



## Individualizing Oral Therapy for Patients With Type 2 Diabetes: Current and Emerging Strategies

### Learning Objectives

After completing this activity, participants should be better able to:

- Review the mechanisms of action of available oral agents when selecting treatment regimens for patients with type 2 diabetes mellitus (T2DM)
- Incorporate treatment strategies for patients with T2DM that minimize treatment-related side effects while enhancing adherence
- Describe the mechanism of action and latest clinical results with sodium-dependent glucose transporter-2 (SGLT-2) inhibitors for the treatment of T2DM as monotherapy and in combination with available oral therapies

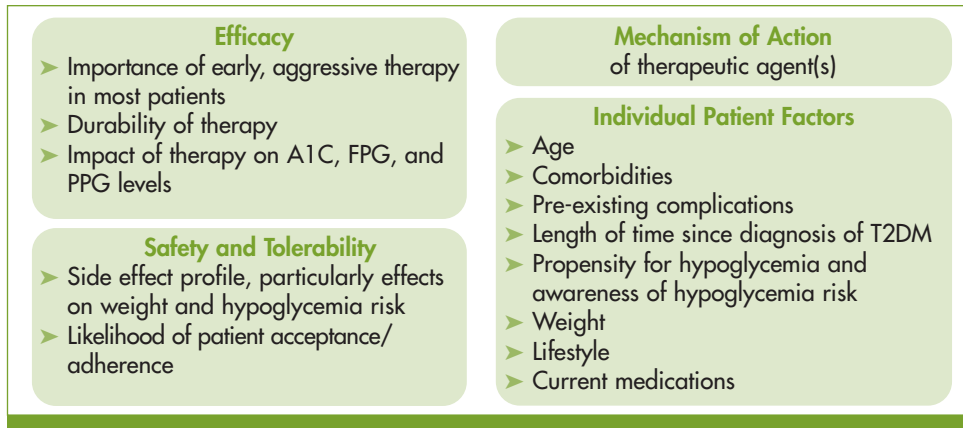
### Introduction

The numbers surrounding diabetes can be staggering. Estimates are that 11.3% of Americans age 20 or older have diabetes, of whom more than 4 in 10 are undiagnosed.<sup>1</sup> If current trends continue unabated, the US population will include as many as 48.3 million people with diagnosed diabetes by 2050.<sup>2,3</sup> Individuals with diabetes are at increased risk for a variety of complications, including blindness, kidney disease, and cardiovascular (CV) disease, and have roughly double the mortality risk of people without diabetes.<sup>1</sup> It also is worth noting that medical costs for individuals with diabetes are 2.3 times higher than those of nondiabetic individuals.<sup>1</sup>

Over time, key principles in management of diabetes have been developed based on the goals of early identification and treatment, close monitoring, and advancing treatment when necessary to achieve and maintain target goals. In general close to 59% of diabetes patients are treated with oral agents only.<sup>4</sup> Eight different classes of oral agents are now available, including 3 classes introduced within the last 5 years. The decisions involved in choosing the appropriate oral agent or combination of agents for each patient are important to proper management of hyperglycemia, minimizing the risk of disease- and treatment-related complications, and optimizing patients' quality of life. Decision making involves not just the goal, but the means to achieve the goal, and must be undertaken in concert with patients, factoring in their individual health issues and preferences (Figure 1).

**Antidiabetic therapy should be evidence-based, but tailored for the individual patient.**

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**Figure 1. It's not just about A1C level: factors to consider when individualizing T2DM therapy.<sup>7</sup>** FPG = fasting plasma glucose. PPG = postprandial plasma glucose.

## Begin Treatment Early to Limit Disease-Related Complications

Approximately 90% to 95% of diabetes in adults is type 2 diabetes (T2DM), a chronic disease characterized by progressive loss of insulin sensitivity and beta-cell function as well as other defects in glucoregulation.<sup>1,5,6</sup> It has been established that maintaining glycosylated hemoglobin (A1C) in the target ranges recommended by the American Association of Clinical Endocrinologists (AACE) ( $\leq 6.5\%$ ) and the American Diabetes Association (ADA) ( $< 7\%$ )<sup>7,8</sup> is strongly associated with reductions in risk of microvascular complications in a continuous way—each 1% decline in A1C is associated with a significant 37% reduction in risk in newly diagnosed patients.<sup>9</sup> In the United Kingdom Prospective Diabetes Study (UKPDS), a significant 25% reduction in risk for microvascular complications was observed in newly diagnosed patients maintained for 10 years at a median A1C level of 7% versus those with a median A1C of 7.9%.<sup>10</sup> UKPDS also found a trend toward a lower risk for fatal and nonfatal myocardial infarction (MI), which, while suggestive, did not meet statistical significance ( $P = .052$ ).<sup>10</sup> At 10-year post-trial follow-up, patients enrolled in the UKPDS study who received intensive therapy shortly after diagnosis of T2DM had a significantly lower risk of MI and death from any cause, as well as reductions in risk of microvascular disease, despite the fact that tight glycemic control had not been maintained after the first year following the end of the trial.<sup>11</sup> It has been proposed that early exposure to hyperglycemia may predispose the T2DM patient to development of a “metabolic memory” resulting in a higher likelihood of complications from the disease. Conversely, the results from UKPDS suggest early, aggressive intervention to lower blood glucose may prevent this putative “legacy of hyperglycemic memory.”

## Choose Glycemic Goals Based on Patient-Specific Factors

A decade after the initial publication of the UKPDS findings, 2 studies that pursued aggressive glucose-lowering strategies were published and appeared to contradict the idea that “lower is always better.” In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, the intensive therapy group was targeted to achieve an A1C of  $< 6.0\%$  versus 7.0% to 7.9% in

the standard therapy group. Yet, although nonfatal MI occurred with greater frequency in the standard therapy group, the intensive therapy group had significantly higher rates of all-cause and CV death, leading to discontinuation of the trial after a mean follow-up of 3.5 years.<sup>12</sup> In the Veterans Affairs Diabetes Trial (VADT), the goal was an A1C level reduction of 1.5% in the intensive therapy arm compared with the standard therapy arm. No significant difference in the time to first occurrence of a CV event or other CV outcomes was noted at a median follow-up of 5.6 years.<sup>13</sup> In both studies, rates of weight gain and hypoglycemia were higher in the intensive than in the standard therapy groups.<sup>13</sup>

Patients in these studies had a long duration of disease, were overweight or obese, and many had a history of CV disease. In ACCORD, patients had a mean age of 62 years, median duration of T2DM of 10 years, and median A1C of 8.1% at baseline. About 35% in each group had a history of CV events, 14% were current smokers, and the mean body mass index (BMI) was 32.2 kg/m<sup>2</sup>.<sup>12</sup> In VADT, the patient population comprised veterans whose mean age was 60.4 years and duration of T2DM was 11.5 years. Baseline A1C was 9.4%, mean BMI was 31.3 kg/m<sup>2</sup>, and 40% had already had a CV event.<sup>13</sup>

From ACCORD and VADT, it is possible to conclude that for patients with longer duration T2DM, aggressive glucose-lowering strategies to get A1C below 7% may carry consequences that undermine other aspects of well-being, such as weight gain, hypoglycemia, or other metabolic changes.<sup>14</sup> For patients with a long duration of disease, history of severe hypoglycemia, or advanced micro- or macrovascular disease, treatment guidelines stress that less stringent A1C goals may be appropriate.<sup>7,8,14</sup>

Table 1 lists the ADA and AACE glyceic goals for most patients with T2DM, with the ADA goals being somewhat broader than those from the AACE.<sup>8,15,16</sup> Nevertheless, the take-away messages from UKPDS, ACCORD, and VADT are to tailor therapy using patient factors of age and comorbidities, pre-existing complications, duration of T2DM, propensity for hypoglycemia and awareness of hypoglycemia risk, weight, lifestyle, and current medications.

Finally, the relative contributions of fasting plasma glucose (FPG) and postprandial glucose (PPG) to glyceic load vary at different A1C levels, with FPG predominating at higher A1C levels (>8.4%) and PPG predominating at lower A1C levels (<7.3%).<sup>17</sup> Therefore, consideration of the impact of therapeutic choices on FPG and PPG, as well as A1C level, is important when planning treatment for the patient with T2DM.<sup>7</sup>

**Table 1.**

**Goals for Glyceic Control: 2011<sup>8,15,16</sup>**

|                   | ADA 2011  | AACE 2011 |
|-------------------|---|-----------|
| A1C (%)           | Around or <7%   | ≤6.5%     |
| FPG (mg/dL)       | 70-130  | <110      |
| PPG (mg/dL)       | <180  | <140      |
| Glyceic Parameter |   |           |
| A1C               | Measures glyceic exposure over 3 months   |           |
| FPG               | Snapshot of basal glucose metabolism (ie, hepatic glucose production)           |           |
| PPG               | Dependent on postprandial glucose excursions; linked to risk of vascular damage |           |

# Individualizing Oral Therapy for Patients With Type 2 Diabetes: Current and Emerging Strategies

## Consider Treatment Efficacy and Durability

The clinician treating the T2DM patient is faced with an array of treatment options, including diet and exercise modifications as well as various pharmacologic interventions. In choosing the right strategy, the clinician must weigh the agent's glucose-lowering potential against side effect profiles, individual patient factors, and the potential for interaction with other treatments the patient may be receiving.<sup>18</sup> Ultimately, the strategy for managing T2DM in a newly diagnosed 30 year old will most likely be different than the strategy for managing long-standing disease in a patient with multiple comorbidities who may have had a CV event.

**A variety of oral agents are available to address different pathophysiologic defects in T2DM.**

There are 8 classes of oral antidiabetic agents (OADs) ranging from the sulfonylurea (SU) class, first available in 1946, to the widely used new class, the dipeptidyl peptidase-4 (DPP-4) inhibitors, first approved in 2006 (Table 2).<sup>19</sup> A newly added agent, bromocriptine mesylate, has been used in nondiabetes applications and recently received an indication for lowering glucose in T2DM in a quick-release (QR) formulation.<sup>20,21</sup> In addition, colesevelam is a bile-acid sequestrant that has been used for lipid-lowering that in 2009 received an additional

indication for lowering glucose in T2DM in combination with other OADs as well as insulin.<sup>22</sup> The glucose-lowering efficacy of these oral agents as monotherapy as measured by A1C ranges from 0.4% to 1.5% (Table 2).<sup>18,21</sup>

A comparative analysis of oral agents as monotherapy supports metformin as first-line oral therapy for most patients, given its favorable benefit-to-risk ratio.<sup>23</sup> Guidelines recommend metformin as a first-line agent, excepting patients with renal impairment or tolerability issues. Depending on baseline A1C, SUs, thiazolidinediones (TZDs), DPP-4 inhibitors, and alpha-glucosidase inhibitors (AGIs) also are options for initial monotherapy in the AACE guidelines.<sup>7</sup>

The efficacy of the DPP-4 agents warrants a closer look, as they are relatively new and finding wide acceptance. Three DPP-4 inhibitors currently are available: sitagliptin, saxagliptin, and linagliptin. As monotherapy, these agents deliver A1C

**Table 2.**

### Efficacy of Traditional and Newer T2DM Oral Agents: Experience and Potency<sup>19,20,30</sup>

| Traditional Oral Agent    | Year              | Efficacy: ↓ in A1C (%) <sup>a</sup> |
|---------------------------|-------------------|-------------------------------------|
| SUs                       | 1946              | 1.5                                 |
| Glinides                  | 1997              | 1.0-1.5                             |
| MET                       | 1995 <sup>b</sup> | 1.5                                 |
| AGIs                      | 1995              | 0.5-0.8                             |
| TZDs                      | 1999 <sup>c</sup> | 0.8-1.0                             |
| Newer Oral Agent          | Year              | Efficacy: ↓ in A1C (%) <sup>a</sup> |
| DPP-4 inhibitors          | 2006              | 0.5-0.8                             |
| Colesevelam               | 2008              | 0.5                                 |
| Bromocriptine mesylate QR | 2009              | 0.4                                 |

<sup>a</sup>Efficacy as monotherapy with the exception of colesevelam, which has been studied in combination with 1 or more oral antidiabetic agents only; <sup>b</sup>MET available in some other countries since 1957; <sup>c</sup>Troglitazone became available in the United States in 1997; withdrawn from US market in 2000. MET = metformin.

reductions ranging from 0.5% to 0.8% (Table 2).<sup>24-26</sup> Each of these is approved for use as monotherapy or in combination with other oral agents.<sup>27-29</sup> These agents are considered weight-neutral and have been studied in combination with metformin, SUs, and in some cases TZDs.<sup>25,30-37</sup>

Unfortunately, because T2DM is progressive, it is common for monotherapies to eventually lose efficacy; with the duration of successful glycemic control being somewhat dependent on the therapy used.<sup>10</sup> On a relative scale, durability of glycemic control appears to be longest with TZDs and shortest with SUs, with metformin falling in-between.<sup>15</sup> At the point when monotherapy no longer adequately controls hyperglycemia, treatment should be advanced with additional agents. Therapy should be monitored using A1C every 2 to 3 months and intensified as necessary to maintain goals.<sup>7</sup>

Given the accepted principle that achieving durable glycemic control is important to reducing complications,<sup>8</sup> it is surprising to learn that despite the introduction of effective new agents and different classes of therapy over the past decade, as many as 43% of patients with diabetes are not achieving target A1C goals, including 23% with A1C  $\geq$ 8%.<sup>4</sup> Patients on monotherapy or combination therapy often do not have their treatment advanced in a timely manner in response to poor A1C control, leaving many at an A1C level  $>$ 8% for years due to clinical inertia.<sup>38</sup>

### Target Multiple Pathophysiologic Defects When Combining Therapies

Depending on the mechanism of action involved, oral agents generally may be sorted by whether they preferentially target FPG or PPG, allowing a rational approach to combining treatments. TZDs, SUs, and metformin primarily act to lower FPG, although other agents, such as DPP-4 inhibitors can also decrease FPG levels.<sup>7,15</sup> Glinides and AGIs primarily impact postprandial hyperglycemia. DPP-4 inhibitors also target PPG in a glucose-dependent manner.<sup>15</sup> Optimizing A1C reduction often requires addressing FPG and PPG glycemic goals.

At diagnosis, T2DM patients have already lost as much as 80% of normal beta cell function, underscoring the need for early intervention.<sup>39</sup> However, there are multiple pathophysiologic defects leading to T2DM and more is involved than simple impaired insulin secretion.

Table 3 outlines the mechanisms of action of the OAD classes.<sup>7,20,40</sup> Note that no single class of agents addresses all of these defects; effective therapy often requires multiple agents used in combination and should not be focused simply on lowering A1C.<sup>39</sup> When choosing an agent to add to existing therapy, consideration should be given to combining agents with complementary mechanisms of action.<sup>18</sup>

DPP-4 inhibitors offer a unique approach to lowering glucose. In response to meals, gut-based hormones called incretins, primarily glucagon-like protein 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), contribute in a glucose-dependent way to normal glucohomeostasis by enhancing insulin secretion, decreasing glucagon secretion, and delaying gastric emptying.<sup>6</sup> Secretion of these hormones is diminished in patients with T2DM.<sup>6</sup> Once activated, the incretin hormones, such as GLP-1, are rapidly degraded by the enzyme DPP-4. By blocking the action of the DPP-4 enzyme, DPP-4 inhibitors increase concentrations of endogenous incretin hormones (Figure 2).

**Many patients treated for T2DM experience sustained hyperglycemia and associated detriments due to clinicians' failure to appropriately advance treatment.**

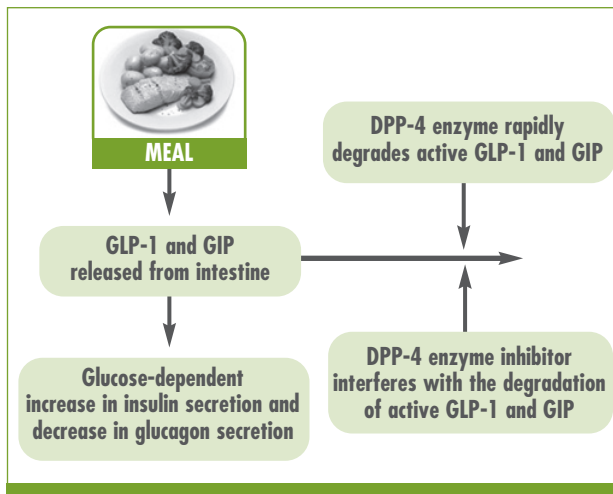
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**Table 3.**

## Mechanisms of Action of Classes of Oral Antidiabetic Drug Classes: No Single Class of Oral Agents Targets All Key T2DM Pathophysiologies<sup>7,20,40</sup>

| Class/Agent       | Mechanism of Action   |
|-------------------|---|
| Biguanides (MET)  | Inhibit glucose output from the liver   |
| TZDs              | Enhance insulin sensitivity   |
| AGIs              | Decrease carbohydrate absorption in GI tract  |
| SUs               | Insulin secretagogues; increase basal and/or postprandial insulin levels  |
| Glinides          | Insulin secretagogues; increase basal and/or postprandial insulin levels  |
| DPP-4 inhibitors  | Increase endogenous incretin levels to inhibit glucagon release and increase insulin levels; glucose-dependent  |
| Colesevelam       | Not known; binds bile acids and alters the enterohepatic metabolism of bile; may delay glucose absorption after meals to improve whole-body insulin sensitivity |
| Bromocriptine, QR | Not known; may act centrally to improve insulin resistance and other metabolic abnormalities  |

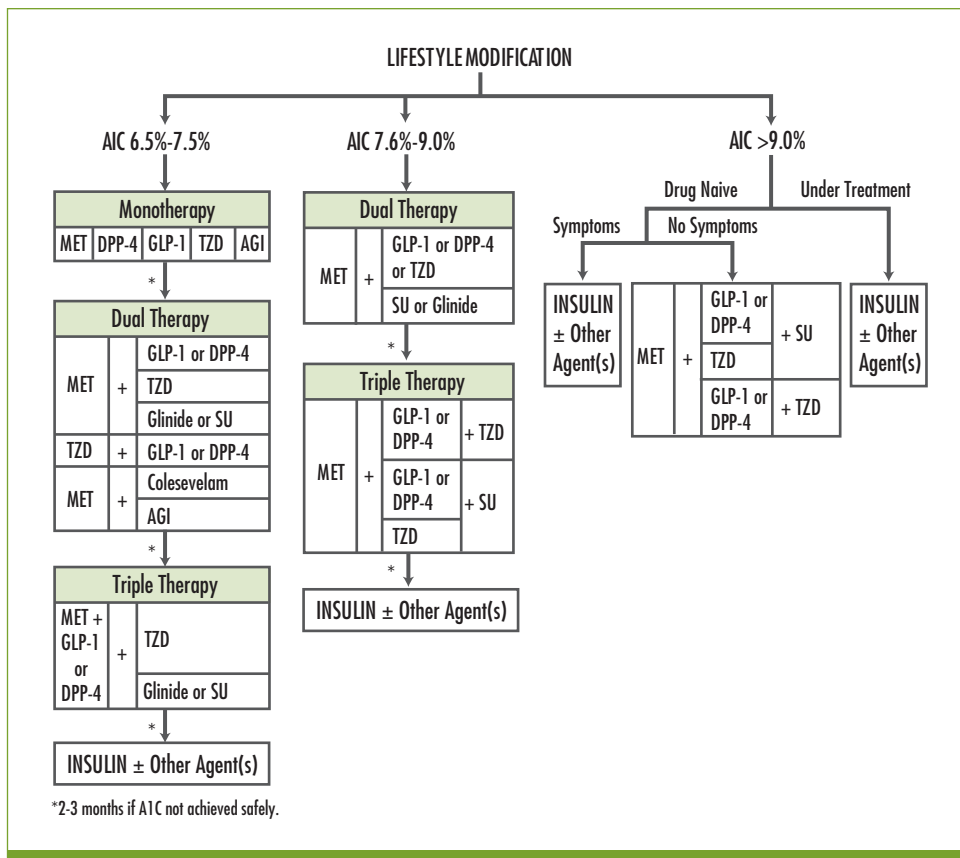
GI = gastrointestinal.



**Figure 2. Gut-based incretin hormones and mechanism of action of DPP-4 inhibitors.**

The AACE algorithm for management of hyperglycemia (Figure 3) delineates recommendations based on A1C and specifies that treatment response should be assessed no later than 3 months after initiation, with treatment advanced if the desired A1C has not been achieved.<sup>7</sup> In general, metformin should be the basis of dual therapy.<sup>7</sup> AACE recommends using a rational approach to combining agents, noting that because metformin is an insulin sensitizer, the second agent should be a DPP-4 inhibitor or insulin secretagogue that targets a different underlying defect.<sup>7</sup> Addition of

a DPP-4 inhibitor to another oral therapy, such as metformin, pioglitazone, or an SU results in an additive effect, lowering A1C by an additional 0.5% to 0.8% depending on the initial OAD with which it is combined (Table 2).<sup>25,31-37</sup> The AACE guidelines also encourage



**Figure 3. AACE/ACE treatment algorithm for T2DM.**

Adapted from <https://www.aace.com/sites/default/files/GlycemicControlAlgorithmPPT.pdf>. Copyright 2009, with permission from the American Association of Clinical Endocrinologists.

consideration of initial combination therapy for patients diagnosed with T2DM characterized by an A1C level >7.5%.<sup>7</sup>

In a study comparing combination therapy with sitagliptin or glipizide added to metformin, both drug combinations demonstrated glycemic durability (ie, satisfactory control of glucose) for more than 2 years on a stable dose.<sup>41,42</sup> Although the 2 agents produced similar reductions in A1C and FPG, the glipizide plus metformin group had weight gain and a 14-fold greater number of hypoglycemic episodes than the sitagliptin plus metformin group, who also experienced weight loss over the 2-year study period.<sup>40</sup>

### Factor in Safety and Tolerability When Choosing Agents

Treatment safety profiles should be considered, especially when agents are combined. Effective patient-centered therapy must minimize the risk of treatment side effects, particularly those that exacerbate T2DM complications, like hypoglycemia and weight gain.<sup>8,14,18</sup>

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Elevated hypoglycemia risk is particularly associated with the insulin secretagogues—SUs and glinides. Weight gain is an unwelcome side effect of the TZDs, SUs, and glinides. In contrast, metformin, the DPP-4 inhibitors, and AGIs are considered weight-neutral and unlikely to induce hypoglycemia (Table 4).<sup>7,18</sup>

Comorbidities should be another consideration in the choice of therapy. Pioglitazone (the only TZD currently available in the United States) is contraindicated in the presence of congestive heart failure or hepatic impairment.<sup>43</sup> Metformin (immediate- and extended-release [XR]) is contraindicated in the presence of renal impairment (serum creatinine levels  $\geq 1.5$  and  $\geq 1.4$  mg/dL in men and women, respectively) because it may increase the risk of lactic acidosis, a rare (<1/100,000 treated patients) but potentially fatal condition.<sup>18,44</sup> Many other oral agents require dosage adjustment in the presence of renal impairment. Those that do *not* require dose adjustment for renal impairment are pioglitazone, nateglinide, and linagliptin.<sup>27,43,45</sup>

Bromocriptine QR has not been studied in patients with renal impairment, and no overall differences in the safety and effectiveness of colesevelam were seen in patients with a creatinine clearance (CrCl) of <50 mL/min compared with patients with a CrCl of  $\geq 50$  mL/min.<sup>21,22</sup> As always, clinicians should familiarize themselves with a drug's most current prescribing information prior to recommending treatment.

In terms of serious side effects, pioglitazone has been associated with an increased risk of congestive heart failure (CHF) as well as increased risk of bone fractures.<sup>43</sup> Evidence has recently emerged of a possible connection between long-term pioglitazone treatment and an increased incidence of bladder cancer. As of June 2011, the Food and Drug Administration (FDA) recommends using pioglitazone with caution in patients with a prior history of bladder cancer, and its use is contraindicated for those with active bladder cancer.<sup>46,47</sup>

DPP-4 inhibitors generally are well tolerated, but hypersensitivity reactions have been reported with these agents. Some patients receiving sitagliptin and linagliptin have developed acute pancreatitis, although whether this is a causative association is under investigation.<sup>27-29</sup> In addition, coadministration of strong CYP3A4/5 inhibitors (eg, ketoconazole) significantly increases saxagliptin concentrations, and the efficacy of linagliptin may be reduced by concomitant administration of strong P-glycoprotein or CYP3A4 inducers.<sup>27,28</sup>

“Tolerability” refers to factors that affect whether patients will be able to take the medicine and continue to take it as prescribed. When queried, patients cite a number of factors that lead to nonadherence with their OAD regimen, including hypoglycemia, gastrointestinal effects,

**Table 4.**

## Safety: Effects of Oral T2DM Agents on Weight and Hypoglycemia Risk<sup>8,18,21,22</sup>

| Agent/Class      | Severe Hypoglycemia | Weight Change |
|------------------|---------------------|---------------|
| MET              | No                  | Neutral       |
| TZDs             | No                  | Gain          |
| SUs              | Yes                 | Gain          |
| Glinides         | Yes                 | Gain          |
| AGIs             | No                  | Neutral       |
| DPP-4 inhibitors | No                  | Neutral       |
| Colesevelam      | No                  | Neutral       |
| Bromocriptine QR | No                  | Neutral       |

weight gain, headaches, and edema.<sup>48</sup> In terms of treatment-limiting side effects, many patients treated with metformin experience gastrointestinal side effects, including 53% experiencing diarrhea, that are mitigated by using the XR formulation.<sup>44,49</sup> Gastrointestinal effects also appear to limit use of AGIs and colesevelam.<sup>15</sup> Weight gain may limit use of SUs and TZDs.

Another important factor in tolerability is a drug's dosing schedule. Many T2DM patients take medica-

tions for multiple ailments. Agents that are dosed on a 1-pill, once-daily schedule, like the SUs and DPP-4 inhibitors, are likely to be better tolerated in this sense than agents requiring multiple daily doses. Fixed-dose combinations (FDC) of commonly combined OADs can help address this issue and improve adherence with therapy.<sup>50,51</sup> Metformin or metformin XR forms the basis for all but 1 FDC, which combines pioglitazone and glimepiride (Table 5).<sup>52-58</sup>

## Educate the Patient: An Informed Patient Is a Better Partner in Shared Decision Making

Such a large percentage of diabetes care falls on patients themselves that successful outcomes depend on their participation in decision making. Patients must be educated about the goals of treatment, the way their medications work, and the types of tolerability issues to expect—and what can be done to mitigate them. Experience suggests that patients often do not understand their medications: in a survey of 261 T2DM patients, 15% understood the correct mechanism of action of their treatment, 10% were aware that SUs may cause hypoglycemia, and 20% were aware that metformin may cause gastrointestinal effects. In the same survey, 62% took their medication as directed in relation to food, 20% forgot to take their medication at least once a week, and only 35% remembered receiving any advice from their clinician regarding their medication.<sup>59</sup> These gaps in knowledge present significant challenges to optimizing care of patients with T2DM using oral agents. Simple solutions, such as written medication descriptions and instructions, are underused (1% in the survey) but represent a cost-effective way to improve adherence and outcomes.

## “On the Horizon”: A New Target for Intervention

Given the prevalence and challenges of T2DM, research continues for new forms of treatment. A new class of agents being investigated takes a unique approach to removing excess glucose from the system by inhibiting renal reabsorption of glucose. A protein called SGLT-2, which

**Table 5.**

### Fixed-Dose Combination Therapy<sup>52-58</sup>

| Tablet Components          | Strengths (mg)           | Dosing (times/d) |
|----------------------------|--------------------------|------------------|
| MET + glyburide            | 250:1.25; 500:2.5; 500:5 | 1-2              |
| MET + glipizide            | 250:2.5; 500:2.5; 500:5  | 1-2              |
| MET + sitagliptin          | 500:50; 1000:50          | 2                |
| MET + repaglinide          | 500:1; 500:2             | 2-3              |
| MET + pioglitazone         | 500:15; 850:15           | 1                |
| MET XR + pioglitazone      | 1000:15; 1000:30         | 1                |
| MET XR + saxagliptin       | 500:5; 1000:2.5; 1000:5  | 1                |
| Pioglitazone + glimepiride | 30:4; 45:4               | 1                |

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is located almost exclusively in the proximal tubules of the kidneys, is involved in reabsorbing excess glucose delivered to the kidney.<sup>60</sup> This new class of agents works by blocking the function of SGLT-2, which in turn inhibits renal glucose reabsorption and leads to urinary glucose excretion (glucosuria).<sup>61</sup> In short, this therapy results in spilling glucose and its associated calories into the urine when blood glucose levels are high, thus regulating hyperglycemia with the expectation of weight loss and little or no hypoglycemia.

The first agent to enter clinical trials was dapagliflozin. At doses of 2.5 mg to 10 mg dapagliflozin reduces A1C 0.71% to 0.85% as monotherapy<sup>61</sup> and an additional 0.67% to 0.84% in combination with metformin,<sup>52</sup> similar to other oral agents. It appears to be well tolerated and is associated with weight loss—taken as monotherapy patients lost up to 2 kg of weight over 12 weeks, and taken in combination with metformin patients lost up to 3 kg over 24 weeks without apparent increase in hypoglycemia risk.<sup>61,62</sup> However, dapagliflozin causes glycosuria and may be associated with an increased rate of genitourinary infections.<sup>61,62</sup> A report presented at the recent ADA 71st Annual Scientific Session revealed that small increases in the risk of breast cancer in women (0.4% vs 0.1%) and bladder cancer in men (0.3% vs 0.05%) were seen in the dapagliflozin treatment arms compared with control arms.<sup>63</sup> Such findings had not been seen in preclinical animal trials. The efficacy and safety of dapagliflozin are undergoing evaluation by the FDA to determine if approval will be granted in the near future.

### Summary

Antidiabetic therapy should be evidence-based but flexible so as to fit the specific needs of the patient. There are many options for oral therapy of T2DM; choosing the right drug or combination depends on clinicians identifying patient factors that influence treatment; using agents with the necessary efficacy and complementary activity to get to goal with minimal tolerability issues, particularly hypoglycemia and weight gain; and working with patients on education and treatment choice to optimize outcomes.<sup>7</sup> Other key factors to keep in mind are starting treatment early in the natural history of T2DM to limit disease-related complications, and to consider the impact of the oral agent(s) on glucose end points, including FPG and PPG, and the various T2DM pathophysiologic defect(s) to be targeted when selecting monotherapy or combination therapy.



## CASE: 52-Year-Old Male Construction Shift Worker Diagnosed With T2DM 1 Year Ago

### Presentation

Jim is a 52-year-old construction shift worker diagnosed 1 year ago with T2DM. He is married with 3 teenaged boys, stopped smoking 5 years ago, and is a social drinker. His father, now deceased, also had T2DM. After starting diabetes treatment with immediate-release metformin and experiencing intolerance, he currently is taking maximum-dose metformin XR (2 750-mg tablets once daily) as well as lisinopril (10 mg) for hypertension and simvastatin (10 mg) for lipids.

### Physical Findings

- Height: 5 ft 10 in
- BMI: 29.2 kg/m<sup>2</sup>
- BP: 135/83 mm Hg on lisinopril

### Laboratory Values

- FPG: 135 mg/dL
- A1C: 7.4%
- Serum creatinine: 0.9 mg/dL
- Total cholesterol: 225 mg/dL
  - Low-density lipoprotein cholesterol (LDL-C): 115 mg/dL
  - High-density lipoprotein cholesterol (HDL-C): 40 mg/dL

When told his antidiabetic therapy must be intensified, Jim emphasized that he does not think he is ready for injectable therapy.

### Clinical Decision Point

#### *How would you adjust Jim's antidiabetic regimen?*

- Add glipizide
- Add an AGI
- Add a TZD
- Add incretin-based therapy

### Comment

Jim requires intensified glycemic control. Because of his night shift work around heavy machinery, hypoglycemia is a real concern. He also needs to better control his blood pressure and lipids. Glipizide could increase his hypoglycemia risk and weight. A TZD is likely to help Jim get his A1C below 7%, and is an option for combination with metformin, although its side effect profile includes weight gain.

The clinician adds pioglitazone 15 mg once daily to Jim's metformin, and increases the doses of his lisinopril (to 20 mg) and simvastatin (to 20 mg) to improve his blood pressure and lipids. Using pioglitazone addresses insulin resistance without increasing hypoglycemia risk. However, an agent more specifically targeting PPG may have been a better choice.

### 3-Month Follow-Up

At his next visit, Jim's A1C has decreased to 6.6%. He complains about gaining weight, which is a common side effect with TZDs. Jim says he's read in the newspapers about the possible CV effects of TZDs, and wonders if there is another option for him. While Jim has

successfully controlled his glucose, his treatment may be exacerbating other metabolic issues associated with diabetes, such as weight and CV risk factors. A better therapy choice for Jim is one that controls glucose with a minimal effect on weight, lipids, and other factors.

### Clinical Decision Point

#### *How could Jim's OAD regimen be adjusted?*

- Decrease TZD dose
- Discontinue TZD, initiate a DPP-4 inhibitor
- Discontinue TZD, initiate AGI
- Add a DPP-4 inhibitor to his existing TZD and metformin

#### Comment

Jim and his clinician talked about his treatment goals and side effects, focusing on Jim's concerns about weight gain and CV effects. They decide to discontinue the TZD and initiate treatment with saxagliptin (5 mg once daily). Initiating a DPP-4 inhibitor is consistent with published guidelines and addresses concerns about weight gain and hypoglycemic avoidance.

The decision pays off when Jim returns in another 3 months and reports happily that he has lost 10 pounds—likely a result of discontinuing the TZD. He says hypoglycemia is rare and minimal on the metformin/saxagliptin combination. Lab results show his A1C remains well controlled at 6.8% and his lipids and blood pressure are within normal limits.

#### Jim's Next Visit

When Jim returns 3 months later for follow-up, his A1C remains at 6.8% and his lipids and blood pressure remain well controlled. He is happy with his treatments, but complains that with all his interventions, he is taking too many pills and is afraid he'll unintentionally skip a dose of something. He asks what his options are going forward.

### Clinical Decision Point

#### *What course of action would you suggest for Jim?*

- Discontinue saxagliptin and add once-daily glipizide
- Discontinue saxagliptin and initiate basal insulin
- Consider a fixed-dose combination of metformin and saxagliptin
- Other

#### Comment

Jim has expressed a desire to stay on oral therapy and is well controlled on his present regimen. Changing from a DPP-4 to a SU is likely to produce weight gain and increase his hypoglycemia risk. A FDC of metformin XR plus saxagliptin (1000 mg/2.5 mg) is available to maintain Jim's current, successful regimen while reducing his pill burden. The clinician recommends Jim switch to metformin XR plus saxagliptin (1000 mg/2.5 mg), taking 2 tablets daily at supper (total dose: 2000 mg/5 mg).

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