

Type 2 Diabetes: Treatment Strategies for Optimal Care

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Faculty

John J. Whyte, MD, MPH, is currently the Chief Medical Officer at WebMD. In this role, he leads efforts to develop and expand strategic partnerships that create meaningful change around important and timely public health issues. Previously, Dr. Whyte was the Director of Professional Affairs and Stakeholder Engagement at the FDA's Center for Drug Evaluation and Research and the Chief Medical Expert and Vice President, Health and Medical Education at Discovery Channel, part of the media conglomerate Discovery Communications. (A complete biography appears at the end of this course.)

Faculty Disclosure

Contributing faculty, John J. Whyte, MD, MPH, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Division Planners/Director Disclosure

The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for all physicians, physician assistants, pharmacists, and pharmacy technicians involved in the care of patients with type 2 diabetes.

Accreditations & Approvals



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In support of improving patient care, NetCE is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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This activity was planned by and for the healthcare team, and learners will receive 5 Interprofessional Continuing Education (IPCE) credits for learning

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Special Approvals

This activity is designed to comply with the requirements of California Assembly Bill 1195, Cultural and Linguistic Competency.

About the Sponsor

The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

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Disclosure Statement

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Course Objective

The purpose of this course is to provide healthcare providers with the information necessary to develop treatment regimens associated with optimal adherence and provide adequate patient education, counseling, and support.

Learning Objectives

Upon completion of this course, you should be able to:

1. Apply epidemiologic trends in type 2 diabetes mellitus (T2DM) to current practice so at-risk patient populations can be more easily identified, assessed, and treated for T2DM.
2. Utilize knowledge of the pathophysiology and diagnosis of T2DM to create comprehensive treatment strategies that target critical pathways in T2DM development and progression.
3. Identify the therapies for T2DM that are supported by contemporary evidence and are in adherence with current guideline recommendations.
4. Discuss the risks and benefits of tight glycemic control when setting and achieving A1c targets in patients with T2DM.
5. Describe strategies to improve patient adherence to T2DM medication by developing treatment regimens associated with optimal adherence and providing adequate patient education, counseling, and support.

Pharmacy Technician Learning Objectives

Upon completion of this course, you should be able to:

1. Outline the epidemiology, pathophysiology, and diagnosis of type 2 diabetes mellitus (T2DM) to current practice so at-risk patient populations can be more easily identified, assessed, and treated for T2DM.
2. Evaluate the therapies used to manage T2DM, including the importance of patient adherence.



Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Diabetes mellitus describes a group of metabolic diseases that cause prolonged, elevated blood glucose levels. This condition affects approximately 37.3 million Americans, or 11.3% of the U.S. population [1]. Although there are several types of diabetes (including type 1 or insulin-dependent diabetes and gestational diabetes), type 2 diabetes mellitus (T2DM) comprises 90% to 95% of all cases [2; 3].

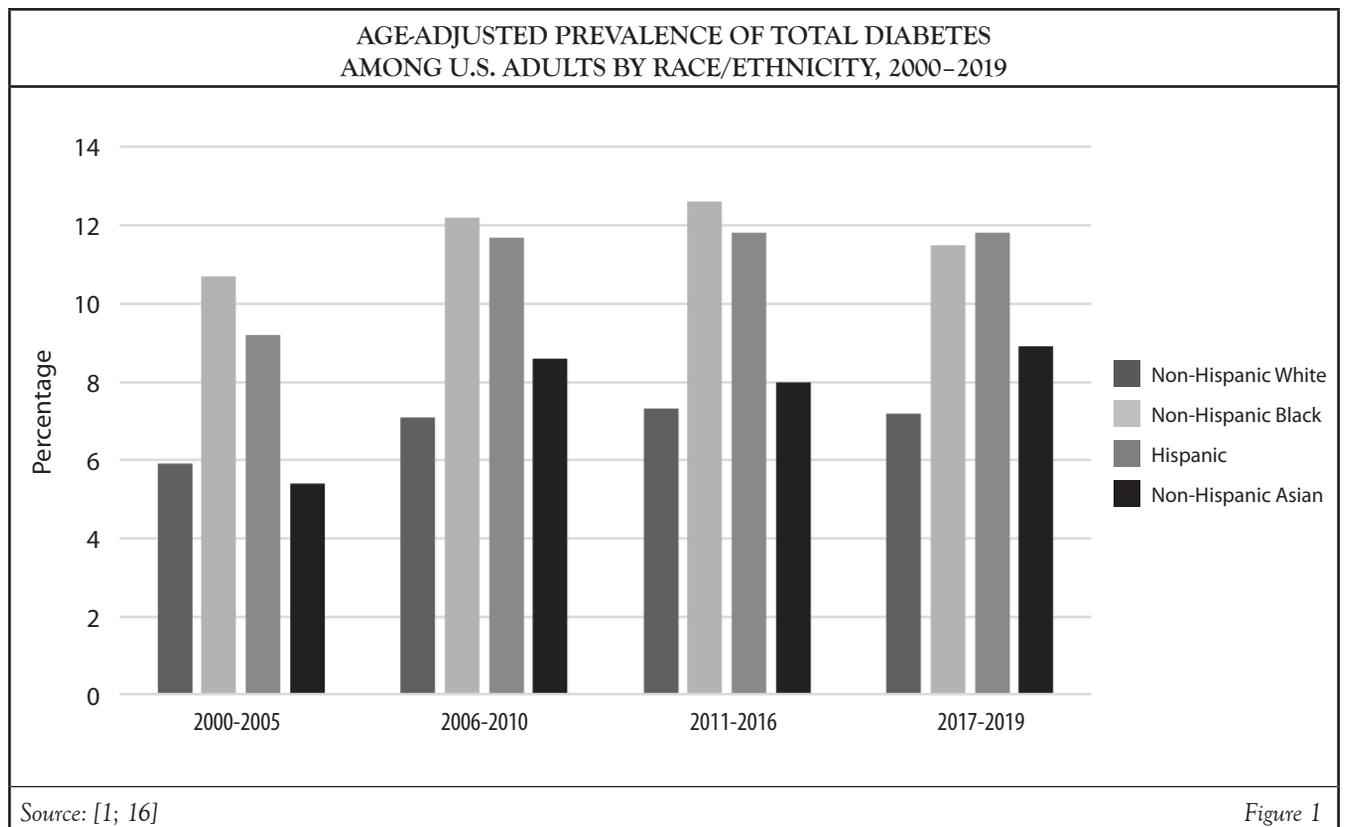
The impact of T2DM is shocking. In 2020, it was the eighth leading cause of death, was the underlying cause of an estimated 102,188 deaths, and was identified as a contributing factor to an additional 282,810 deaths in the United States [1]. Much of the morbidity and mortality of T2DM results from the numerous complications associated with the disease, including heart disease, stroke, elevated blood pressure, blindness, kidney disease, and neuropathy [1]. These conditions contribute to a total U.S. cost of diabetes of \$327 billion, including \$237 billion in direct medical costs and \$90 billion in indirect costs such as disability, work loss, and premature mortality [1]. The economic burden of T2DM is paralleled by an equally substantial personal and social burden; T2DM is associated with significant decreases in health-related quality of life [4]. Given the extensive negative impact of T2DM, it is critical that healthcare providers optimize treatment of this condition to minimize its negative effects on morbidity, mortality, and quality of life.

EPIDEMIOLOGY OF TYPE 2 DIABETES

INCIDENCE, PREVALENCE, AND TRENDS

Trends in T2DM have rapidly changed in the past 50 years, with a sharp increase in prevalence and incidence seen in the early 1990s and leveling out in the late 2000s. While the prevalence, or total number of existing cases, of T2DM continues to rise, the incidence, or rate of new cases of diagnosed T2DM, has been declining since 2008 [5]. Rates of incidence in 1990 were 0.32% of the total adult population, increasing to 0.88% in 2008, slightly decreasing to 0.71% in 2012, and continuing to drop to 0.57% in 2019 [1; 5]. Additional data are needed to determine the cause for the decline and if the incidence will continue to decrease.

The prevalence of T2DM is still increasing, but at a much slower pace than seen in previous decades; this slower rate is thought to be in part due to improved self-management techniques and healthcare services, resulting in patients living longer [5]. One study illustrates the upward trend, noting that the prevalence of diabetes among U.S. adults increased 74% between 1976–1980 and 1999–2004, from 5.08% to 8.83% [6]. In the United States, the crude prevalence of diagnosed diabetes in adults (age ≥18 years) increased from 7.1% in 2001–2004 to 10.1% in 2017–2020 [7]. In 2010, researchers estimated that the U.S. prevalence of diabetes could be as high as 28% of the total population by 2050, but based on updated trends of diabetes, newer estimates using similar methods estimate that the prevalence of diabetes will be approximately 18% in 2060 [8; 9].



Several causes for the extreme increase in incidence of T2DM in the late 20th century have been noted. First, the U.S. population is expanding annually, resulting in an increase in the number of people with T2DM [10]. Second, rising rates of overweight and obesity correlate with the rising incidence of T2DM, as these factors have a positive association [5; 11]. Rates of obesity were 15% in 1980, 23% in 1994, 31% in 2000, 35% in 2011–2012, and more than 42% in 2017–2018 [5; 12; 13]. Among those with diabetes, 89.8% of patients are overweight or obese, with 45.8% being obese (body mass index [BMI] >30 kg/m² to ≤39.9 kg/m²) and 16.2% being classified as severely obese (BMI >40 kg/m²) [1; 6]. Third, because T2DM disproportionately affects elderly individuals, rising rates of T2DM are anticipated to reflect the steadily growing population of adults 65 years of age and older [10; 14]. It has also been observed that T2DM appears to be occurring at a greater frequency in younger adults. Between 1988–1994 and 1999–2000, the mean age at diag-

nosis of T2DM decreased from 52 years to 46 years, and in 2015, more than one-half of new cases were among adults 45 to 64 years of age [5; 15]. Rates of incidence, both increasing and decreasing, can be attributed to changing diagnostic criteria, improved physician recognition of T2DM, and increased public awareness, making additional research necessary to determine if changes in incidence rates are due to prevention and treatment strategies or if the rates reflect a shifting trend toward earlier onset of T2DM [15].

DISPARITIES

T2DM is marked by a number of disparities among affected groups, most notably within specific racial and ethnic populations. For example, while the number of non-Hispanic Whites in the United States with T2DM far exceeds the number of non-Hispanic Blacks with this condition, the percentage of non-Hispanic Blacks with T2DM (11.5%) is significantly greater than that of non-Hispanic Whites (7.2%) (**Figure 1**) [1; 16]. Hispanic Americans also

appear to be disproportionately affected by T2DM, with studies indicating rates of T2DM to be significantly higher in this population compared to non-Hispanic Whites (11.8% and 7.2%, respectively) [1]. Asian Americans have a slightly higher rate (8.9%) compared to non-Hispanic Whites (7.2%) [1]. In addition, the group reporting the largest percentage of T2DM, at 14.5% of the total adult population, is American Indians and Alaska Natives, with rates ranging from 6.0% among Alaska Natives to as high as 22.2% among American Indians located in certain areas of the Southwest [1]. Increasing numbers of members of high-risk minority groups in the United States contribute to the overall projected rise of T2DM [8]. Therefore, targeting these populations for prevention, intervention, and education is a strategy that can be employed to mitigate the impact of T2DM across the nation.

PATHOPHYSIOLOGY OF TYPE 2 DIABETES

RISK FACTORS

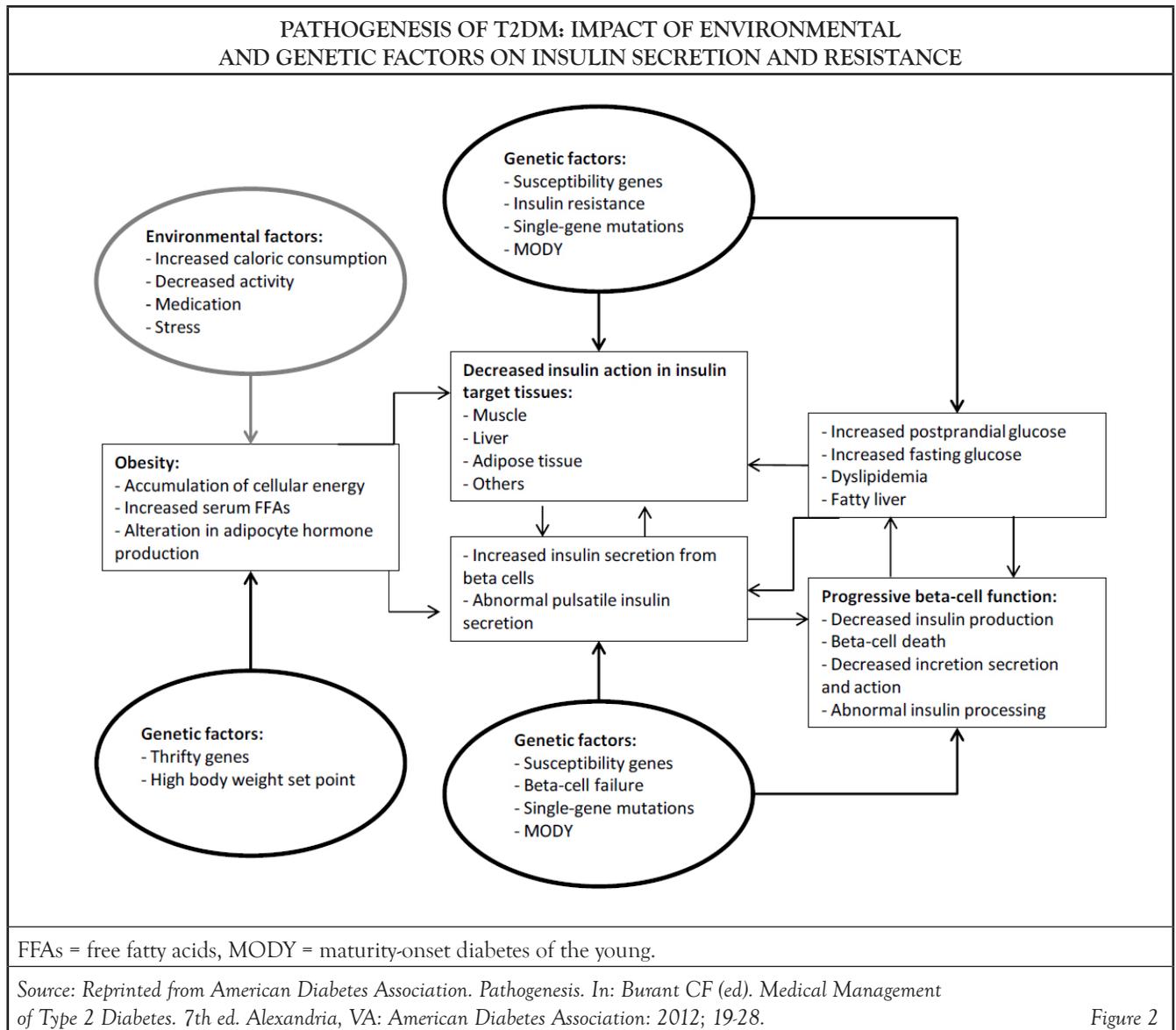
A number of predisposing risk factors have been attributed to the development of T2DM, most notably obesity, which affects cellular metabolism, serum free fatty acids, and adipocyte hormone production (**Figure 2**) [17; 18; 19]. Other environmental factors, including poor diet (evidenced by increased caloric intake as well as decreased food quality) and decreased activity, amplify these effects, as can certain medications and ongoing stress [17; 20]. However, these factors alone are not adequate to initiate T2DM; certain genetic characteristics must also be present. To date, a large number of loci possessing common variants have been implicated in diabetes susceptibility, aided in great part by genome-wide association—a hypothesis-generating approach directed at linking new loci with a disease or trait of interest (in this instance, T2DM) [21]. The exact combination of genetic and environmental factors that generates T2DM is as yet unknown, but research continues to elucidate potential contributors.

IMPAIRED INSULIN SECRETION

Impaired insulin secretion is a key mechanism in the development of T2DM. The framework for this process is built on the understanding that insulin is secreted from beta cells and hyperglycemia occurs when beta-cell secretion of insulin is inadequate relative to the glucose load [22]. In healthy individuals, glucose ingestion (and resultant increase in plasma glucose concentration) triggers the production and release of insulin by pancreatic beta cells [22]. In those with T2DM, insulin response to glucose declines as a result of a functional beta-cell deficiency [23]. This defect has been demonstrated by findings that islet function appears to be approximately 50% of normal at the time of diagnosis and is supported by data from the United Kingdom Prospective Diabetes Study (UKPDS), in which patients who achieved beta-cell function greater than 55% with sulfonylurea monotherapy were less likely to require additional therapy to maintain glycemic targets [24]. Thus, it is now understood that insulin sensitivity is inversely and proportionally related to beta-cell function [24]. These processes are further exacerbated when the inability of the pancreas to adapt beta-cell mass to insulin demand (referred to as pancreas plasticity) results in a decrease in functional beta-cell mass [17]. Studies have revealed an approximate 40% reduction in beta-cell mass in patients with impaired glucose tolerance and a 60% reduction in beta-cell mass in patients with T2DM compared to healthy individuals [24].

THE INCRETIN EFFECT

Incretin hormones, hormones released from gut endocrine cells during meals, also play a significant role in insulin secretion [25]. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) may be responsible for as much as 70% of postprandial insulin secretion in healthy individuals, but demonstrate severely reduced or even absent effects in those with T2DM, often referred to as the incretin effect. This incretin effect is believed to contribute to the impaired insulin regulation and glucagon secretion that are the hallmarks of T2DM, and studies have demonstrated that



improved glycemic control in patients with T2DM partially restores the impaired action of GLP-1 and GIP [17].

INSULIN RESISTANCE

Another central mechanism of T2DM is insulin resistance, which is characterized by the failure of insulin to decrease plasma glucose levels through hepatic glucose suppression and stimulation of glucose uptake in skeletal muscle and adipose tissue [22]. Consequently, inefficient glucose utilization is replaced by cellular utilization of fats and proteins.

Factors that contribute to insulin resistance are complex and may include defective insulin-mediated cell signaling pathways, decreased muscle glycogen syntheses, and reduced numbers of skeletal muscle, liver, and adipose tissue insulin receptors (particularly in obese individuals). In many cases, insulin resistance may be the earliest detectable marker for T2DM [22]. Patients who transition from normal glucose tolerance to T2DM typically experience a 40% decrease in insulin sensitivity, which is further accentuated by chronic hyperglycemia and elevated free fatty acids.

HEPATIC GLUCOSE OUTPUT

An additional regulator of glucose homeostasis is the liver, which is involved in several processes, including hepatic glucose output/uptake and insulin clearance [26]. In healthy individuals, peripheral glucose uptake is equal to circulatory glucose input from the liver, gut, and kidney [26]. The hyperglycemia of T2DM is the result of abnormally high hepatic glucose output stemming from hepatic insulin insensitivity (unlike healthy individuals, in which hyperinsulinemia would suppress hepatic glucose output) [26]. This increased hepatic glucose output closely correlates with the severity of fasting hyperglycemia. Although the postabsorptive levels of chronic hyperinsulinemia observed in mild hyperglycemia offset hepatic insulin resistance and maintain normal hepatic glucose output, moderate fasting hyperglycemia is associated with significant increases in hepatic glucose output [22].

ADIPOCYTE DYSFUNCTION

Adipocyte dysfunction has been implicated in abnormal metabolism and altered fat disposition, an important pathway of glucose intolerance in T2DM [22]. Excessive caloric intake causes adipocytes to undergo excessive hypertrophy, resulting in adipocyte dysfunction and adipose tissue endocrine and immune reactions [27]. As fat accumulates (with preference to the abdominal-perivisceral region), excessive free fatty acids are released into the portal system [27]. This, combined with the resistance of fat cells to insulin's antilipolytic effects, induces hepatic/muscular insulin resistance and impairs insulin secretion—disturbances that are referred to as lipotoxicity [22]. This phenomenon also causes fat cells to produce excessive amounts of insulin resistance-inducing, atherosclerotic-provoking, and inflammatory cytokines (inducing a state of chronic, low-grade inflammation). It also diminishes fat cells' ability to secrete adequate amounts of insulin-sensitizing adipocytokines [22; 27]. All of these effects contribute to the development of insulin resistance, impaired insulin secretion, and ultimately, T2DM.

DIAGNOSIS OF TYPE 2 DIABETES

EVOLVING ROLE OF GLYCATED HEMOGLOBIN (A1C)

Diagnosis of T2DM primarily focuses on glycated hemoglobin (A1c), a shift from historical methods of assessing fasting plasma glucose (FPG) or the two-hour value derived from the 75-gram oral glucose tolerance test (OGTT) [28]. This method of T2DM diagnosis was recommended in 2009 by an international expert committee comprised of representatives from the American Diabetes Association (ADA), the International Diabetes Federation (IDF), and the European Association for the Study of Diabetes (EASD). The recommendation was based on epidemiologic data demonstrating a corresponding relationship between A1c, FPG, and two-hour plasma glucose (PG) thresholds. A1c offers several advantages over FPG and OGTT, such as improved patient convenience, greater stability, and less daily deviations resulting from stress and illness. However, this test is more costly and has limited availability worldwide. Moreover, limited (controversial) data suggest that glycation rates can vary according to race. Perhaps most importantly, A1c results do not 100% correlate with FPG and the two-hour PG test [28]. Still, the reduced sensitivity of A1c is generally believed to be offset by the benefits of enhanced practicality convenience, thus the recommendation from the ADA, IDF, and EASD.

DIAGNOSTIC CRITERIA

According to the ADA, a diagnosis of T2DM can be confirmed in patients whose A1c level is 6.5% or higher. T2DM can also be diagnosed with FPG ≥ 126 mg/dL, two-hour PG ≥ 200 mg/dL during an OGTT, or random plasma glucose ≥ 200 mg/dL in patients with classic symptoms of hyperglycemia or hyperglycemia crisis [28]. Prediabetes—a condition in which glucose levels are below diagnosis criteria but higher than a normal range—can also be diagnosed in those with FPG 100–125 mg/dL, two-hour PG 140–199 mg/dL in OGTT, or A1c level of 5.7% to 6.4%, although the World Health Organization and several other diabetes groups define prediabetes at a FPG of 110 mg/dL [28].



The Institute for Clinical Systems Improvement recommends diagnosing a patient with type 2 diabetes through the use of an A1c test with a threshold $\geq 6.5\%$, fasting plasma glucose ≥ 126 mg/dL or a two-hour plasma glucose ≥ 200 mg/dL on a

75g oral glucose tolerance test. Additionally, if a patient has symptoms of hyperglycemia and casual plasma glucose ≥ 200 mg/dL, diabetes may be diagnosed.

(<https://www.icsi.org/wp-content/uploads/2019/02/Diabetes.pdf>. Last accessed February 11, 2022.)

Strength of Recommendation/Level of Evidence:
Strong/Low

In asymptomatic patients, T2DM testing should be considered in adults of any age with a BMI ≥ 25 kg/m² (or ≥ 23 kg/m² in Asian Americans) who have one or more additional risk factors for diabetes. Those without risk factors should undergo testing beginning at 45 years of age. Because as much as one-quarter of Americans, and nearly one-half of Asian and Hispanic Americans, with diabetes may be undiagnosed, efforts are underway to assess the efficacy of prediabetes identification in preventing T2DM [28].

TREATMENT OPTIONS IN TYPE 2 DIABETES

Several specialty organizations, including the American College of Endocrinology (ACE), the American Association of Clinical Endocrinologists (AACE), and the ADA, have published position papers addressing the standards of care and approach to therapy for patients with diabetes [28; 29; 30; 31]. The American College of Physicians (ACP), in a practice guideline published in 2012, and updated in 2017, provides a good overview of clinical considerations and recommendations for oral therapy (*Table 1*) [32]. These groups are in agreement that effective management of T2DM requires careful attention to nonpharmacologic and pharmacologic modalities of therapy combined with patient education and self-management training.

LIFESTYLE MODIFICATION

Diet

Despite skepticism by some clinicians, providing dietary information to patients has been found to be an effective intervention. The U.S. Preventive Services Task Force, an independent panel of experts in primary care and prevention that systematically reviews the evidence of effectiveness and develops recommendations for clinical preventive services, found good evidence that medium- to high-intensity counseling interventions can produce medium-to-large changes in average daily intake of core components of a healthy diet (including saturated fat, fiber, fruits, and vegetables) among adult patients at increased risk for diet-related chronic disease [33]. Instead of counseling patients about specific diets, it is more useful to focus on healthy eating.

In a retrospective review of 125 obese patients (who also met the criteria for metabolic syndrome) enrolled in a weight-loss program, a mean weight loss of 15% of initial body weight resulted in an average 19 mg/dL decrease in fasting glucose [34]. Weight reduction of as little as 5% body weight (often as little as 5 to 10 pounds) is associated with lower incidence of diabetes and related complications.

Reviewing and modifying diet is one of the most important steps in helping patients manage diabetes and, if indicated, lose weight. Strong evidence shows that eating patterns that are low in calorie density improve weight loss and weight maintenance and moderate evidence suggests that healthy eating patterns are associated with a reduced risk of T2DM in adults [35]. The U.S. Department of Agriculture Food Patterns and the Dietary Approaches to Stop Hypertension (DASH) Eating Plan are examples of eating patterns that are low in calorie density. In addition, patients with diabetes are advised to consume less sodium per day (less than 1,500 mg) than the maximum recommendation for healthy adults [35].

**AMERICAN COLLEGE OF PHYSICIANS RECOMMENDATIONS
AND CLINICAL CONSIDERATIONS FOR ORAL MEDICATION IN T2DM**

Recommendations

ACP recommends that clinicians prescribe metformin to patients with type 2 diabetes when pharmacologic therapy is needed to improve glycemic control. (*Grade: strong recommendation; moderate-quality evidence*)

ACP recommends that clinicians consider adding either a sulfonylurea, a thiazolidinedione, an SGLT-2 inhibitor, or a DPP-4 inhibitor to metformin to improve glycemic control when a second oral therapy is considered. (*Grade: weak recommendation; moderate-quality evidence*)

ACP recommends that clinicians and patients select among medications after discussing benefits, adverse effects, and costs.

Clinical Considerations

Nonpharmacologic therapy includes dietary modifications, regular exercise, lifestyle modifications, and weight loss.

Management of T2DM often involves pharmacologic and nonpharmacologic therapies and includes patient education, evaluation, patient self-management for microvascular and macrovascular complications, treatment of hyperglycemia, and minimization of cardiovascular and other long-term risk factors.

Initiation of pharmacologic therapy is an important approach for the effective management of T2DM when weight loss or lifestyle modification fails.

Metformin effectively decreases glycemic levels when used in monotherapy and combination therapy with a second agent. Metformin also reduces body weight.

Although combination therapy reduces hemoglobin A1c levels more effectively than monotherapy, it is associated with more adverse events.

The DPP-4 inhibitors saxagliptin and alogliptin may increase the risk for heart failure, especially in patients who already have heart or kidney disease.

Metformin is considered safe for patients with mild chronic kidney disease and some patients with moderate kidney impairment (but is contraindicated in those with an estimated glomerular filtration rate <30 mL/min/1.73 m²).

Source: [32]

Table 1

As a simple rule, to induce weight loss, patients' caloric intake should be reduced by 500–1,000 calories per day from the current level. This reduction will produce the recommended weight loss of one to two pounds per week in most patients [35].

Because of the complexities associated with diet-related behavior and because meal planning is so important to diabetes management, medical nutrition therapy provided by a registered dietitian is advocated [28; 30; 36]. Medical nutrition therapy is defined as nutritional diagnostic, therapy, and counseling services for the purposes of disease management, which are furnished by a registered dietitian or nutrition professional. Medical nutrition therapy, when provided by a registered dietitian, is reimbursed by the Medicare program [36; 37]. Whenever possible, healthcare providers should be prepared to

work with dietitians as part of an interdisciplinary diabetes care team. Frequently, however, access to a dietician is not feasible for patients whose health-care plans do not cover this service or for those who live in remote geographic areas. In some settings, a nurse may assume responsibility for teaching dietary management to patients with diabetes.

Physical Activity

The primary benefit of exercise to people with diabetes is that it has been found to increase glucose utilization by the tissues, thereby lowering blood glucose concentration [38]. In some people with T2DM, a regular program of physical activity can increase insulin sensitivity to the degree that medications can be reduced or discontinued. Because people with diabetes are at increased risk for heart disease, exercise has the added benefit of its favor-

able effect on cardiovascular status. The benefits of regular exercise to people with diabetes can be summarized as:

- Improved insulin sensitivity
- Reduction in body fat and weight
- Reduction in incidence of cardiac disease
- Improved lipid profile
- Increase in high-density lipoproteins
- Improved control of hypertension
- Improved self-esteem
- Reduced psychologic stress

The ADA, along with other authorities, recommends at least 150 minutes of moderate intensity aerobic exercise per week [38; 39]. Adults with T2DM should engage in both aerobic and resistance training for optimal glycemic outcomes. Because reduction in insulin resistance from a single bout of exercise lasts for 24 to 72 hours afterward, there should be no more than two consecutive days between exercise sessions [38].

It is important to inform patients that assuming a more active lifestyle does not necessarily mean that they must adopt a structured exercise program. Experts advocate the benefits of incorporating moderate-intensity exercise into everyday activities. For example, making it a habit to use stairs instead of an elevator on a regular basis contributes to a more active lifestyle with cardiovascular benefits. Likewise, keeping active by doing such routine tasks as walking the dog, raking leaves, or washing the car can also be beneficial. It is suggested that, if done in increments lasting at least 10 minutes per session with an accumulation of 30 minutes or more per day, these types of activities can increase overall health and fitness [38; 39].

Although physical activity can provide health benefits to a variety of patients, individuals with diabetes should be advised to seek a physician's approval before beginning an exercise program if they plan to engage in something more vigorous than brisk

walking [38]. Several comorbidities associated with diabetes must be considered prior to recommending a more strenuous exercise program to ensure the program is safe and enjoyable. The role of routine stress testing before beginning an exercise program is controversial [38].

Patients who use insulin or sulfonylureas are at risk for hypoglycemia during or after exercise if proper adjustments are not made. Several factors influence the blood glucose response to exercise, including the timing, amount, and intensity of the exercise. Patients at risk for hypoglycemia are advised to carefully monitor their blood glucose before and after exercise to determine their response to a particular activity. Adjustments to medications and/or food intake can then be made prior to exercise based upon these findings.

PHARMACOLOGIC TREATMENT CONSIDERATIONS

Treatment of T2DM should be administered with the goal of conserving beta-cell function and mass, delaying disease progression, and preventing complications [2]. Due to the heterogenic nature of T2DM, treatment of this condition should not be approached with a "one-size-fits-all" mindset [30]. Instead, therapeutic selection should be individualized based on the patient's specific characteristics. A1c level is typically used to monitor long-term glycemic control and can help to indicate treatment inefficiency and guide therapeutic selection and adjustment [2]. Target A1c levels vary according to organization, but most recommend an A1c level of either $\leq 7\%$ or $\leq 6.5\%$. (Further discussion of A1c targets is provided in the next section.) Although lifestyle modification, such as weight reduction and increased physical activity, continues to be the cornerstone of diabetes therapy, this approach may not sufficiently control A1c depending upon the extent of disease progression. When this is the case, a number of different pharmacotherapies can be used either alone or together to help patients achieve their target A1c level (**Table 2**) [28; 29].

PROFILES OF ANTIDIABETIC MEDICATIONS											
Benefits/ Risks	Medications										
	MET	GLP-1 RA	SGLT-2i	DPP-4i	AGi	TZD	SU/GLN	COLSVL	BCR-QR	Insulin	PRAML
Hypoglycemia	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	SU: Moderate to severe GLN: Mild	Neutral	Neutral	Moderate to severe	Neutral
Weight	Slight loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Neutral	Neutral	Gain	Loss
Renal/GU	Contra- indicated if eGFR <30 mL/ min/ 1.73m ²	Exenatide not indicated CrCl<30 Possible benefit of liraglutide	Not effective with eGFR <45 Genital mycotic infections Possible benefit of empa- gliflozin	Dose adjust- ment necessary (except with lina- gliptin) Effective in reducing albumin- uria	Neutral	Neutral	More risk of hypogly- cemia	Neutral	Neutral	More risk of hypogly- cemia	Neutral
GI symptoms	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate
CHF	Neutral	Neutral	Neutral	Neutral ^c	Neutral	Moderate	Neutral	Neutral	Neutral	CHF risk	Neutral
ASCVD	Neutral	Neutral ^a	Possible benefit ^b	Neutral	Neutral	May reduce stroke risk	Possible ASCVD risk	Benefit	Safe	Neutral	Neutral
Bone	Neutral	Neutral	Mild fracture risk	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral	Neutral	Neutral
Ketoacidosis	Neutral	Neutral	DKA can occur in various stress settings	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

AGi = alpha-glucosidase inhibitor; ASCVD = atherosclerotic cardiovascular disease; BCR-QR = bromocriptine-QR; CHF = chronic heart failure; COLSVL = colesevelam; DPP-4i = DPP-4 inhibitor; eGFR = estimated glomerular filtration rate; GI = gastrointestinal; GLN = secretagogues (meglitinides); GLP-1 RA = GLP-1 receptor agonist; GU = genitourinary; MET = metformin; PRAML = pramlintide; SGLT-2i = Sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione.

^aLiraglutide is FDA approved for prevention of major adverse cardiovascular events.
^bEmpagliflozin is FDA approved to reduce cardiovascular mortality. Canagliflozin is shown to reduce major adverse cardiovascular events.
^cPossible increased hospitalizations for heart failure with alogliptin and saxagliptin.

Source: Reprinted from Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm—2020 executive summary. *Endocr Pract.* 2020;26(1):107-139, with permission from the American Association of Clinical Endocrinologists.

Table 2

When selecting therapy, it is important to remember several points: duration of disease correlates with decreased beta-cell function, the desired degree of A1c decrease can help to guide therapeutic selection, and side effect profiles of T2DM medications vary substantially and should be incorporated into treatment decisions [2]. It is also important to consider

the patient’s preferred route of administration and any comorbid conditions (e.g., obesity, cardiovascular disease, depression, or osteoporosis) [2]. After these factors are assessed, treatment selection can more successfully address both treatment goals and patient preferences.

Biguanides

Biguanides, specifically metformin, are the most widely used first-line T2DM medication. Both the AACE/ACE and the ADA/EASD recommend metformin as first-line therapy in most patients with T2DM, except where contraindicated [29; 30]. Biguanides inhibit expression of hepatic gluconeogenic genes, thereby reducing fasting plasma glucose levels [2]. Metformin offers several benefits, including an oral route of administration (to be dosed once or twice daily) and a weight-neutral, non-hypoglycemia-inducing side-effect profile [30]. Metformin may also provide some cardiovascular benefit, although a meta-analysis does not support this claim [30; 40]. In addition, generic formulations of metformin are available, which may be preferred in patients who are unable to afford the cost of this agent due to high co-pays or lack of prescription insurance [2].



According to the American Diabetes Association, metformin is the preferred initial pharmacologic agent for the treatment of type 2 diabetes.

(<https://www.acpjournals.org/doi/10.7326/M20-2470>. Last accessed February 11, 2022.)

Level of Evidence: A (Well-designed clinical trials or high-quality meta-analyses)

However, metformin is associated with gastrointestinal side effects and should be avoided in patients at risk for lactic acidosis (rare) [30]. Another drawback of metformin lies in its clearance through the kidneys. Historically, one of the most important risk factors for elevated metformin concentrations (leading to lactic acidosis) was the inability to clear the drug efficiently [41]. As a result, there was a long-standing FDA warning contraindicating metformin in men and women with serum creatinine concentrations ≥ 1.5 mg/dL and ≥ 1.4 mg/dL, respectively. However, in 2016, after a review of literature, the FDA

removed this warning and labeling now indicates that metformin can be safely used in those with mild kidney function impairment and in some patients with moderate impairment [29; 30; 41; 42]. Because this treatment is typically unable to maintain long-term glycemic control throughout the duration of the disease, additional therapy is typically necessary [2]. Metformin can be easily combined with other T2DM agents, including secretagogues, dipeptidyl peptidase-4 (DPP-4) inhibitors, thiazolidinediones (TZDs), GLP-1 agonists, and insulin.

Secretagogues

Secretagogues (meglitinides), one of the oldest classes of oral antidiabetic agents, work to stimulate insulin release through the closure of adenosine triphosphate-sensitive potassium channels on pancreatic beta cells [43]. Thus, they are most useful in cases where beta-cell function is still detectable [2]. Despite the fact that secretagogues quickly and effectively lower A1c, they are not considered a first-line treatment due to the short-term sustainability of this effect [2].

The various secretagogues have different profiles. Sulfonylureas are relatively long-acting secretagogues that can decrease both fasting plasma and postprandial glucose levels, whereas glinides are short-acting secretagogues that decrease postprandial glucose levels only [2]. These oral agents are intended to be taken with meals; the morning meal if dosed daily, or the morning and evening meals (or bedtime with food) for twice-daily dosing [2]. Both types of secretagogues are associated with modest weight gain and risk of hypoglycemia, although glinides may carry a lower risk of the latter [29]. In addition, some studies have suggested these agents may be associated with a secondary failure rate in excess of other T2DM drugs resulting from exacerbation of islet dysfunction [30]. The central benefit of secretagogues is cost. These agents have generic equivalents, and many are available in combination with other drugs, such as metformin or the TZD pioglitazone [2].

Thiazolidinediones

TZDs enhance glucose uptake in peripheral tissue, improving insulin sensitivity in skeletal muscle (thereby lowering both fasting plasma and postprandial glucose levels) and reducing hepatic glucose production [2; 30]. The beneficial effects of TZDs on blood glucose levels appear to be more durable and longer lasting compared to metformin and the secretagogues [2]. This drug class has been found in clinical trials to reduce visceral adipose tissue and carotid intima-media thickness [2; 44; 45]. It has also demonstrated a modest benefit on cardiovascular events as a secondary outcome [30]. It is important to note that TZDs require the presence of insulin (either endogenous or exogenous) for adequate glucose uptake into peripheral tissue, and beneficial effects are not typically observed until four to eight weeks of therapy [2]. Still, when used as a second- or third-line therapy, TZDs can be highly effective, especially when used early in the disease course and combined with other antidiabetic agents. Pioglitazone is now the only TZD that is approved for T2DM. In 2010, use of the TZD rosiglitazone was restricted by the FDA after studies linked the drug to increased risk of myocardial infarction [46; 47]. The agency continued to monitor the drug's safety, and, in 2013, removed several of the prescribing and dispensing restrictions. In 2015, the FDA removed the final remaining restrictions placed on the use of rosiglitazone [48]. The weight gain that is associated with pioglitazone is counter-balanced by a low risk for hypoglycemia and an oral dosing scheme that does not necessarily require food [2]. Pioglitazone has also been associated with an increased risk for bladder cancer. Although this is still being studied, the FDA recommends that the use of pioglitazone be avoided in patients with active bladder cancer [46; 49].

GLP-1 Agonists

Because GLP-1 release in the gut has been found to play a key role in postprandial insulin secretion, GLP-1 agonists have been developed to help stimulate insulin and amylin secretion from pancreatic beta cells in a glucose-dependent fashion and suppress postprandial glucagon secretion, leading to decreased hepatic gluconeogenesis, slowed gastric emptying, and consequentially, increased satiety [2; 30]. These agents provide 6 to 10 times more pharmacologic concentrations of GLP-1 than the endogenous hormone. The reduction in appetite caused by GLP-1 agonists offers an advantage of weight loss, which is modest in most cases but can be significant in some individuals [29]. However, use of this agent can be limited by nausea and vomiting, particularly during the early phase of treatment, as well as by its injectable route of administration and the potential for increased risk of pancreatitis [29].

There are long-acting (liraglutide, exenatide, albiglutide, dulaglutide) and short-acting (exenatide, lixisenatide) GLP-1 agonists. Long-acting agents can be dosed once weekly, while short-acting therapies require twice-daily administration with meals [2]. Long-acting GLP-1 agonists appear to help reduce triglyceride levels and free fatty acids, and short-acting GLP-1 agonist use has been associated with a reduced likelihood of cardiovascular events compared to other glucose-lowering agents [2]. These agents are not approved as first-line therapy but are effective in combination with other agents including metformin, pioglitazone, sulfonylureas, and basal insulin (although concomitant use with secretagogues or insulin may increase the risk of hypoglycemia) [2].

DPP-4 Inhibitors

DPP-4 inhibitors (alogliptin, saxagliptin, linagliptin, sitagliptin) also target GLP-1 and the incretin effect. But unlike GLP-1 agonists, DPP-4 inhibitors restrict DPP-4 to prevent enzymatic inactivation of endogenous GLP-1, thereby prolonging the availability of endogenous GLP-1 and increasing GLP-1 concentrations in the gastrointestinal tract [2]. By inhibiting more than 80% of DPP-4 activity over a 24-hour period, these agents produce an estimated 1.5-to 4-fold increase in active postprandial GLP-1 levels, resulting in increased insulin and amylin secretion from beta cells and decreased glucagon secretion and liver glucose production [2]. DPP-4 inhibitors offer many benefits, including oral route of administration (with or without food), low hypoglycemia risk, a weight-neutral profile, and a potential cardiovascular benefit [2]. They are also associated with a lower incidence of nausea and vomiting compared to GLP-1 agonists. However, like TZDs, DPP-4 inhibitors require the presence of insulin (either endogenous or exogenous) for efficacy [2]. These second-or third-line drugs are often used in combination with other agents; they have been studied and are often used with metformin, pioglitazone, sulfonylureas, and basal insulin [2].

Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors

Canagliflozin, the first in the new class of diabetes medications referred to as sodium-glucose co-transporter 2 (SGLT2) inhibitors, was approved by the FDA in 2013, with dapagliflozin and empagliflozin, approved in 2014, ertugliflozin, approved in 2017, and bexagliflozin approved in 2023 [46; 50; 51; 52]. This class acts by inhibiting SGLT2 in the proximal renal tubules, which reduces reabsorption of filtered glucose from the tubular lumen and lowers the renal threshold for glucose. SGLT2 is the main site of filtered glucose reabsorption, and reduction of filtered glucose reabsorption and lowering the renal threshold result in increased urinary excretion of glucose and improved plasma glucose concentra-

tions. The recommended initial dose of canagliflozin is 100 mg once daily prior to the first meal of the day [46; 50]. The dose may be increased up to 300 mg/day, unless the patient has impaired renal function. Dapagliflozin is dosed at 5 mg once daily in the morning and may be increased to 10 mg/day, while empagliflozin is started at 10 mg daily and may be increased to 25 mg per day, if necessary. Ertugliflozin is dosed at 5 mg once daily to a maximum of 15 mg daily [46; 51; 52]. The daily dose of bexagliflozin is 20 mg every morning [46]. These agents are approved for use with diet and exercise to improve the control of T2DM in adult patients. They have been studied for use as monotherapy and in combination with other antidiabetics, including metformin, sulfonylureas, pioglitazone, and insulin [50; 51; 52]. The most common side effects are vulvovaginal candidiasis and urinary tract infection.

An FDA safety review has resulted in new warnings to the labels of all SGLT2 inhibitors about the risks of ketoacidosis and serious urinary tract infections, which could result in hospitalization [53]. The review identified 73 cases of ketoacidosis in patients with type 1 or type 2 diabetes treated with SGLT2 inhibitors between March 2013 and May 2015. In addition, 19 cases of life-threatening blood and kidney infections that started as urinary tract infections were reported between March 2013 and October 2014. The FDA advises that patients should stop taking their SGLT2 inhibitor and seek immediate medical attention if any symptoms of ketoacidosis arise (e.g., dehydration, excessive thirst, excessive or frequent urination). The agency also recommends that healthcare providers assess for ketoacidosis and urinary tract infections in patients with suggestive symptoms, and discontinue the drug and institute treatment promptly if ketoacidosis is suspected [46; 53]. In 2017, the FDA added a boxed warning to canagliflozin due to an increased risk of leg and foot amputation, as confirmed by data from two large clinical trials [54]. In 2018, the FDA issued a warning about rare but serious necrotizing fasciitis of the perineum associated with SGLT2 inhibitor

therapy [55]. In 2020, the FDA approved changes to the prescribing information for SGLT2 inhibitors recommending that they be stopped temporarily before scheduled surgery [56]. Canagliflozin, dapagliflozin, empagliflozin, and bexagliflozin should each be stopped at least three days prior to surgery, and ertugliflozin should be stopped at least four days prior to surgery [56].

Other Non-Insulin Agents

Amylin, or islet amyloid polypeptide, is co-secreted with insulin in the islets of Langerhans of patients with diabetes [57]. Amylin directly targets the brain and indirectly targets the gastrointestinal tract, pancreas, and liver to delay gastric emptying, induce satiety, and suppress postprandial glucagon secretion [2; 46]. Pramlintide is an amylin analogue that works synergistically with insulin to decrease hepatic gluconeogenesis [2; 46; 57]. As an injectable monotherapy, this agent carries a low risk of hypoglycemia. It also imparts weight-loss and cardiovascular benefits [2]. Pramlintide is approved for use as an adjunct to bolus insulin therapy (with or without metformin or sulfonylureas) and is therefore typically used later in the disease course [46].

Dopamine agonists also work directly on the brain to increase dopamine levels, resulting in decreased hepatic glucose output and postprandial glucose levels [2]. Like amylin analogues, dopamine agonists are associated with weight loss and beneficial cardiovascular effects and have little association with hypoglycemia. They, too, are infrequently used as first-or second-line agents, as studies of these agents as combination therapy are limited.

AGIs work in the gastrointestinal tract to decrease postprandial excursions by delaying the absorption of carbohydrates [2]. Due to their side effects (primarily flatulence), these agents are infrequently used in the United States [2; 29].

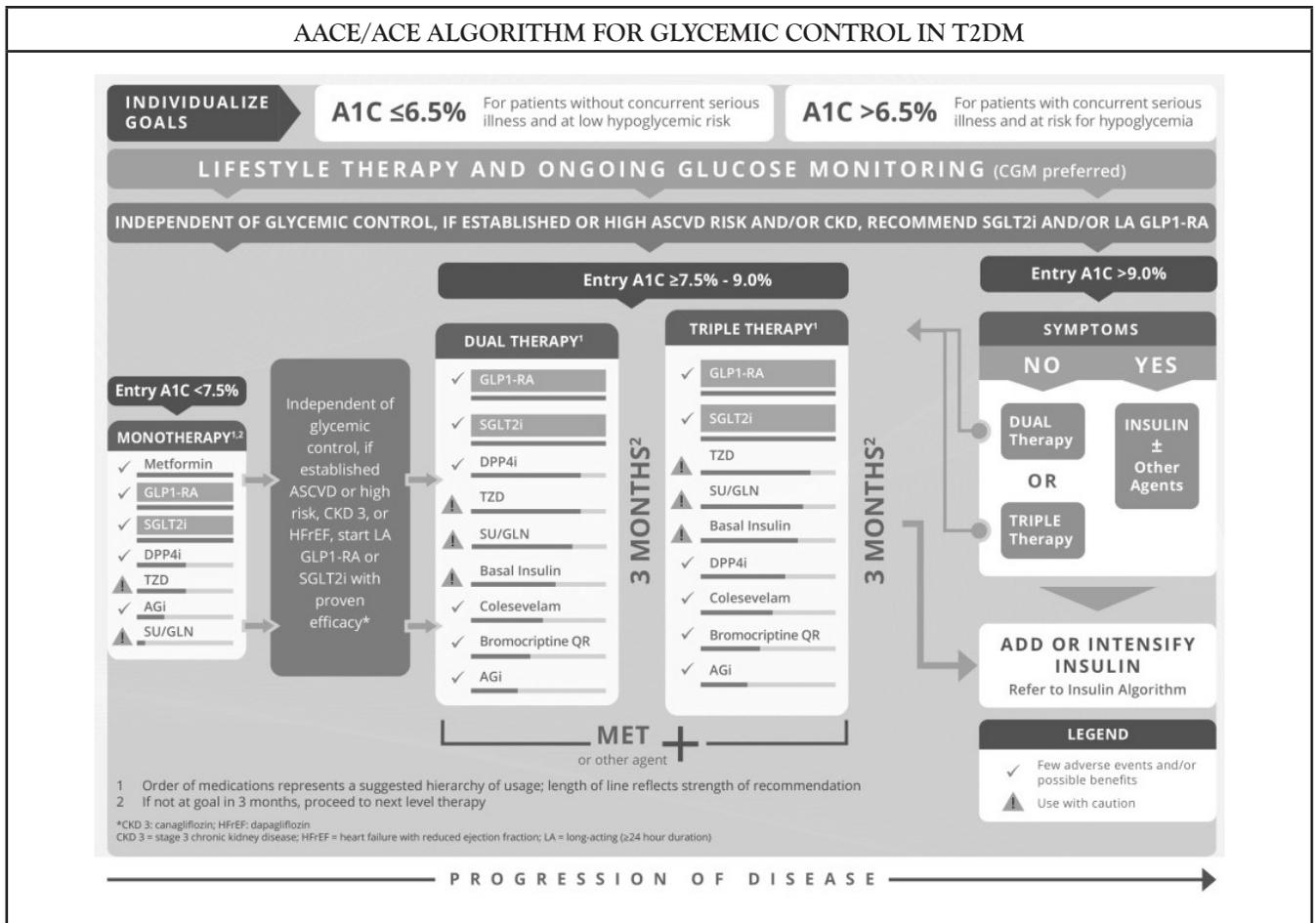
Insulin

Exogenous insulin works much like endogenous insulin in that it causes cells in the liver, muscle, and fat tissue to take up glucose from the blood and store it as glycogen. Due to the progressive nature of T2DM, injectable or inhaled insulin therapy is typically required at some point in the disease course, with the goal of creating as normal a glycemic profile as possible without causing unacceptable weight gain or hypoglycemia [30]. Basal insulin is usually offered first when insulin therapy becomes necessary, as this approach offers relatively uniform insulin coverage over a 24-hour period, with peakless time-action curves producing a more consistent effect [29; 30]. Intermediate-acting, long-acting, and insulin detemir formulations are available, with the latter two offering a slightly lower risk for overnight hypoglycemia and weight gain.

Due to progressive diminution of insulin secretory capacity, prandial insulin therapy with short-acting insulins is typically initiated eventually [30]. These types of insulin provide improved (and more affordable) postprandial glucose control but have more complicated pharmacokinetic profiles. At all times, insulin therapy should be tailored to an individual patient's prevailing glucose trends and dietary/exercise habits.

GUIDELINE RECOMMENDATIONS

The ACE, the AACE, and the ADA have each provided guidelines for the step-wise selection of therapies for T2DM (**Figure 3** and **Figure 4**) [28; 29; 30; 31]. Lifestyle modification (e.g., healthy diet, weight control, increased physical activity) is recommended as a first step in glycemic control, although a consensus statement from the AACE/ACE states that lifestyle optimization efforts should not delay needed pharmacotherapy in higher risk individuals [29]. The AACE/ACE emphasize that minimizing risk of weight gain and promoting weight loss in patients with adiposity-based chronic disease should be a high priority [29].

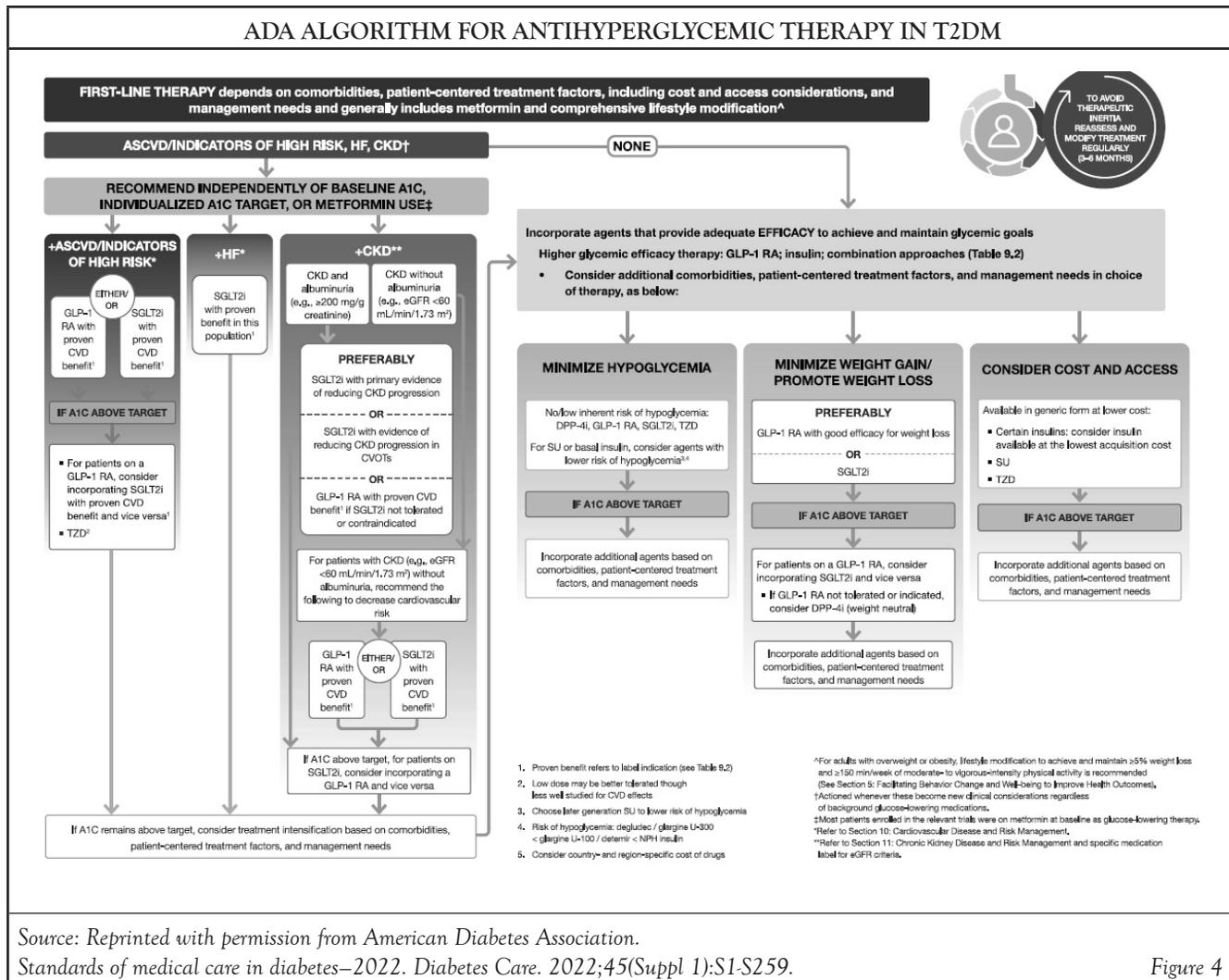


Source: Reprinted from Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm—2020 executive summary. *Endocr Pract.* 2020;26(1):107-139, with permission from the American Association of Clinical Endocrinologists.

Figure 3

Should pharmacotherapy become necessary, metformin should be the initial drug of choice, although an AACE/ACE algorithm denotes that TZDs, sulfonylureas, DPP-4 inhibitors, GLP-1 agonists, or alpha-glucosidase inhibitors (AGIs) can be used alone or together for therapeutic initiation depending on the presenting A1c level and with consideration of other factors [29]. Two- or three-drug combinations with metformin plus other oral

antidiabetes drugs are recommended when first-line therapy is deemed inadequate, with all organizations agreeing that insulin should be reserved for failure of triple combination therapy. To measure efficacy, all groups recommend regular assessment of A1c. Although target A1c levels vary slightly according to organization, all agree that elevated A1c indicates treatment inadequacy and warrants treatment escalation.



1. Proven benefit refers to label indication (see Table 9.2)

2. Low doses may be better tolerated though less well studied for CVD effects

3. Choose later generation SU to lower risk of hypoglycemia

4. Risk of hypoglycemia: degludec / glargine U-300 < glargine U-100 / detemir < NPH insulin

5. Consider country- and region-specific cost of drugs

[†]For adults with overweight or obesity, lifestyle modification to achieve and maintain >5% weight loss and ≥150 min/week of moderate- to vigorous-intensity physical activity is recommended (See Section 5: Facilitating Behavior Change and Well-being to Improve Health Outcomes)

[‡]Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

[§]Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

[¶]Refer to Section 10: Cardiovascular Disease and Risk Management.

^{**}Refer to Section 11: Chronic Kidney Disease and Risk Management and specific medication label for eGFR criteria.

Source: Reprinted with permission from American Diabetes Association. Standards of medical care in diabetes—2022. Diabetes Care. 2022;45(Suppl 1):S1-S259.

Figure 4

ISSUES SURROUNDING TIGHT GLYCEMIC CONTROL

It has been well documented that poor glycemic control is associated with additional disease and economic burden. Uncontrolled blood glucose has been found to impose multiple care requirements, additional healthcare costs, and greater risk of disabling complications such as diabetic retinopathy, chronic kidney disease, and cardiovascular disease [30; 58]. Likewise, reducing A1c levels has been

shown to significantly reduce the risk for microvascular complications. Therefore, it seems reasonable T2DM outcomes should universally improve as A1c decreases. However, some evidence has shown that tight glycemic control, defined as A1c ≤6.5%, may impose additional risks compared to a more modest A1c level of <7.0% [59]. As a result, a divergence in recommended A1c targets has occurred in guideline recommendations, causing confusion and disagreement among providers who care for patients with T2DM.

The AACE recommends an A1c target level of $\leq 6.5\%$ unless contraindicated by specific factors, such as age and hypoglycemia risk [29]. This goal is different than that set forth by the ADA and EASD, which recommend a target A1c of $< 7.0\%$ [30]. In addition, in 2018, the ACP controversially recommended a target A1c of 7% to 8% for most patients with diabetes [60; 61]. The recommendation for tight glycemic control by the AACE is based on data from numerous older trials. The Diabetes Control and Complications Trial, the Epidemiology of Diabetes Interventions and Complications Study, and the UKPDS trial data between 1993 and 2008 are supportive of an A1c target of $\leq 6.5\%$, as are findings from the 2000 Kumamoto Study and the Steno-2 trial by Gaede et al. [62; 63; 64; 65; 66; 67; 68; 69; 70]. Although some of these trials are relatively dated, further evidence was provided by three landmark trials: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, the Action in Diabetes and Vascular disease (ADVANCE) trial, and the VA Diabetes Trial (VADT) [71; 72; 73]. In these studies, lower A1c levels correlated with reduced incidence of microvascular and sometimes macrovascular complications.

Of these studies, the ADVANCE trial provides a particularly strong rationale for tight glycemic control, as it was designed specifically to evaluate the effect of intensive glycemic control on death from cardiovascular disease, nonfatal myocardial infarction or nonfatal stroke, and new or progressing neuropathy or retinopathy [59; 72]. More than 11,000 patients with T2DM were enrolled in this trial, with a median age of 67 years, a median duration of T2DM of 8 years, and a mean A1c of 7.5% upon study entry. Patients were required to have a history of major macrovascular or microvascular disease or at least one risk factor for macrovascular disease. Outcomes of this study revealed no adverse effects of intensive glycemic therapy (with an A1c target of $\leq 6.5\%$). In fact, tight glycemic control was associated with a non-significant trend toward

lower cumulative mortality and a beneficial effect on macrovascular and microvascular complications (when assessed collectively) [59]. Both intensive and standard glycemic control groups also experienced improvements in blood pressure and low-density lipoprotein cholesterol levels.

These findings have been supported by other studies. A 2011 meta-analysis evaluated the effect of intensive glucose-lowering treatment on all-cause mortality, cardiovascular death, and microvascular events in T2DM [74]. In this meta-analysis, intensive therapy was associated with reductions in risk of non-fatal myocardial infarction and microalbuminuria, as well as a 9% reduction in all-cause mortality and a 14% reduction in cardiovascular death, causing authors to conclude that intensive glucose-lowering treatment demonstrated “limited benefit.” In a 2010 meta-analysis assessing the impact of intensive versus standard glucose control on microvascular and macrovascular complications in both type 1 and type 2 diabetes in more than 30,000 patients, intensive glucose control was found to reduce the risk of developing microvascular complications, including retinopathy, nephropathy, and neuropathy, by 25% to 76% [75]. Moreover, intensive control was associated with a 10% to 15% decrease in nonfatal myocardial infarction, particularly in patients with T2DM. Similar results were demonstrated in a separate 2010 meta-analysis studying the effect of intensive glucose control on all-cause and cardiovascular mortality, myocardial infarction, and stroke in T2DM [76]. In this analysis of six reports from four randomized trials including more than 27,000 patients, intensive glucose control (mean A1c: 6.6%) was associated with a 14% reduction in non-fatal myocardial infarction, but it did not affect mortality or the risk for non-fatal stroke. Although two of the studies noted a significantly increased risk of hypoglycemia in intensive glycemic control groups, none concluded that this risk definitively outweighed the benefits of this strategy to lower A1c target [74; 75].

Alternatively, some data challenge the importance of tight glycemic control in T2DM. In the VADT study, no beneficial effect of intensive glycemic control was observed when the entire study population was taken into consideration [59]. In fact, a deleterious effect was observed in association with tight glycemic control in patients who had T2DM for 15 years or more. This is suggestive of a potential “window of opportunity” early in the disease course for intensive control that closes over time [59]. Moreover, in the ACCORD study, the intensively treated group experienced a number of negative effects, including a three-fold increased risk of hypoglycemia and severe hypoglycemia and excessive weight gain—a well-known risk factor for increased mortality [59]. However, it is important to note that in the ACCORD trial, a 1.4% reduction in A1c was achieved within four months in the intensive control group [59]. The more gradual reduction in A1c observed in the ADVANCE trial may have influenced the apparent beneficial effect of intensive glycemic control on outcomes [59]. Still, in the ADVANCE trial, much like in the ACCORD study, excessive weight gain (and associated morbidity and mortality) was positively correlated with intensive glycemic control. Likewise, in a 2011 meta-analysis of 14 clinical trials involving approximately 28,600 patients with T2DM, intensive glycemic control did not appear to significantly impact the relative risk of all-cause or cardiovascular mortality, and study authors were unable to find sufficient evidence for the beneficial effect of intensive control on microvascular outcomes [77]. Given the severe risk of hypoglycemia that was found to accompany intensive glycemic control (with a 30% increased relative risk), authors concluded that intensive glycemic control does not appear to reduce all-cause mortality and that data fail to clearly demonstrate a benefit on cardiovascular mortality, non-fatal myocardial infarction, or microvascular complications. Other questions remain regarding the benefit of intensive glycemic control in T2DM, including duration of follow-up required to demonstrate beneficial effects, extent of influence glycemic control has on outcomes (given the numerous risk factors in T2DM), and extent of influence glycemic control has on pre-existing macrovascular outcomes [59].

Based on these data, it appears that although tight glycemic control may have a beneficial effect on microvascular outcomes and mortality, the risk for hypoglycemia and weight gain that accompany this therapeutic approach might detract from the appeal of this strategy. While most experts concede that the evidence is currently inconclusive, future studies are anticipated to shed further light on this subject. In the interim, it is important that physicians weigh the risks and benefits of intensive glycemic control when setting A1c targets in their patients.

PATIENT AGE

Patient age must also be considered when assessing the risks and benefits of intensive glycemic control. Hypoglycemia (especially severe hypoglycemia) poses a considerable risk to elderly patients [78]. The hypothesized benefit of intensive glycemic control in this population stems from improved cardiovascular outcomes. However, the ACCORD, ADVANCE, and VADT trials failed to demonstrate a positive correlation between intensive glucose control and reduced cardiovascular events [79]. In fact, the ACCORD study found that intensive glucose control was associated with an increased risk for cardiovascular and all-cause mortality in certain cases [79]. On the other hand, a 10-year follow-up of the tight glucose intervention arm of the UKPDS study demonstrated reduced risk for myocardial infarction, diabetes-related death, and all-cause mortality, indicating a long-term benefit of intensive glycemic control that eventually translates into a protective cardiovascular effect. These findings suggest that intensive control may provide a cardiovascular benefit if initiated early in the disease course, but not in elderly patients with advanced T2DM [78; 79]. Despite the prospective cardiovascular benefits of an A1c level $\leq 6.5\%$, achieving reduced A1c levels without exposing elderly patients to increased hypoglycemia-related risk is challenging. It is therefore critical that A1c targets be individualized in this patient population so reduced A1c is not achieved at the expense of overall patient health. Medical, psychological, functional (i.e., self-management abilities), and social domains should be assessed in this patient population to determine appropriate treatment targets and therapeutic approaches. Elderly

patients also should be screened for polypharmacy, cognitive impairment, depression, urinary incontinence, fall risk, persistent pain, and frailty as these may affect diabetes self-management and diminish quality of life [28].

THE ROLE OF ADHERENCE IN ACHIEVING TREATMENT GOALS

As with many chronic diseases, medication adherence is a significant barrier to optimal outcomes in T2DM. Adequate adherence to T2DM therapies, which is typically defined as collecting and/or taking >80% of prescribed medication, appears to vary significantly, although the vast majority of studies on this topic report some level of nonadherence among most patients with T2DM. An estimated 36% to 93% of individuals with T2DM are believed to practice inadequate adherence to oral antidiabetic agents, a considerably broad percentage [80]. Insulin nonadherence is similarly indefinite, reported to affect between 19% and 46% of patients with T2DM [81; 82]. Paradoxically, anticipated patient nonadherence actually dissuades a significant number of providers from initiating insulin [83]. Research suggests that nonadherence is a relatively immediate response in many patients with T2DM. Rather than tapering off medication over a substantial period of time, evidence suggests that patients often fail to fill second or additional prescriptions, and many discontinue medication within a year of prescription, actions suggestive of causative factors beyond simple medication fatigue [84]. The consequences of medication nonadherence are significant, ultimately resulting in hundreds of billions of dollars in additional economic cost and increased risk of mortality among nonadherent individuals compared to adherent patients with T2DM [82; 85; 86]. To reduce the personal and societal burden of nonadherence to antidiabetes medication, it is important that healthcare professionals understand the factors that contribute to suboptimal compliance, as well as strategies to overcome these barriers (*Table 3*).



The American Diabetes Association asserts that the medication regimen and medication-taking behavior should be re-evaluated at regular intervals (every three to six months) and adjusted as needed to incorporate specific factors that affect choice of treatment.

(<https://www.acpjournals.org/doi/10.7326/M20-2470>. Last accessed February 11, 2022.)

Level of Evidence: E (Expert consensus or clinical experience)

ORAL AND NON-INSULIN THERAPIES

The challenges associated with adherence to all T2DM therapies, including oral and non-insulin therapies, are multifactorial and complex, exponentially increasing the level of difficulty many patients have in overcoming these obstacles. Among the numerous reasons for reduced adherence to T2DM medication, the most frequently reported include fear of side effects (especially weight gain, hypoglycemia, and injection site reactions), inconvenience or complexity of prescribed treatment regimens, cost-associated access challenges, and low levels of patient knowledge and education regarding the importance of therapies for glycemic control [86; 87]. It is important to note that hypoglycemia, a side effect that is experienced by 38% of those receiving combination oral antidiabetic therapy, is a significant risk factor for suboptimal adherence and negatively affects patient perceptions of treatment efficacy, convenience, and safety [87; 88]. Effectively balancing therapeutic efficacy with tolerability is one action that can greatly increase the likelihood for treatment adherence, although it not an achievement that is easily obtained. The use of newer medications can help to reduce the impact of side effects, such as prescribing GLP-1 agonists in patients who are concerned with weight gain. Taking steps that swiftly and effectively correct hypoglycemic events can also help to improve both treatment adherence and glycemic control. To address treatment complexity, oral fixed-dose combination therapy can reduce the number of

STRATEGIES FOR OVERCOMING BARRIERS TO MEDICATION ADHERENCE IN T2DM	
Barrier	Strategy
Oral and Non-Insulin Therapies	
Fear of side effects	Attempt to balance therapeutic efficacy and tolerability. Utilize agents associated with fewer side effects. Discuss side effects before starting. Provide education regarding the symptoms and treatment of hypoglycemia.
Treatment complexity	Utilize oral fixed-dose combination therapy. Reduce dosing frequency whenever possible.
Insulin Therapy	
Fear of side effects	Attempt to balance therapeutic efficacy and tolerability. Utilize agents associated with fewer side effects. Discuss side effects before starting.
Needle anxiety/ treatment complexity	Discuss developments that have improved ease and comfort of injections. Utilize pen devices. Tailor therapy to patients' needs utilizing optimal formulations.
Negative patient attitude	Provide education regarding the importance of insulin in maintaining glycemic control. Dispel beliefs that insulin therapy is punishment or an indication of failure.
Other Barriers	
Medication cost	Work with managed care programs and patient financial profile to ensure easy access to medication.
Clinical inertia	Improve patient-provider communication to obtain feedback on adherence.
<i>Source: Compiled by Author</i>	

Table 3

pills to be taken in any given day, thereby improving adherence. Studies have found that switching from multiple, individual oral therapies (often referred to as “loose-pill combinations”) to fixed-dose combinations can significantly increase adherence [87; 89; 90; 91]. Likewise, reducing the frequency of dosing (e.g., from twice-daily to once-daily regimens) has been found to increase adherence by as much as 19% [87; 92]. Beyond these measures, taking steps to ensure that a patient’s individual concerns and preferences are addressed and educating patients regarding the consequences of hyperglycemia and the importance of glycemic control can further optimize adherence [87].

INSULIN THERAPY

Many of the barriers to insulin adherence are similar to those of oral medications, including side effect concerns and inconvenient dosing schedule, which can be overcome utilizing the previously discussed recommendations [93]. However, insulin therapy is accompanied by additional factors that can reduce adherence, such as needle anxiety and negative patient perceptions. Many patients associate insulin therapy with poor prognosis or as a form of punishment for inadequate self-management [86; 93].

A number of steps can be taken to improve adherence to insulin therapy. Numerous developments have addressed patients’ concerns regarding needles. Needles are now smaller and narrower, reducing the fear and pain associated with injections, and pen devices can improve convenience, dosing accuracy, and dosing discretion [93]. In fact, studies have found that pen devices significantly improve medication adherence compared to syringes [93; 94; 95].

Newer formulations of insulin offer variations in characteristics, such as onset of effect, peak effect, and duration of effect. These formulations provide patients with a more customized therapeutic strategy that can better meet their physiologic needs [93]. Finally, providing adequate patient education on the importance of insulin and dispelling misguided beliefs that insulin therapy is a form of punishment or an indication of self-management failure can improve psychologic responses to insulin and increase the likelihood of adherence.

OTHER STRATEGIES TO MAXIMIZE ADHERENCE

Additional factors have been found to affect adherence, regardless of therapeutic selection. Increased medication cost is one factor that has been correlated with nonadherence in T2DM. One study found that for each \$5 increase in patient cost, the adjusted odds of being adherent decrease by 15% [96]. Working with patients to reduce costs through utilization of managed care and other programs designed to limit patient spending can help to overcome this barrier.

Clinical inertia is another phenomenon that has been attributed to high rates of nonadherence to T2DM medications. Clinical inertia is characterized by recognition of a problem paired with failure to take corrective action and contributes to nonadherence when physicians acknowledge their patients are not adhering to their prescribed T2DM regimen and achieving glycemic control, but take no steps to correct the problem [97]. Improving provider-patient communication is a critical step in interrupting clinical inertia and improving adherence [98]. Research suggests that patient-provider communication in T2DM is largely inadequate, with physicians tending to misinterpret patients' needs and patients often wishing for more active involvement, information, and access to their physicians [99]. Good communication involves determining the patient's attitudes and beliefs to ascertain what education is needed.

To obtain feedback on adherence, clinicians must be able to work within cultural attitudes and modify language to meet the health literacy level of the patient. Optimal patient-provider communication can help to alleviate patient concerns, set achievable goals, and improve overall patient satisfaction. Some communication behaviors that have been found to be positively associated with health outcomes include empathy, reassurance and support, explanations, positive reinforcement, humor, discussion of psychosocial issues, health education and information sharing, courtesy, and summarization and clarification [100]. Other factors essential for effective communication and a successful relationship are knowledge of the patient's language preference; an understanding of and respect for the patient's personal cultural values, beliefs, and practices (referred to as cultural competency); and an awareness of the patient's health literacy level [101; 102; 103].

Language, cultural competency, and health literacy are significant issues, given the growing percentages of racial/ethnic populations. According to U.S. Census Bureau data from 2019, more than 65 million Americans speak a language other than English at home, with more than 25.6 million (8.4% of the population) reporting that they speak English less than "very well" [104]. Clinicians should ask their patients what language they prefer for their medical care information, as some individuals prefer their native language even though they have said they can understand and discuss symptoms in English [105].

The national standards on Culturally and Linguistically Appropriate Services (CLAS) include four behaviors related to language access services that are mandated for healthcare organizations [101]. Although they are not mandated for individual healthcare providers, the Office of Minority Health encourages clinicians to meet the standards to make their practices more culturally and linguistically accessible. These standards are [101]:

- Offering and providing language assistance services, including bilingual staff and interpreter services, at no cost to each patient/consumer with limited English proficiency at all points of contact in a timely manner during all hours of operation
- Providing patients with both verbal offers and written notices (in their preferred language) that inform them of their right to receive language assistance services
- Ensuring the competence of language assistance provided to patients with limited English proficiency by interpreters and bilingual staff and avoiding the use of the patient's family and friends as interpreters
- Making easily understood patient-related materials available and posting signage in the languages of the commonly encountered groups and/or groups represented in the practice area

Convenience and cost lead many clinicians to use “ad hoc” interpreters (e.g., family members, friends, bilingual staff members) instead of professional interpreters. However, professional interpreters are preferred for several reasons. Several states have laws about who can interpret medical information for a patient, so healthcare professionals should check with their state's health officials about the use of ad hoc interpreters [106]. Even when allowed by law, the use of a patient's family member or friend as an interpreter should be avoided, as the patient may not be as forthcoming with information and the family member or friend may not remain objective [106]. Children should especially be avoided as interpreters, as their understanding of medical language is limited and they may filter information to protect their parents or other adult family members [106]. Individuals with limited English language skills have actually indicated a preference for professional interpreters rather than family members [107].

Most important, perhaps, is the fact that clinical consequences are more likely with ad hoc interpreters than with professional interpreters [108]. A systematic review of the literature showed that the use of professional interpreters facilitates a broader understanding and leads to better clinical care than the use of ad hoc interpreters, and many studies have demonstrated that the lack of an interpreter for patients with limited English proficiency compromises the quality of care. The use of professional interpreters improves communication (errors and comprehension), utilization, clinical outcomes, and patient satisfaction with care [109; 110].

Cultural competency is essential for addressing healthcare disparities among minority groups [101]. Among the issues that clinicians should understand are the patients' belief systems regarding health, healing, and wellness; their perceptions on illness, disease, and their causes; their health behaviors and attitudes toward healthcare providers; and the role of the family in decision making [101; 111]. Understanding these aspects is integral to a successful patient-clinician relationship as well as to optimal health outcomes. For example, healthcare professionals should raise the topic of health-related customs, such as the use of complementary and alternative medicines, as the use of these therapies varies substantially among racial/ethnic populations, may compromise the effect of traditional therapies, and is often not disclosed by the patient [112; 113].

Knowledge of the patient's health literacy is also important, as the patient's understanding of his or her disease and its management is essential to ensuring adherence to the treatment plan and the patient's role in self-management. Yet most individuals lack adequate health literacy. According to the National Assessment of Health Literacy, 14% of individuals in the United States have “below basic” health literacy, which means they lack the ability to understand health information and make informed health decisions [114; 115]. A systematic review of more than 300 studies showed that an estimated 26% of patients had inadequate literacy and an additional 20% had marginal literacy [116]. Health

literacy varies widely according to race/ethnicity, level of education, and gender, and clinicians are often unaware of the literacy level of their patients [103; 117]. Predictors of limited health literacy are poor self-rated reading ability, low level of education, male gender, and non-White race [117; 118]. Several instruments are available to test patients' literacy levels, and they vary in the amount of time needed to administer and in their reliability in identifying low literacy [103; 114; 117; 119].

Clinicians should adapt their discussions and educational resources to a patient's identified health literacy level and degree of language proficiency. The use of plain language (free of medical jargon), asking patients to repeat pertinent information, regularly assessing recall and comprehension, providing educational resources in a variety of formats (e.g., print, oral, web-based, video), and using culturally appropriate and translated educational materials can all help ensure that patients better understand their disease and its management, ultimately leading to higher quality care.

An excellent patient-provider relationship can also set a framework of ongoing support, which is critical for any chronic, long-term condition. Modern technology is starting to be incorporated into adherence improvement strategies. Studies of short message service and real-time medication monitoring suggest these strategies may be useful for improving adherence to T2DM medication, and Internet self-management programs hold great promise for assisting patients in all aspects of diabetes care, including medication adherence [120; 121; 122]. It is likely that strategies will be developed in the near future that successfully merge technology and health care for improved adherence in T2DM.

CONCLUSION

T2DM represents a growing healthcare crisis on a national and worldwide scale. As the population increases, including growing subpopulations of obese and elderly individuals, T2DM is anticipated to endure as one of the top causes of morbidity and mortality in the United States. Fortunately, novel agents, formulations, and devices have been developed that can help patients reach A1c goals with less negative impact on quality of life, although balancing patient needs, glycemic targets, and unwanted side effects is still considered to be difficult by many healthcare professionals. Significant barriers in T2DM remain. Research has yet to determine the optimal A1c target that should be assigned to most patients with T2DM, and low levels of therapeutic adherence continue to counteract treatment efficacy. Still, as knowledge and technology advance, there is the potential these obstacles will be overcome and outcomes in T2DM will be vastly improved.

FACULTY BIOGRAPHY

John J. Whyte, MD, MPH, is currently the Chief Medical Officer at WebMD. In this role, he leads efforts to develop and expand strategic partnerships that create meaningful change around important and timely public health issues. Previously, Dr. Whyte was the Director of Professional Affairs and Stakeholder Engagement at the FDA's Center for Drug Evaluation and Research and the Chief Medical Expert and Vice President, Health and Medical Education at Discovery Channel, part of the media conglomerate Discovery Communications.

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Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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