

## In Brief

The American Diabetes Association emphasizes the importance of individualized patient care in the management of diabetes. One of the important considerations in choosing an antihyperglycemic agent is its side-effect and safety profile. This article reviews the common and clinically significant side effects of each class of agents, including ways to prevent and overcome their occurrence.

# Update on Safety Issues Related to Antihyperglycemic Therapy

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The treatment of diabetes has progressed significantly in the past 15 years, with new antihyperglycemic agents in the market and several more on the way. However, diabetes continues to have a significant impact on public health. A total of 28.5 million people, or 8.3% of children and adults in the United States, have diabetes, with 1.9 million new cases diagnosed in 2010.<sup>1</sup> In 2012, the cost of diabetes care was estimated to reach \$245 million.<sup>2</sup> Health care providers are presented with the continuous challenge of providing ever-improving care for this population.

The American Diabetes Association emphasizes the importance of individualized patient care in the clinical decision-making process to achieve the best management plan for patients with diabetes.<sup>3</sup> One of the important considerations in choosing an antidiabetic agent is its side-effect and safety profile. This article reviews the most common and clinically significant side effects for each class of antidiabetic agents (summarized in Table 1), including ways to prevent and overcome their occurrence.

## INSULIN SENSITIZERS

### Metformin

Metformin is the preferred initial pharmacological treatment for type 2 diabetes if not contraindicated and if tolerated.<sup>3</sup> It is the only biguanide available in the United States since phenformin was discontinued in 1976 because of a significant associa-

tion with lactic acidosis.<sup>4,5</sup> Metformin acts mainly to reduce hepatic insulin resistance and, in turn, decrease gluconeogenesis and lipogenesis. It is also said to increase insulin sensitivity in peripheral tissues, decrease gut absorption of glucose, decrease the oxidation of fatty acids, and promote weight loss or stabilize weight gain. There is no risk of hypoglycemia because it is an insulin sensitizer and not an insulin secretagogue.<sup>6,7</sup>

Gastrointestinal (GI) manifestations are the most common side effects in this drug class and include nausea, vomiting, abdominal pain, diarrhea, and impaired sense of taste. These are usually mild, transient during initiation of therapy, and dose-related.<sup>6-10</sup> GI upset may be prevented or minimized by starting with low-dose, once-daily administration and slowly titrating upward. Other methods of minimizing symptoms include taking metformin with meals and avoiding overeating. Extended-release formulations are also available, and these decrease upper GI symptoms.<sup>7,8</sup>

Lactic acidosis is a well-known, albeit rare, side effect of metformin. Its incidence is 9 per 100,000 person-years, compared to the incidence of lactic acidosis with phenformin, which was 40–64 per 100,000 person-years.<sup>11</sup> It almost exclusively develops in patients with severe precipitant disease such as renal or hepatic dysfunction and cardiorespiratory insufficiency.<sup>12</sup> Metformin undergoes renal clearance 90–100% of the time and hence is contraindicated in

**Table 1. Side Effects and Safety Considerations for Antihyperglycemic Agents**

Antihyperglycemic Agent	Risk of Hypoglycemia?	Effect on Weight	Common Side Effects	Less Frequent Side Effects	Contraindications/Precautions
Metformin/biguanides	No	Mild decrease to none	Gastrointestinal upset	Lactic acidosis, vitamin B12 deficiency	Renal failure (serum creatinine > 1.5 mg/dl in males and 1.4 in females), decreased creatinine clearance, hepatic failure (especially with alcohol abuse), metabolic acidosis
TZDs 1. Pioglitazone 2. Rosiglitazone	No	Increase	Edema, anemia	Fracture risk; rosiglitazone: myocardial infarction; pioglitazone: bladder cancer	Hepatocellular disease, alanine aminotransferase > 2.5 times the upper limit of normal, New York Heart Association class III or IV heart failure
Sulfonylurea complex drugs 1. SUs a. 1 <sup>st</sup> generation agents b. Glyburide c. Glipizide d. Glimepiride e. Gliclazide 2. Meglitinides 3. Nateglinide	Yes	Increase		Cardiotoxicity; disulfiram-like reaction with alcohol; hyponatremia, jaundice	
α-Glucosidase inhibitors 1. Acarbose 2. Miglitrol	No	Decrease	Flatulence	Acarbose: hepatotoxicity, anemia	Intestinal disease; acarbose: liver cirrhosis; miglitrol: renal failure
GLP-1 receptor agonists 1. Exenatide 2. Liraglutide	No	Decrease	Gastrointestinal upset	Pancreatitis; exenatide: renal failure; liraglutide: MTC	History of pancreatitis and presence of severe hypertriglyceridemia, renal failure (estimated glomerular filtration rate < 30 ml/min/1.73 m <sup>2</sup> ); liraglutide: multiple endocrine neoplasia type 2, personal/family history of MTC
DPP-4 inhibitors 1. Sitagliptin 2. Saxagliptin 3. Vildagliptin	No	Neutral	Predisposition to nasopharyngitis or UTI; saxagliptin: headache, UTI; vildagliptin: headache, dizziness	Pancreatitis; sitagliptin: slight neutrophilia, allergic reactions; saxagliptin: hypersensitivity; vildagliptin: hepatic dysfunction	History of pancreatitis
Pramlintide	Yes	Initial decrease	Gastrointestinal upset		Gastroparesis
SGLT-2 inhibitors	No	Neutral	UTI and genital mycotic infections		Renal failure
Colesevelam	No	Neutral	Gastrointestinal upset		History of bowel obstruction, triglyceride-induced pancreatitis, or triglyceride level > 500 mg/dl
Bromocriptine	No	Decrease	Gastrointestinal upset		History of syncopal migraines or severe hypotension
Insulin	Yes	Increase		Chronic skin reaction: lipodystrophy	

*MTC, medullary thyroid cancer; UTI, urinary tract infection.*

patients with renal insufficiency based on a serum creatinine level  $\geq 1.5$  mg/dl in males and  $\geq 1.4$  mg/dl in females.<sup>12</sup> It is also contraindicated in patients with severe infection, cardiopulmonary insufficiency, and hepatic dysfunction, especially with concomitant alcohol abuse. If lactic acidosis develops, recommendations include hydration, treatment of the underlying illness, and, in severe cases such as overdose toxicity, hemodialysis.<sup>13</sup>

Precaution must be taken in patients receiving contrast for radiological procedures to avoid increasing the risk of contrast-induced nephropathy (CIN). Nearly 8% of metformin-associated lactic acidosis occurs in the setting of CIN.<sup>14,15</sup> It is suggested that patients with an estimated glomerular filtration rate (eGFR)  $> 60$  ml/min/1.73 m<sup>2</sup> who are receiving contrast may continue metformin normally.<sup>16</sup> If the creatinine level is  $> 1.5$  mg/dl or the eGFR is  $< 60$  ml/min/1.73 m<sup>2</sup>, metformin may be replaced by an alternative anti-diabetic agent a few days before the procedure. Some sources recommend stopping metformin 48 hours before such procedures, whereas others do not.<sup>16-18</sup> Hydration with normal saline or sodium bicarbonate may reduce the incidence of CIN.

Vitamin B<sub>12</sub> deficiency may occur in 10–30% of patients with diabetes who are taking metformin and should be a consideration in patients who develop paresthesias and neuropathy while using the drug. Metformin affects calcium-dependent membrane function in the ileal cell surface, thereby decreasing B<sub>12</sub>-intrinsic factor uptake.<sup>19</sup> There is no consensus about screening for B<sub>12</sub> deficiency. B<sub>12</sub> supplementation with over-the-counter multivitamins was not found to be effective.<sup>20</sup> Metanx, a combination of L-methylfolate, methylcobalamin, and pyridoxal-5'-phosphate is approved for the alleviation of diabetic peripheral neuropathy symptoms, particularly in those taking metformin.<sup>21</sup>

### Thiazolidinediones

Thiazolidinediones (TZDs, or “glitazones”) are insulin sensitizers that act through agonistic binding to peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ), a family of nuclear transcription factors. This leads to increased expression of glucose transporters (including glucose transporters 1 and 4), reduced free fatty acid levels, reduced hepatic

glucose release, and reduced preadipocyte-to-adipocyte differentiation.<sup>12</sup> They do not cause hypoglycemia, similar to metformin. Troglitazone, the first TZD introduced in the United States in 1997, was withdrawn from the market in 2000 after rare but sometimes fatal cases of hepatic dysfunction were documented.<sup>7</sup> At present, the commonly used agents in this class in the United States are rosiglitazone and pioglitazone.

This class of agents is metabolized in the liver. Unlike troglitazone, the second-generation TZDs have not been proven to cause hepatotoxicity, and only isolated and reversible cases have been reported.<sup>22</sup> Despite this, the U.S. Food and Drug Administration (FDA) has given recommendations to maintain a record of safety. Liver function tests are required on initiation of the drug and periodically thereafter. Contraindications include patients with active liver disease and in anyone with serum alanine aminotransferase levels  $> 2.5$  times the upper limit of normal.<sup>7,12</sup> Renal adjustment is not needed, and timing is not dependent on meal intake.<sup>9</sup>

Common adverse effects of TZDs include weight gain, edema, and anemia. Weight gain results from both fluid retention and accumulation of subcutaneous fat, leading to increased total fat mass. In contrast, there is actually a reduction in visceral, hepatic, and intramyocellular fat. In any case, increased weight negatively affects patient and provider satisfaction. Hence, counseling regarding lifestyle and dietary changes should be emphasized.<sup>7,12</sup> It is possible to prevent or manage weight gain through caloric restriction and behavior modification.<sup>23</sup>

About 2.5–16.2% of patients on monotherapy with TZDs may develop fluid retention and edema.<sup>24-26</sup> This is postulated to occur because of increased renal sodium reabsorption with resulting plasma volume expansion, capillary leakage, or a combination of both.<sup>26,27</sup> One study suggested that the risk of edema is greater with rosiglitazone than with pioglitazone.<sup>28</sup> Other factors that increase the risk include preexisting edema, insulin use (10–15%), female sex, obesity, genetic predisposition (via a polymorphism in the NFATC2 locus), preexisting renal insufficiency, and diastolic dysfunction.<sup>6,7</sup>

A more significant implication of worsening edema is the risk of developing or exacerbating congestive heart failure (CHF). Heart failure is said to be more likely several months after starting the medication, with a median treatment time of 24 weeks.<sup>29</sup> Because of this, TZDs are contraindicated in patients with New York Heart Association class III or IV cardiac status.<sup>12,26</sup> Patients being considered for TZD therapy should be evaluated for underlying cardiac disease (i.e., previous myocardial infarction [MI], coronary artery disease, CHF, or valvular disease); ongoing edema; shortness of breath, especially with exertion; and use of other medications that could predispose them to fluid retention or pedal edema (e.g., nonsteroidal anti-inflammatory drugs, vasodilators, and calcium channel blockers).<sup>7,30</sup>

It is recommended that patients be started on the lowest dose possible (pioglitazone 15 mg daily or rosiglitazone 4 mg daily), particularly if they have preexisting edema. If glycemic control is still inadequate and no significant edema has occurred, the dose may be increased after 1–3 months.<sup>7</sup> Interestingly, a study in 2011 did not show any increase in CHF occurrence among patients using TZDs.<sup>31</sup>

Anemia may develop in ~ 4% of patients on TZDs. This is more likely because of the dilutional effect from increased plasma circulating volume than from actual cell mass reduction.<sup>12</sup>

TZDs are also associated with an increased fracture risk in both pre- and postmenopausal women of ~ 1.9 per 100,000 patient-years. This increase in risk is not apparent until 1 year after initiating the drug.<sup>32</sup> Although initial data showed that men were not at increased risk, some studies have shown that men  $> 50$  years of age are also more likely to have fractures.<sup>33</sup> Distal sites such as the upper and lower limbs were primarily affected, although some cases of lumbar spine affectation were also reported.<sup>7,34</sup> The proposed pathogenesis is stimulation of bone marrow adipogenesis, thereby decreasing osteoblastogenesis and decreasing bone mineral density (BMD).<sup>12</sup> There are no recommendations for the prevention or management of decreased BMD in relation to TZD use, although bone density screening and fracture risk assessment would be wise.<sup>7</sup>

There are also individual safety concerns for each PPAR- $\gamma$  agonist. There was a suggestion that rosiglitazone was linked to a higher risk of MI or angina pectoris and transient ischemic attack based on a meta-analysis of 42 randomized clinical trials.<sup>35</sup> The RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes) trial, on the other hand, showed no increase in the risk of overall cardiovascular morbidity and mortality.<sup>25</sup> The FDA had been limiting the use of rosiglitazone only if adequate glucose control was not achieved with other medications or if patients were unable to tolerate pioglitazone.<sup>12</sup> However, these restrictions have now been lifted.

Pioglitazone was found to have an association with bladder cancer in some studies.<sup>36,37</sup> Short-term use did not increase the incidence, but use for > 2 years or a cumulative dose of > 28,000 mg was associated with increased risk.<sup>38-41</sup>

TZDs are metabolized through cytochrome P450 and hence may have interactions with other medications metabolized through the same pathway. Ketoconazole may increase the effect of TZDs through the inhibition of its metabolism. On the other hand, ethinyl estradiol/norethindrone plasma levels may be reduced, leading to a loss of contraceptive effect.<sup>9</sup>

## DRUGS AFFECTING THE SULFONYLUREA COMPLEX

### Sulfonylureas

Sulfonylureas (SUs) bind to sulfonylurea receptor-1 (SUR1), which is a subunit of the ATP-sensitive potassium channel found on the surface of pancreatic  $\beta$ -cells. This leads to closure of the channel, depolarization of the cell, and calcium influx, thereby causing insulin secretion. SUs undergo metabolism in the liver, with resultant inactive or weakly active metabolites, which are then excreted renally. Hence, SUs are contraindicated in severe hepatic or renal impairment.

Hypoglycemia is the main adverse effect of SUs. This is more likely in the presence of risk factors such as advanced age, decreased oral intake or poor nutrition, liver and kidney disease, alcohol intake, polypharmacy, or a history of frequent hospitalizations.<sup>9,10</sup> Because of their duration of action, the SUs most likely to cause

prolonged hypoglycemia are chlorpropamide, glyburide, and long-acting glipizide.<sup>9,10</sup> SU activity may also be enhanced or attenuated by drug interactions. Warfarin, chloramphenicol, H<sub>2</sub> blockers, phenylbutazone, and sulfonamides compete with SUs for hepatic oxidation such that co-administration results in increased active SU in the plasma and increased risk for hypoglycemia. Probenecid and allopurinol decrease the renal tubular excretion of chlorpropamide, resulting in increased risk of hypoglycemia.<sup>9,12</sup>

Another concern is the possibility of cardiotoxicity with increased arrhythmic and ischemic events. Sulfonylurea receptor-2 (SUR2) is present in the vascular and cardiac tissues, which may be affected by the SUs, resulting in the inability to undergo protective autoregulatory mechanisms such as ischemic preconditioning.<sup>7,9,42,43</sup>

Secondary treatment failure has been noted in some patients who initially have successful control of their type 2 diabetes with SU therapy. This has been postulated to be multifactorial, with the following factors coming into play: intrinsic disease progression, noncompliance because of weight gain and hypoglycemia, and possible desensitization of  $\beta$ -cells from prolonged stimulation.<sup>9,44</sup>

First-generation SUs are no longer commonly used and therefore will not be discussed in detail. Some notable side effects of chlorpropamide include symptomatic hyponatremia, alcohol-induced flushing or disulfiram-like effect, and cholestatic jaundice that is reversible.<sup>7,12,32,45,46</sup>

Second-generation SUs include glyburide, glipizide, gliclazide, and glimepiride. They are more lipid soluble, allowing greater permeability and more selective binding. They are also more potent, with fewer adverse effects and drug interactions. Glyburide has only a few side effects other than hypoglycemia. However, hypoglycemia from glyburide may be significant and prolonged, making it a less attractive option for elderly patients. Glipizide has less potency and a shorter half-life, making hypoglycemia less of an issue. It is the preferred SU for use in the elderly. This is not the case for the slow-release preparation of glipizide. This agent undergoes 90% enterohepatic metabolism, with a small amount excreted unchanged in the urine. Thus, it is contraindicated in liver failure but is more acceptable

than glyburide in renal failure.<sup>12,32</sup> Gliclazide is not available in the United States. Glimepiride is the newest SU, with a similar hypoglycemic profile to the other second-generation SUs. Its most common adverse effects are dizziness and headaches. Rare side effects include hyponatremia, anemia, leukopenia, and thrombocytopenia. Propranolol is said to increase glimepiride concentrations by 20%.<sup>12,32,47</sup>

### Meglitinides

Repaglinide is a meglitinide that has been approved for use in the United States. It has a similar structure to glyburide but does not have the sulfonic acid-urea moiety. This produces closure of the ATP-sensitive potassium channel via a more distinct SUR1 binding site.<sup>12</sup> Repaglinide is more rapidly absorbed, with a faster and shorter duration of stimulus for insulin secretion. This results in less hypoglycemia and weight gain. It is metabolized through cytochrome P4503A4 in the liver, so precaution must be used in patients receiving other agents that may inhibit or induce this isoenzyme.<sup>7,12</sup> Based on these characteristics, repaglinide may be a better option than an SU in elderly patients or those with renal disease. Mitiglinide, another meglitinide, has been approved for use only in Japan.

### Nateglinide

Nateglinide is a delta-phenylalanine derivative that binds to the SUR1 receptor, closing the ATP-sensitive potassium channel. It is rapid acting and causes a rapid increase in insulin, with peak onset of action within 1 hour.<sup>12</sup> Repaglinide and nateglinide bind more specifically to the SUR1 receptors, with very little binding to the SUR2 receptors in cardiac and vascular smooth muscle, making cardiotoxicity less of a concern. However, there remains a risk for hypoglycemia and weight gain, but perhaps less so than with SUs.<sup>7,12</sup>

## OTHER INSULIN SECRETAGOGUES/INCRETINS

Incretins are intestinal hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). GLP-1 amplifies postprandial secretion of insulin in a glucose-dependent manner, inhibits inappropriate elevation of glucagon, reduces appetite, length-

ens the gastric emptying time, and increases satiety.

### GLP-1 Receptor Agonists

GLP-1 receptor agonists are peptides that act to magnify GLP-1 activity, leading to lower fasting and postprandial glucose levels, as well as weight loss. The commonly used agents today include exenatide and liraglutide.

#### *Exenatide*

Exenatide, or exendin 4, has a short-acting formulation requiring twice-daily dosing and a longer-acting formulation requiring weekly dosing (QW). The most common side effect is nausea, occurring in 40–50% of patients (although this occurred in just 9% of patents in the DURATION-6 study of exenatide QW)<sup>48</sup> and leading to withdrawal from the therapy ~ 3–5% of the time.<sup>7,48</sup> Nausea is usually dose-dependent and is worse at initiation of treatment, with improvement over time. Therefore, it is recommended to start at the lowest dose, then titrate upward slowly over a period of weeks. Other common GI side effects include diarrhea (6%) and vomiting (4%).<sup>48</sup>

A concern raised regarding the efficacy of exenatide is the development of anti-exenatide neutralizing antibodies. High titers of these antibodies in some patients may decrease the glucose-lowering capacity of this agent. In such cases, switching to liraglutide, another GLP-1 receptor agonist, has been shown to improve glucose control.<sup>49,50</sup>

Because exenatide slows gastric emptying, absorption of other medications may be impaired. To prevent this interaction, oral contraceptives and antibiotics should be taken 1 hour before the administration of exenatide.<sup>12</sup> Exenatide does not cause hypoglycemia but may increase the glucose-lowering effects of other agents such as SUs. To prevent hypoglycemia in these situations, the recommendation is to reduce the SU to the lowest dose on initiation of exenatide. The secretagogue dose may then be increased later on.<sup>7</sup>

There has been concern about a link between exenatide use and pancreatitis. This emerged when the FDA received reports of 30 initial cases of pancreatitis through postmarketing surveillance. However, other risk factors for pancreatitis were present in >90% of the patients involved.<sup>51</sup> Since then, various rodent-based and clinical

trials have studied this, but no causal link has been proven, nor has any specific pathophysiological mechanism been determined.<sup>52,53</sup> Regardless, it is best to refrain from using incretin-based therapies in patients with a history of pancreatitis or significant risk factors such as hypertriglyceridemia.<sup>7</sup> Instructions to patients should also include advice regarding monitoring for severe, persistent, and unexplained abdominal pain.<sup>12</sup>

Exenatide is cleared from the plasma through glomerular filtration and thus should not be given to patients with advanced renal failure (eGFR < 30 ml/min/1.73 m<sup>2</sup>).<sup>7</sup> There have also been reports of acute renal failure in patients receiving exenatide. However, most of these patients had underlying chronic renal disease or had one or more risk factors for kidney disease. One study<sup>54</sup> concluded that diabetes itself and not exenatide use predisposed patients to renal disease. Another<sup>55</sup> suggested that the mechanism for the renal failure may be through worsening prerenal azotemia caused by nausea, vomiting, diarrhea, and anorexia.<sup>7,12,55</sup>

#### *Liraglutide*

Liraglutide is a longer-acting GLP-1 receptor agonist requiring once-daily dosing. Nausea is its most common side effect, affecting 10–21% of patients. This is followed by diarrhea in 13% and vomiting in 11%.<sup>48</sup> Tolerance may be improved by slow up-titration. Decreasing the dose to the last tolerated value also helps to lessen these side effects.<sup>50</sup> There have also been reports of pancreatitis with liraglutide.<sup>56,57</sup>

A major concern with this agent is the possibility of medullary thyroid cancer (MTC). In rats and rodents, liraglutide was shown to stimulate calcitonin secretion and increase the incidence of C-cell hyperplasia and therefore medullary thyroid carcinoma.<sup>58</sup> It is important to note that human C cells have significantly fewer GLP-1 receptors than those of rodents, and studies have not shown the same changes in monkeys, which are more closely related to humans.<sup>58</sup> Despite the absence of a definite relationship between MTC and liraglutide in humans, it is recommended that the agent not be given to patients with a personal or family history of MTC or multiple endocrine neoplasia syndrome type 2. Screening for MTC

before initiating liraglutide therapy is not presently recommended.<sup>7,12,52,53</sup>

### Dipeptidyl Peptidase-4 Inhibitors

GLP-1 is broken down by dipeptidyl peptidase-4 (DPP-4) through proteolysis. DPP-4 inhibitors therefore prevent the breakdown of endogenously produced GLP-1 and GIP, resulting in a twofold increase in their levels and prolonging their action. DPP-4 inhibitors commonly used in the United States include sitagliptin, saxagliptin, and linagliptin.

Unlike the GLP-1 receptor agonists, DPP-4 inhibitors do not cause nausea, vomiting, or weight loss. This is likely because they cause a less significant increase in GLP-1 activity compared to GLP-1 receptor agonists. Although hypoglycemia is not a problem in patients on DPP-4 inhibitor monotherapy, it may occur when a DPP-4 inhibitor is used in combination with other agents. Again, starting insulin or insulin secretagogues at a lower level in such situations may prevent this from happening.

Although there have been post-marketing reports of pancreatitis with DPP-4 inhibitors, as with exenatide, no causal relationship or mechanism of action has been proven.<sup>52,53</sup> Still, it would be prudent not to prescribe an agent in this class for patients with a history of pancreatitis and to advise those who do take one to self-monitor for abdominal symptoms.

The main adverse effects of DPP-4 inhibitors are a predisposition to upper respiratory tract infections or nasopharyngitis and headaches. These agents are renally excreted and hence must be prescribed with caution to patients with renal disease. Smaller doses are recommended for patients with end-stage renal disease (stage 3 or higher).

Sitagliptin has been associated with significant allergic reactions such as angioedema, anaphylaxis, and exfoliative skin conditions, including Stevens-Johnson syndrome.<sup>59</sup> The pathogenesis for these reactions is unknown, although they may be related to DPP-4 expression in subsets of CD4 and CD8 T cells, B cells, and natural killer cells.<sup>59</sup> Saxagliptin has been shown to predispose patients to urinary tract infections and also to some hypersensitivity reactions.<sup>12</sup> When saxagliptin is given with TZDs, peripheral edema may occur.<sup>60</sup> Because saxagliptin is metabolized through the

cytochrome P450 CYP 3A4/5 enzyme complex, strong inhibitors or inducers may affect its pharmacokinetics. When used with CYP3A4 inhibitors such as ketoconazole, the dose should be limited to 2.5 mg daily.

### **α-GLUCOSIDASE INHIBITORS**

α-Glucosidase inhibitors (AGIs) competitively inhibit the α-glucosidases in the brush border of the terminal epithelium, thereby inhibiting the terminal step of carbohydrate digestion. This delays carbohydrate absorption, which then attenuates the postprandial glucose peak and gives time for insulin secretion to build up.

The most common side effect associated with AGIs is flatulence caused by gas produced by bacterial flora from the undigested carbohydrates reaching the lower intestines. This occurs in ~20–30% of patients. Other GI symptoms such as diarrhea (3%), bloating, abdominal distention, and borborygmi may also occur. To improve tolerance, patients should be started with a low, once-daily dose and uptitrated slowly. Symptoms sometimes improve with continued use and appropriate dietary adjustments such as minimizing sucrose intake and following a diet high in complex carbohydrates. Studies have shown that these symptoms are dose-dependent, making dose reduction an option. Of note, lactose intolerance does not occur with AGIs because lactase is a β-galactosidase and hence is not affected by these drugs.<sup>7,12,32,61,62</sup>

The AGI acarbose, as monotherapy, has not been shown to cause hypoglycemia. However, it may increase the risk for hypoglycemia if given with insulin or SUs. In such cases, sucrose or simple sugars will not be effective in treating hypoglycemia, and glucose should be administered instead. Although infrequent, some studies have shown acarbose to cause hepatic dysfunction, especially with doses > 300 mg/day.<sup>63,64</sup> The hepatic dysfunction is mostly asymptomatic and reversible when the drug is stopped. Predisposing characteristics include female sex, obesity, race (African Americans), and duration of diabetes > 5 years. It would be prudent to perform hepatic function tests at baseline and periodically thereafter. Anemia was noted in some studies and is postulated to be the result of poor absorption of iron, leading to its deficiency in the body.<sup>12,32,62–65</sup> Miglitol

is excreted unchanged in the kidney and hence should not be used in renal failure.<sup>12,18,66</sup>

### **PRAMLINTIDE**

Pramlintide is a synthetic analog of human amylin or islet amyloid polypeptide, a neuroendocrine hormone that is co-secreted with insulin by pancreatic β-cells. Its mechanism of action is through decreased glucagon secretion, decreased appetite, and delayed gastric emptying.

The most common adverse effect is nausea, occurring in 30–50% of patients. The nausea is dose-related and improves with continuation of therapy. To address this, patients should start at a low dose (15 μg before each meal for type 1 diabetes and 60 μg before each meal for type 2 diabetes) and then uptitrate.

Pramlintide alone does not cause hypoglycemia. However, because it is co-administered with insulin, hypoglycemia is a major issue. As a precaution, prandial insulin should be reduced by 50% when starting pramlintide. Because this drug delays gastric emptying, carbohydrate absorption may be delayed as well, which becomes a concern for hypoglycemia episodes. Glucagon pens may be an option in these situations. Oral medications that need rapid absorption should be taken 1 hour before or 2 hours after pramlintide administration.<sup>7,12</sup>

### **INSULIN**

Insulin continues to be the mainstay of therapy for patients with type 1 diabetes and for those with type 2 diabetes who have poor glucose control despite taking antidiabetic agents.<sup>7,12</sup> The major adverse effects associated with insulin are hypoglycemia and weight gain.

The risk for hypoglycemia may be minimized through patient education and regular self-monitoring of blood glucose. Expectant monitoring may be done intermittently in the early morning or with strenuous exercise, which are times when unrecognized hypoglycemia is more common. Insulin analogs more closely mimic physiological insulin secretion and therefore also decrease the risk for hypoglycemia.<sup>67</sup> Certainly, knowledge of the onset, peak, and duration of action of each type of insulin is an essential tool for prescribing health care providers.

Weight gain is a major concern because it can affect the cardiovascular

risk profile and patients' compliance and motivation. Recommendations to minimize or prevent weight gain include increasing insulin sensitivity by exercising and following a healthy diet or using insulin-sparing medications such as pramlintide or metformin.

Rare side effects include allergies and chronic skin reactions such as lipodystrophy and lipohypertrophy. Such skin reactions may be prevented through rotation of insulin administration sites. Some studies have shown a strong correlation between cancer risk and insulin dose, especially for glargine. Glargine has also been linked to increased mitogenicity compared to human insulin in a human osteosarcoma cell line.<sup>12,68</sup>

### **SODIUM GLUCOSE CO-TRANSPORTER 2 INHIBITORS**

The sodium glucose co-transporter 2 (SGLT-2) protein in the proximal tubules is responsible for reabsorption of the filtered glucose load. SGLT-2 inhibitors therefore prevent glucose reabsorption and promote renal excretion, resulting in improvement in A1C of ~0.5–0.7%. SGLT-2 inhibitors are third-line agents that are usually considered when patients remain hyperglycemic despite combination therapy with two oral agents.<sup>69</sup> Canagliflozin and dapagliflozin are approved for use in the United States.

Common side effects include urinary tract infections and genital mycotic infections, most of which can be treated with standard antibiotics or antifungals, respectively, without discontinuing the drug.<sup>70–72</sup> There have also been reports of increases in LDL cholesterol, although long-term data are not yet available.

### **COLESEVELAM**

Colesevelam, a bile acid sequestrant, has been shown to moderately decrease glucose and LDL cholesterol levels, leading to an A1C improvement of ~0.5% and an LDL reduction of ~15%. The most common side effect is GI upset, which occurs in ~10% of patients, although it is not usually severe enough to cause discontinuation of the drug. Colesevelam can cause an increase in triglycerides of ~5–20%, and hence it is contraindicated in patients with a history of triglyceride levels of > 500 mg/dl or triglyceride-induced pancreatitis.<sup>7,73–75</sup>

## BROMOCRIPTINE

Quick-release bromocriptine, a D2 dopamine receptor agonist, has been shown to cause modest improvement in A1C. If given within 2 hours of awakening, a circadian peak in central dopaminergic tone leads to heightened insulin sensitivity. The most common side effect is nausea, occurring in ~ 30% of patients and resulting in withdrawal in ~ 10% of patients taking higher doses. It is therefore suggested to use lower doses and to ingest with food for better tolerance.<sup>7,76,77</sup>

## CONCLUSION

Diabetes management continues to present a challenge to clinicians worldwide, requiring individualization of care and physician-patient collaboration. Numerous antihyperglycemic agents with different mechanisms of action and various side-effect profiles comprise the diabetes armamentarium. Knowledge and understanding of the above factors should serve as a guide in medical decision-making to enable providers to provide the best possible care to patients with diabetes.

## References

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