal/bolus therapy are that it is more patient-specific given the insulin needs and can be more easily adjusted to patient lifestyles. If a patient eats more carbohydrates at one meal, the bolus therapy can be increased accordingly. If the patient skips a meal, the bolus therapy can be skipped at that time. Disadvantages include a higher number of daily injections than with premixed formulations because neither of the currently available basal insulins should be mixed with other insulins in the same syringe. Two 6-month studies comparing basal/bolus therapy with premixed analog insulin therapy (either 50:50 or 70:30 protamine/rapid-acting analog) showed greater, though small, improvements in A1C with basal/bolus therapy (a 0.17%–0.33% difference between groups) (Liebl 2009; Rosenstock 2008). The incidence of significant hypoglycemia was higher with basal/bolus therapy in one study, whereas the other study found no differences. Yet another study showed that basal/bolus therapy provided a 0.47% improvement in A1C compared with a premixed alternative; no difference in hypoglycemia was seen, and basal/bolus therapy was more cost-effective per drop in A1C (Vora 2011; Fritsche 2010).

Despite due diligence and patient adherence to insulin regimens and diet, hyperglycemic excursions still occur. When this happens, patient-specific plans to reduce glucose concentrations must be in place. Historically, sliding-scale insulin regimens have been used; however, these regimens treat each patient the same, even

though insulin requirements vary with the individual. Correctional dosing for hyperglycemic excursions provides more patient-specific insulin regimens based on total daily insulin needs. It is best to implement correctional dosing after the basal insulin has been employed and found to be accurate. The *rule of 1800* provides an estimate of a patient's insulin sensitivity. This rule assists in estimating how much of a decrease in blood glucose will occur with a specific amount of rapid-acting insulin. When 1800 is divided by the patient's total daily insulin needs (i.e., the sum of the patient's current or estimated bolus and basal insulin daily use), the quotient provides an estimate of the milligram-per-decimeter reduction in glucose that 1 unit of a rapid-acting insulin might provide (Peters 2011). If using regular human insulin for bolus therapy, the numerator should be modified from 1800 to 1500. Because individual patient's daily insulin requirements vary, correctional dosing is more patient-specific than sliding scales, which are more "one size fits all." The patient care scenario describes a practical example of formulating a basal/bolus and correctional dosing regimen.

## UPDATES IN NONCARDIAC DIABETES DRUG SAFETY

### GLP-1 Agonists and Thyroid Carcinoma

In their early stages of development, both liraglutide and exenatide LAR showed an increased risk of thyroid C-cell focal hyperplasia and medullary thyroid cancer in rodent studies (Knudsen 2010). There are no such data suggesting that twice-daily exenatide formulation causes this same problem. This lower risk of cancer may be because the other two GLP-1 formulations allow a more constant exposure to GLP-1 activity. Clinical trial data in humans have not shown an increased risk of such events with any of these agents, but the rarity of this type of cancer means it cannot be completely ruled out.

Serum calcitonin concentrations, a potential biomarker for medullary thyroid cancers, are no higher in patients receiving liraglutide than in control patients in studies lasting up to 2 years (Parks 2010). The potential cause of this adverse effect in rodents is not understood. Recent studies show that GLP-1 receptors are expressed

### Patient Care Scenario

A male patient (weight 238 lb) with newly diagnosed T2DM has an A1C today of 11.2%. You have been charged by the endocrinologist to develop an insulin-only medication strategy to aid in the control of the patient's hyperglycemia using basal/bolus insulin. Calculate this patient's basal, bolus, and correctional insulin needs, and design an appropriate initial regimen for him.

#### Answer

The first step is to estimate the patient's total daily insulin needs. Estimates of total daily insulin needs vary, but for this case, assume that 0.5 unit/kg/day is sufficient. Doses of both basal and bolus insulin can be quickly optimized after initiation on the basis of patient-attained glucose concentrations. This patient weighs 238 lb, or 108 kg. Total daily insulin requirements are thus estimated to be 54 units ( $0.5 \times 108$ ). The patient's basal insulin requirements are one-half of the total daily needs estimate—in this case, 27 units ( $0.5 \times 54$ ). The other half of the total daily needs estimate is the bolus insulin requirements (again, 27 units); this is split among the daily meals. Assuming the patient eats breakfast, lunch, and dinner, premeal bolus requirements equal 9 units ( $27 \div 3$ ). The alternative method of 0.1 unit/kg before meals gives 10.8 units, which can be rounded up or down.

Selections for basal insulin include insulin detemir and glargine. Although NPH is an alternative, it carries a greater risk of hypoglycemia and does not mimic physiologic insulin secretion as well as the others. Selections for bolus insulin include the rapid-acting insulins aspart, lispro, and glulisine. Regular insulin can be used, but it has a slower onset and a longer duration than the rapid-acting insulins. Hence, an appropriate insulin regimen for this patient could include 27 units of insulin glargine once daily and 9 units of insulin aspart administered 15 minutes before meals.

After implementing the basal and bolus insulin regimen, the correctional insulin needs can be estimated. Correction insulin needs for hyperglycemic excursions commonly use the "rule of 1800." The quotient of 1800/total daily insulin estimates the mg/dL decrease in blood glucose that 1 unit of rapid-acting insulin may achieve (in this case,  $1800 \div 54 = 33$  mg/dL). This can be rounded up (35) or down (30) for simplicity. A patient-specific sliding scale can then be developed around this estimate. Assume a goal of 100–130 mg/dL is the target to achieve after hyperglycemia is detected. One unit can be administered if the blood glucose is between 130 mg/dL and 160 mg/dL, 2 units can be administered if it is 160–190 mg/dL, and so on.

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in C-cells of normal rodent thyroid tissue but not in normal human tissue. However, 27% of human medullary thyroid carcinomas express GLP-1 receptors (Waser 2011). As part of its Risk Evaluation and Mitigation Strategy, liraglutide's manufacturer issued a reminder to health care professionals in June 2011 to be more attentive to this rare potential adverse effect to their patients. The manufacturer of once-weekly exenatide is following the same strategy and is implementing a medullary thyroid carcinoma registry to monitor this risk. To avoid potential risk, neither liraglutide nor once-weekly exenatide should be used in patients with a personal or family history of medullary thyroid carcinoma. Routine monitoring of serum calcitonin is of uncertain use and is not deemed necessary.

### **Incretin-Based Therapies and Pancreatitis**

Patients with diabetes have an almost 3-fold higher rate of pancreatitis compared with patients without the disease (Noel 2009). When GLP-1 agonists and DPP-4 inhibitors entered the market, case reports of acute pancreatitis began to emerge for both agent classes. The FDA issued its first warning on this phenomenon in 2007. Although this alarming potential adverse effect has led to much speculation, neither the cause nor the extent of risk has been discerned. This has prompted meta-analyses and epidemiologic studies.

A 5-year review of the FDA's Adverse Event Reporting System found 6-fold higher odds of reported pancreatitis for exenatide and sitagliptin than with other diabetes medications used as a control (Elashoff 2011). However, meta-analyses of 19 clinical trials lasting 12–52 weeks and including more than 5500 patients suggest that exenatide is not associated with a higher risk of the adverse event than active comparator drugs (MacConnell 2012). Another meta-analysis evaluated the six most-studied DPP-4 inhibitors in trials lasting at least 24 weeks and found no increased risk compared with either placebo or active comparators (Monami 2011). Recent large cohort studies evaluating medical and pharmacy claims data also suggest there is no increased risk with the use of exenatide or sitagliptin. One such study found the risk of pancreatitis to be 1.9, 5.6, 5.7, and 5.6 cases per 1000 patient-years for patients without diabetes, patients receiving other diabetes drugs, exenatide, and sitagliptin, respectively (Garg 2010).

It is still unclear whether either class is truly associated with pancreatitis or whether an individual agent within each class may produce greater risk. There are more reports associated with sitagliptin and exenatide, but these agents have also been on the market longer. The FDA recommends that providers stay vigilant of this potential risk, monitor for possible signs and symptoms, and obtain further laboratory assessment if pancreatitis is suspected.

### **Pioglitazone and Bladder Cancer**

The potential association between pioglitazone and bladder cancer has been a matter of debate dating back to the drug's U.S. approval in 1999. The concern was increased after a cardiovascular secondary prevention study reported a higher rate of bladder neoplasm in patients receiving pioglitazone than in those receiving placebo (0.5% vs. 0.2%, respectively) (Dormandy 2005). The difference was not statistically significant. Since then, several epidemiologic studies have provided additional information regarding the risk of this adverse event. In April 2011, two cohort studies from a large health care provider data registry found no association between pioglitazone use and bladder cancer (Ferrara 2011; Lewis 2011). However, one of these studies, a planned midpoint analysis of a 10-year FDA-requested study, found a weak association with pioglitazone use greater than 24 months (hazard ratio 1.4; 95% confidence interval [CI], 1.03–2.0) (Lewis 2011). A study using the FDA's Adverse Event Reporting System cited a greater than 4-fold increased odds ratio for pioglitazone use and bladder cancer compared with other diabetes agents, together with an odds ratio of 4.3 (95% CI, 2.82–6.52) (Piccinni 2011). More recently, a cohort study using the French national health system information found that patients using pioglitazone had a 22% adjusted relative increased risk of bladder cancer compared with patients never exposed to the agent (crude incidence per 100,000 person-years was 49.4 and 42.8, respectively) (Neumann 2012). This study found that higher cumulative doses had a stronger link and confirmed the risk to be higher with pioglitazone use for more than 24 months.

Given the three studies in the United States and in review of the French data, the FDA in June 2011 required additional safety information to the labeling of pioglitazone, recommending against its use in patients with active bladder cancer and caution with its use in those with a history of bladder cancer. Both France and Germany subsequently suspended pioglitazone use, and both the FDA and European Medicines Agency continue to evaluate this issue.

### **Thiazolidinediones and Fracture Risk**

Type 2 diabetes mellitus is considered a risk factor for osteoporotic fracture, particularly in women. Fractures of the foot, arm, and hip are more common in patients with T2DM, even in the presence of normal bone mineral density. Thiazolidinediones may adversely affect bone homeostasis by reducing osteoblastic activity and increasing urinary calcium excretion.

Data collected between 2006 and 2008 suggested that rosiglitazone, compared with metformin or a sulfonylurea, was associated with a higher incidence of fractures in women but not men (Kahn 2008). A meta-analysis of 10 randomized clinical trials confirmed a 45% increased

risk of fractures in patients who received either pioglitazone or rosiglitazone, but this risk was observed in women, not in men (Loke 2009). Two other large epidemiologic studies using U.S. and Canadian medical and pharmacy claims data suggested the risk is also increased in men at least 50 years of age (15%–25% relative risk), although the incidence is lower than in women (34%–47% relative risk) (Aubert 2010; Dormuth 2009). The fracture rate per 100 patient-years in one study was estimated to be 1.7 in men and 2.9 in women for those receiving treatment with a thiazolidinedione (Dormuth 2009). The more common fracture sites include the foot/ankle, wrist/forearms, hand/fingers, and humerus (Aubert 2010). More recently, a cohort study using a Dutch database compared the risk of fractures of thiazolidinediones with other diabetes agents and found a 25% increased risk of fractures; however, the risk was only significant in women receiving thiazolidinediones (Bazelier 2012).

Although the overall risk of fractures appears to be greater in women than in men, both sexes may be affected. Caution is advised in the use of thiazolidinediones in patients with existing osteoporosis or osteopenia, particularly women.

## NEWER PHARMACOTHERAPIES IN THE PIPELINE

Several new agents within existing classes of T2DM drugs are currently being evaluated in human clinical trials. The DPP-4 inhibitor dutogliptin is currently in phase III studies. Alogliptin is currently available in Japan and was submitted for FDA label approval; however, the FDA rejected the application in April 2012, stating that more studies were needed before this agent could be approved in the United States. Several once-daily and once-weekly GLP-1 agonists are also in various phases of development; these include taspoglutide, albiglutide, dulaglutide, and lixisenatide. A once-monthly formulation of exenatide is being investigated.

Novel insulin administration has been a goal of many manufacturers for decades in an effort to do away with subcutaneous administration. Inhaled insulin formulations are still in development, although concerns about lung damage have limited their ability to gain approval. The only approved inhaled insulin product was voluntarily removed from the market in 2008 because of poor sales and provider/patient acceptance. Oral formulations for insulin delivery are also being investigated.

A new long-acting insulin, insulin degludec, has been evaluated in phase III studies. As with insulin detemir, insulin degludec has a fatty acid moiety attached to it, allowing a 24-hour half-life twice that of insulin glargine (Owens 2011). This extended half-life may not

only allow once-daily administration, but some patients may also be able to administer it only three times/week.

Several new therapeutic classes have shown promise in treating hyperglycemia and are in various stages of development. A novel new class, sodium-glucose cotransporter type 2 inhibitors, reduces the reabsorption of glucose in the proximal tubules of the kidney. The best-studied agent, dapagliflozin, reduces hyperglycemia when used as monotherapy or in addition to metformin. Dapagliflozin also shows efficacy comparable with the sulfonylurea glipizide when added to metformin (Anderson 2012). A pooled analysis of 19 clinical trials involving more than 5000 patients showed a small (0.2%) occurrence of bladder cancer compared with placebo and a small risk of breast cancer in women. The FDA has requested additional safety data and has so far rejected dapagliflozin for approval. Another agent within this class, canagliflozin, has also been evaluated in the treatment of T2DM, and its manufacturer filed a new drug application with the FDA in the summer of 2012.

The interleukin-1 blocker diacerein is used for osteoarthritis in some countries, although it is not approved in the United States. Diacerein has been shown to lower glucose concentrations, but its mechanism is not known. TAK-875 is a free fatty acid receptor agonist thought to stimulate insulin secretion. When evaluated in a phase II study, TAK-875 reduced A1C by up to 1.1%, with efficacy comparable with glimepiride (Burant 2012).

Finally, the dual peroxisome proliferator activated receptor (PPAR) (alpha and gamma) agonist aleglitazar also shows promise in treating T2DM. Having dual properties combines the efficacy of both a fibrate-type and thiazolidinedione-type agent. A phase III study is currently evaluating aleglitazar's efficacy and safety in patients with T2DM and cardiovascular disease. Of note, two other dual PPAR agonists have failed to gain approval because of adverse events, particularly cardiovascular outcomes.

## PATIENT EDUCATION

The pharmacist should counsel patients receiving the once-weekly formulation of exenatide regarding missed doses. A missed dose can be administered as long as it is at least 3 days before the next scheduled dose. If it is within 1–2 days before, the dose should be skipped, and the patient should resume the regular schedule. The day of the week it is administered can be switched as long as the last dose was at least 3 or more days before switching. Patients should also be instructed on how to reconstitute the agent with the supplied diluents and syringes and be warned not to use other types of syringes than what is supplied. The diluent is provided within the supplied syringe. An adapter is used to connect the syringe to a vial containing the dry powder formulation. The

diluent is injected into the vial, which the patient should agitate thoroughly to reconstitute the drug. Once in solution, the formulation can be withdrawn back into the syringe, and air bubbles should be removed. Once reconstituted and in the syringe, the once-weekly formulation must be administered immediately. It is best to inject at a different injection site each week but to use the same region of the body (e.g., arm, thigh, abdomen).

Patients receiving either the once-weekly exenatide formulation or liraglutide should be counseled to report any symptoms potentially associated with thyroid tu-

mors (e.g., dyspnea, dysphagia, hoarseness, a lump in the neck). Patients receiving a DPP-4 inhibitor or GLP-1 agonist should be instructed to report any symptoms consistent with pancreatitis, including severe abdominal pain (especially if it radiates to the back), nausea, or vomiting. If any of these occur, the patient should discontinue the drug and contact a health care professional. Although the risk of bladder cancer with pioglitazone is a matter of debate and continued evaluation, patients should be educated to report blood in the urine, urinary urgency, abdominal pain, or pain on urination.

Both men and women, and particularly those with osteoporosis or osteopenia, should be warned of the possible increased risk of bone fractures with pioglitazone use. Patients should be told of the more common fracture sites associated with its use, which mainly involve the distal upper and lower limbs as previously described.

### Practice Points

Many challenges face the clinical pharmacist in their efforts to optimize pharmacotherapy for their patients with T2DM. New data continue to emerge regarding how to treat hyperglycemia associated with T2DM. As a result, guidelines/recommendations, new indications for existing medications, new therapeutic entities, and safety issues continue to evolve:

- The ADA recently updated its therapeutic recommendations in the treatment of T2DM hyperglycemia. It recommends a patient-centered approach to care and a need to evaluate the advantages and disadvantages of the various agents used to treat hyperglycemia when making therapeutic changes to patients.
- The various guidelines differ in their recommendations in treating hyperglycemia, and the clinical pharmacist should be aware of these differences.
- The DPP-4 inhibitors are a viable option to add to metformin when the latter no longer provides adequate glycemic control. They have a very low rate of adverse effects, are weight neutral, and provide a modest decrease in A1C.
- The GLP-1 agonists are also good options to add to metformin when metformin no longer controls hyperglycemia. They offer significant decreases in A1C and modest weight loss. Nausea, vomiting, and the need for self-injection are potential drawbacks to their use.
- Bromocriptine and colesevelam have limited efficacy in treating T2DM hyperglycemia, but the clinical pharmacist should be aware of their use and adverse effect profile.
- Insulin offers a very effective addition to oral medications, and it may be used without oral medication. Pharmacists should be proficient in developing basal/bolus therapy recommendations or plans to optimize hyperglycemic control.
- Clinical pharmacists need to be vigilant of the increased risk of bladder cancer and bone fracture with pioglitazone use and keep abreast of any new data regarding the risk of pancreatitis or thyroid carcinoma with GLP-1 agonists.
- New agents and new formulations of existing agents in the treatment of hyperglycemia continue to evolve.

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# SELF-ASSESSMENT QUESTIONS

Questions 1 and 2 pertain to the following case.

R.S., a 34-year-old man (weight 86 kg) with type 2 diabetes mellitus (T2DM) and an A1C of 10.2%, is being converted from oral diabetes drug therapy to basal/bolus insulin with insulin glargine and insulin aspart. His endocrinologist wants to start R.S.'s total daily insulin at 0.5 unit/kg/day.

- Which one of the following is the most appropriate initial dose estimate of rapid-acting insulin aspart before breakfast for R.S.?
  - 2.
  - 4.
  - 7.
  - 14.
- After initiating and assessing the basal and bolus insulin regimen as accurate in this patient, which one of the following is the best estimate for how much 1 unit of insulin aspart would decrease R.S.'s serum glucose concentration in the case of hyperglycemic excursions?
  - 10.
  - 20.
  - 40.
  - 80.
- A patient with T2DM is currently receiving an insulin-only regimen of premixed insulin 70/30. The morning dose is 20 units before breakfast, and the evening dose is 10 units before dinner. The patient has frequent bouts of low blood glucose concentrations between 1 a.m. and 3 a.m. The average morning fasting glucose concentration is 75 mg/dL, and the average after-dinner glucose concentration is 250 mg/dL. Which one of the following would be the best option for this patient to optimize glycemic control?
  - Convert to insulin glargine and glulisine.
  - Increase the evening insulin 70/30 dose.
  - Increase the morning insulin 70/30 dose.
  - Convert to insulin neutral protamine Hagedorn and detemir.
- A patient is currently receiving 43 units of insulin 70/30 in the morning and 20 units in the evening. The patient is experiencing hypoglycemic events four or five times/week, primarily in the early morning hours. During the past 2 weeks, the average fasting morning glucose concentration has been 110 mg/dL; after-meal glucose concentrations have averaged 165 mg/dL and been consistent after each meal of the day; and the A1C has been 6.9%. The patient's endocrinologist today switched the insulin regimen to insulin detemir and lispro. Which one of the following is the best patient counseling point regarding this regimen change?
  - It will provide a substantial reduction in A1C.
  - It will increase the number of daily insulin injections.
  - It will increase the frequency of nocturnal hypoglycemia.
  - It will improve the patient's morning fasting glucose concentrations.
- A 62-year-old man with T2DM for 8 years began receiving metformin 1000 mg twice daily 2 years ago. His A1C today is 7.9% (personal goal less than 7%). His fasting morning blood glucose readings are consistently at goal (average 95 mg/dL). His after-meal glucose readings average 190–200 mg/dL. Which one of the following would be most appropriate for this patient?
  - Add sitagliptin 100 mg once daily.
  - Add insulin aspart 6 units once daily prior to the evening meal.
  - Switch from metformin to insulin glargine 10 units once daily.
  - Add bromocriptine 0.8 mg once daily.
- A 54-year-old woman with newly diagnosed T2DM presents to the clinic today. She has an A1C of 10.4% and a random glucose concentration of 330 mg/dL. The patient is not experiencing any symptoms of hyperglycemia. In addition to improvements in diet and physical activity, which one of the following is the best initial treatment option for this patient?
  - Metformin.
  - Liraglutide.
  - Insulin.
  - Bromocriptine.
- You have been asked to provide an update in diabetes guidelines to a group of family practice physicians. Which one of the following is the most important message to convey regarding the current diabetes guidelines/recommendations?
  - The American College of Physicians' recommendations are most prescriptive and recommend the use of several agents in addition to metformin.

- B. In the American Association of Clinical Endocrinologists recommendations, drug therapy is based on baseline weight.
- C. The National Institute for Health and Clinical Excellence recommendations promote the use of incretin-based therapies as first line.
- D. The American Diabetes Association (ADA) recommends weighing the therapeutic advantages or disadvantages of T2DM agents when adding to metformin.
8. Which one of the following best characterizes the differences in drug therapy management of T2DM hyperglycemia between the 2009 and 2012 ADA recommendations?
- A. The 2012 recommendations provide an algorithmic approach to treatment decisions.
- B. The 2009 recommendations are more prescriptive in treatment decisions.
- C. The 2012 recommendations base treatment decisions on the quality and quantity of clinical data.
- D. The 2009 recommendations recommend sulfonylureas as first-line agents.
9. A 56-year-old man with T2DM has been treated successfully with metformin for 5 years. Despite his adherence to pharmacotherapy, diet, and physical activity, the last two A1Cs obtained have been mildly elevated (7.3% and 7.4%, goal less than 7%). The patient's medical history includes depression, hypertension, and schizophrenia, for which he takes sertraline, hydrochlorothiazide, and clozapine. Each of these comorbidities is under good control. The patient is initiated on bromocriptine for his diabetes by his physician. Which one of the following would be of most concern given the change in this patient's regimen?
- A. Bromocriptine will not likely get this patient to their goal A1C.
- B. Bromocriptine may exacerbate the patient's schizophrenia.
- C. Bromocriptine should not be used due to the patient's history of hypertension.
- D. Bromocriptine will increase the likelihood of pituitary tumor in this patient.
10. A patient new to your diabetes clinic has a history of T2DM, hypertension, and dyslipidemia. For 6 months, his drug regimen has included metformin 1000 mg twice daily, bromocriptine 4.8 mg at bedtime, lisinopril 10 mg at bedtime, and atorvastatin 40 mg at bedtime. He currently has no adverse effects from his drugs. His A1C today is 7.4%, and the patient states it has been this way for 6 months. Which one of the following would be best to recommend to improve this patient's glycemic control?
- A. Discontinue metformin and add another oral T2DM agent.
- B. Discontinue bromocriptine and add another oral T2DM agent.
- C. Alter the timing of bromocriptine administration.
- D. Continue the current therapy; no changes are necessary.
11. A 58-year-old man with a 10-year history of T2DM and a history of not tolerating metformin has an A1C of 7.4% (goal less than 7%). His current anti-hyperglycemic regimen includes pioglitazone 45 mg/day. SCr is 2.1 mg/dL, and his estimated CrCl is 28 mL/minute. Which one of the following would be most appropriate to add to this patient's drug regimen?
- A. Sitagliptin 100 mg/day.
- B. Liraglutide 0.6 mg/day.
- C. Once-weekly exenatide 2 mg/day.
- D. Linagliptin 5 mg/day.
12. Which one of the following agents, if coadministered with exenatide, would be most likely to increase the risk of hypoglycemia?
- A. Glyburide.
- B. Metformin.
- C. Pioglitazone.
- D. Saxagliptin.
13. A patient with T2DM is taking metformin 500 mg twice daily for glycemic control. However, the patient has had consistent diarrhea since starting the drug. Current laboratory values include A1C 7.3% (goal less than 7%), LDL cholesterol 111 mg/dL (goal less than 100 mg/dL), TG 155 mg/dL (goal less than 150 mg/dL), and SCr 0.5 mg/dL. The patient's other drugs include atorvastatin 80 mg/day and aspirin 81 mg/day. Which one of the following would be best to recommend for this patient?
- A. No change in therapy is necessary.
- B. Add colestevam 1,875 mg twice daily.
- C. Add bromocriptine 0.8 mg once daily.
- D. Switch metformin to acarbose 25 mg once daily.
14. A patient who started once-weekly exenatide in addition to metformin is suspected of having developed thyroid carcinoma. Which one of the following is most appropriate for this patient?

- A. Change exenatide to liraglutide as it has a lower risk of thyroid carcinoma.
- B. Continue current therapy and refer the patient to an oncologist for further evaluation.
- C. Notify the exenatide manufacturer and the FDA of the potential adverse event.
- D. Obtain a serum calcitonin concentration and refer the patient to an endocrinologist.
15. Which one of the following is the most appropriate education point for a patient with established osteoporosis who is receiving pioglitazone therapy for T2DM?
- A. Patients with T2DM are at increased risk of osteoporosis, but in general all T2DM drugs pose a further increased risk.
- B. There is a risk of bone fracture with pioglitazone, but it appears to be greater in women than in men.
- C. There is a risk of bone fractures with pioglitazone, but it appears to be limited to the spine and hip.
- D. Patients with T2DM are at decreased risk of osteoporosis, but pioglitazone may increase the risk more than other T2DM drugs.
16. A patient with a new diagnosis of T2DM understands that metformin is usually the initial drug of choice but has heard news reports regarding the benefits of incretin-based therapies. Which one of the following education points is most important for this patient?
- A. Once-weekly exenatide offers greater reductions in weight compared with metformin.
- B. Metformin offers greater reductions in A1C compared with once-weekly exenatide.
- C. Sitagliptin is a more cost-effective initial treatment than metformin.
- D. Sitagliptin is less effective in A1C reduction than metformin.
17. Which one of the following statements best expresses the comparison of twice-daily versus once-weekly exenatide?
- A. Tolerability with one formulation is required before switching to the other.
- B. The formulations are considered equally effective in reducing A1C.
- C. Both formulations can be used with basal and bolus insulin therapy.
- D. The once-weekly formulation better reduces fasting glucose concentrations.
18. Six months ago, a patient was initiated on pioglitazone 15 mg/day and she has since experienced very good glycemic control. She has recently heard a lot of information regarding pioglitazone and bladder cancer, and her physician told her to discontinue the drug. Which one of the following is the most appropriate response to these concerns?
- A. There appears to be an increased risk of bladder cancer, but the risk appears to be in rodents but not in humans.
- B. There appears to be an increased risk of bladder cancer, but the risk appears to be dependent on the daily dosage.
- C. There appears to be an increased risk of bladder cancer, but the risk appears to be dependent on the duration of use.
- D. There appears to be an increased risk of bladder cancer, but the risk appears to be dependent on the duration of diabetes since diagnosis.
19. During the past year, a patient has received twice-daily exenatide in addition to metformin and has experienced good glycemic control. Now he is concerned about news reports of pancreatitis with exenatide and wants to switch to another incretin-based agent. Which one of the following is the most appropriate counseling point to provide to this patient?
- A. The risk of pancreatitis is derived mainly from epidemiologic studies, but no case reports have been provided to the FDA.
- B. There are case reports of pancreatitis with both GLP-1 agonists and DPP-4 inhibitors, and meta-analysis data from clinical trials support this risk.
- C. Patients with T2DM have an increased risk of pancreatitis, but the risk with GLP-1 agonists or DPP-4 inhibitors does not appear greater than with other agents.
- D. Epidemiologic studies have shown a greater risk of pancreatitis with DPP-4 inhibitors compared with GLP-1 agonists.
20. A patient with T2DM is receiving metformin 1000 mg twice daily. An A1C obtained today is 7.8%. The patient has a known history of hypertension, pancreatitis, dyslipidemia, and depression. The patient has low blood pressure with dizziness on a near-daily basis. Which one of the following would best facilitate glycemic control for this patient?
- A. Liraglutide 0.6 mg once daily.
- B. Bromocriptine 0.8 mg once daily.
- C. Linagliptin 5 mg once daily.
- D. Pioglitazone 15 mg once daily.

## LEARNER CHAPTER EVALUATION: NEW PHARMACOTHERAPIES FOR TYPE 2 DIABETES.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
  - Agree
  - Neutral
  - Disagree
  - Strongly disagree
1. The content of the chapter met my educational needs.
  2. The content of the chapter satisfied my expectations.
  3. The author presented the chapter content effectively.
  4. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
  5. The content of the chapter was objective and balanced.
  6. The content of the chapter was free of commercial bias.
  7. The content of the chapter was useful to me.
  8. The teaching and learning methods used in the chapter were effective.
  9. The active learning methods used in the chapter were effective.
  10. The learning assessment activities used in the chapter were effective.
  11. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

12. Compare and contrast the differences between the drug therapy recommendations of several of the latest and leading diabetes guidelines.
13. Assess the differences in incretin-based therapies for the treatment of type 2 diabetes mellitus (T2DM) and tell how they compare with other agents to treat hyperglycemia.
14. Delineate the role and place in therapy of bromocriptine and colesevelam in the treatment of T2DM.
15. Convert a patient with T2DM with significant hyperglycemia to an insulin-only drug regimen.
16. Evaluate the latest noncardiac precautions, contraindications, or warnings with agents used in the treatment of hyperglycemia.
17. Please expand upon any of your above responses, and/or provide any additional comments regarding this chapter: