Diabetes Pharmacology

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Faculty

Diane Thompson, RN, MSN, CDE, CLNC, has an extensive history in nursing and nursing education. She possesses a strong background in diabetes and cardiac care, starting her professional career at the cardiac care area of the Cleveland Clinic in Cleveland, Ohio. Ms. Thompson took the knowledge and experience she learned from the Cleveland Clinic and transferred it into the home health arena in rural Ohio, after which she moved to Florida and obtained further knowledge while working as a PRN nurse in all areas, including medical/surgical, intensive care, emergency, critical care, and cardiology. With a desire to have a specific area to concentrate her profession, Ms. Thompson accepted a position as a pneumonia case manager, which led into a diabetes case manager career. (A complete biography appears at the end of this course.)

Faculty Disclosure

Contributing faculty, Diane Thompson, RN, MSN, CDE, CLNC, 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 pharmacy professionals and nurses in any practice setting with a desire to familiarize themselves with the medications used in the treatment of type 2 diabetes.

Accreditations & Approvals

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About the Sponsor

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Disclosure Statement

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Course Objective

The purpose of this course is to meet the needs of healthcare professionals seeking a better understanding of the actions, dosages, onset of action, and adverse effects of diabetes medications in order to provide optimal care to their patient population.

Learning Objectives

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

1. Outline the epidemiology of diabetes in the United States.
2. Describe normal fuel metabolism and the pathogenesis of type 1 and type 2 diabetes.
3. Analyze the current state of diabetes research.
4. Identify the diagnostic criteria and screening guidelines for diabetes.
5. Discuss the role of sulfonylureas in the treatment of diabetes, including potential side effects.
6. Review the pharmacology of nonsulfonylurea secretagogues.
7. Compare and contrast the alpha-glucosidase inhibitors available for the treatment of diabetes.
8. Describe the role of metformin in diabetes management.
9. Assess the strengths and weaknesses of thiazolidinediones and dipeptidyl peptidase-4 inhibitors to control blood glucose levels.
10. Identify various bolus insulin options, and outline the risk and response to related hyperglycemic crises.
11. Discuss the importance of basal insulin in the treatment of type 1 and type 2 diabetes.
12. Compare the efficacy and actions of incretin mimetics and amylin analogs.
13. Choose key topics that should be included in patient education plans for individuals being treated with oral or injectable diabetes medications.

Pharmacy Technician Learning Objectives

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

1. Describe diabetes, its impact on community health, and recommendations for diagnosis and screening.
2. Outline pharmacologic approaches to managing diabetes.
3. Identify key components of patient education for patients prescribed medications for diabetes.

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 is a serious and growing problem in the United States. Behavior change, diet, and exercise are first in the line of treatment for this chronic disease. However, diabetes is a progressive disease, and these techniques will only work for a small portion of patients. Oral medications will eventually be necessarily incorporated into treatment plans in order to preserve control of the disease at an optimal level, and injectable medications are started in the second tier of therapy when glucose levels are significantly greater than the goal range [1]. Healthcare professionals are required to sustain a fundamental understanding of diabetes medication classes, including action, maximal safe dosing, and side effects, when caring for their patients. Oral medications for diabetes impact individuals to differing degrees and are associated with differing safe practice recommendations. Furthermore, although insulin and other injectable medications are beneficial, patient acceptance of injectable medications continues to be a significant barrier to achieving optimal blood glucose control [2]. Laboratory results, drug effects, and patient response to treatment should all be monitored.

DIABETES EPIDEMIOLOGY

Diabetes, known clinically as diabetes mellitus, is a progressive disease process affecting the fuel metabolism functioning within the body [3]. According to the Centers for Disease Control and Prevention (CDC), the prevalence of diagnosed diabetes has increased from less than 1% of the U.S. population in 1958 to 7.4% in 2015 [4]. As of 2019, 11.3% of the U.S. population, or 37.3 million Americans, have diabetes. Unfortunately, 8.5 million of these individuals are unaware of their diabetes diagnosis [5; 6]. Diabetes has been considered epidemic since the 1970s, and the percentage of Americans expected to have diabetes or impaired glucose tolerance (IGT) is estimated to reach 15% to 20% by the year 2025 [7].

The scope of the problem is vast and diverse. From 1994 through 2015, the prevalence of diagnosed diabetes increased across all states. In 1994, only one state had a prevalence greater than 6.0%. In 2018, all states had prevalences greater than 6.0%, and 35 exceeded 9.0% [8]. According to data from the Behavioral Risk Factor Surveillance System, West Virginia has the highest rate of adults with diabetes (13.4%). Eight of the 10 states with the highest rates (12% to 12.9%) are in the South. Colorado ranked last at 6.6% [8]. Genetics, race, age, and lifestyle influence the onset and progression of the disease process significantly [9]. According to the 2022 National Diabetes Statistics Report, the percentage of adults with diagnosed diabetes was highest among American Indians/Alaska Natives (14.5%), non-Hispanic Black Americans (12.1%), and people of Hispanic origin (11.8%), followed by non-Hispanic Asians (9.5%) and non-Hispanic White Americans (7.4%) [10]. Native Americans/Alaskan Natives present the greatest risk for the development of type 2 diabetes; their risk is more than two times greater than that of White Americans. Among Native American subgroups, the rate of diabetes among Alaska Natives is 6.0%, while Native Americans in Southern Arizona have rates of 22% [6].

The most rapid increase in prevalence in the last decade has been among adolescents. Historically, children and adolescents with hyperglycemia have been diagnosed with type 1 diabetes, a result of the body being unable to produce adequate amounts of insulin. However, the rate of new cases of diabetes in those younger than 20 years of age increased in the United States between 2002 and 2015, with a 4.8% increase per year for type 2 diabetes and a 1.9% increase per year for type 1 diabetes [11]. The incidence of type 1 diabetes increased in all age, sex, and race/ethnicity groups, except for those younger than 5 years of age and American Indians primarily from one southwestern tribe. The steeper increases in incidence of type 1 diabetes were seen among non-Hispanic Black Americans (2.7% per year), Hispanics (4.0% per year), and Asians/Pacific Islanders (4.4% per year) while the increase among non-Hispanic White Americans was much lower (0.7%

per year). For type 2 diabetes, incidence during the period increased in all age, sex, and race/ethnicity groups, with the exception of non-Hispanic White Americans. The steepest increase was seen among Asians/Pacific Islanders (7.7% per year) followed by Hispanics (6.5% per year), non-Hispanic Blacks (6.0% per year), and American Indians primarily from one southwestern tribe (3.7% per year) [11].It has been predicted that children born in this millennium will have a one in three chance of developing diabetes in their lifetime; among high-risk ethnic groups, the estimate is as high as one in two [12].

PATHOGENESIS OF DIABETES

Individuals with type 1 diabetes typically present to their primary care office or hospital emergency department with a sudden weight loss and severe hyperglycemia [13]. The consequences of the disease can take years to impact the body if optimally controlled. In contrast, an individual with type 2 diabetes may be unaware of the disease process for years prior to being diagnosed. The onset of type 2 diabetes is insidious, with the loss of first-phase insulin response to postprandial levels. The first elevation may be detected at the time of screening as prediabetes or IGT [7]. During this time, the disease progression and hyperglycemia are ravening the body's micro- and macrovascular systems [3].

In a healthy body, carbohydrate consumption results in an initial swell in serum glucose levels and hyperglycemia. In response to this escalation, the body releases insulin from pancreatic beta cells into the circulatory system to assist with glucose transport into muscle, liver, and adipose tissues; this causes a lowering of the blood glucose levels.

In the case of type 1 diabetes, pancreatic beta cells fail to produce and release insulin, and the only treatment option is exogenous insulin and other appropriate injectables [7]. However, the pathogenesis of type 2 diabetes is more complex. Virtually all individuals diagnosed with type 2 diabetes have insulin resistance in conjunction with some degree of insulin deficiency [14]. In response, the body's inability to react to the mounting glucose level is magnified by insulin deficiency in the functioning pancreatic beta cells, insulin resistance in the muscular tissue, or both [3]. Unlike the therapy for type 1 diabetes, type 2 diabetes is initially treated with lifestyle modification therapy (e.g., medical nutrition therapy, exercise, behavior change) and frequently with an oral medication, such as a biguanide. Within five years of type 2 diabetes diagnosis, it is estimated that as many as 90% of people will fail this initial therapy and require further oral medications or injectables to achieve adequate glucose control. As a result of this failure rate, medication therapy is initiated early (in the prediabetes stage) in diabetes medical treatment algorithms [15].

PHYSIOLOGY OF INSULIN RELEASE IN FUEL METABOLISM

In order to fully comprehend the action of exogenous insulin, healthcare providers require a solid understanding of insulin physiology. Glucose regulation is maintained by a sophisticated mechanism of regulatory and counter-regulatory reactions. When an individual consumes food, specifically carbohydrates, sugars are released into the blood circulatory system [16]. The chemical reactions to this sugar introduction help maintain homeostasis in the body.

Phases of Insulin Response

The concentration of plasma glucose is dependent on the rate glucose enters the circulation in contrast to the rate it is removed [17]. Fuel homeostasis within the body can be explained in a five-phase approach [18]. Phase 1, or the fed state, occurs immediately and up to 3.9 hours after consumption of food. During this phase, the circulating glucose is predominantly from an exogenous source. Plasma insulin levels are elevated, glucagon levels are minimal, and triglycerides are synthesized in the liver. Insulin impedes the breakdown of glycogen and triglyceride reservoirs. The brain and other glucose-dependent organs utilize some of the glucose absorbed from the intestinal tract, and the excess glucose is stored in the liver, muscle, adipose tissue, and other tissues for use later.

Phase 2 occurs 4 to 15.9 hours after consumption of food and is referred to as the postabsorptive state. In phase 2, blood glucose originates from the breakdown of glycogen and hepatic gluconeogenesis. There is a decrease in plasma insulin levels, and glucagon levels begin to increase. Anabolism (energy storage) ends in this phase and catabolism (energy production) begins. There is a mobilization of carbohydrate and lipid stores. Hepatic glycogen breakdown provides maintenance of circulating plasma glucose to ensure an adequate supply of glucose to the brain and other organs. Adipocyte triglyceride begins to break down, and free fatty acids are released into the circulatory system for use by the liver and skeletal muscle as the primary energy source and as a substrate for gluconeogenesis. The brain continues to utilize glucose, provided mainly by gluconeogenesis, due to its inability to use free fatty acids.

Phase 3 is the early starvation state. About 16 to 47.9 hours after the consumption of food, the blood glucose is generated from hepatic gluconeogenesis and glycogenolysis. Gluconeogenesis continues to generate most of the hepatic glucose. In this phase of starvation, lactate makes up half of the gluconeogenesis substrate along with amino acids (specifically alanine) and glycerol. The secretion of insulin is suppressed, and counter-regulatory hormone (i.e., glucagon, cortisol, growth hormone, epinephrine) secretion is stimulated.

Phase 4 begins 48 hours to 23 days after food consumption. During this preliminary prolonged starvation state, blood glucose originates from hepatic and renal gluconeogenesis. Within 60 hours of starvation, gluconeogenesis provides more than 97% of hepatic glucose output. The secretion of insulin is distinctly diminished and counter-regulatory hormone secretion is stimulated.

Phase 5, or the secondary prolonged starvation state, begins 24 days after food consumption. Blood glucose during this phase originates from hepatic and renal gluconeogenesis, just as in phase 4. However, in phase 5 the rate of glucose being utilized by the brain and the rate of gluconeogenesis diminishes.

The relationship between the glucoregulatory and the counter-regulatory hormones and the many factors that contribute to the fuel metabolism should be considered. There is a sophisticated relationship between the metabolic-regulatory hormones insulin (a glucoregulatory hormone), glucagon, and epinephrine. When insulin is elevated, glucagon and epinephrine are suppressed [19]. This process occurs to prevent the continued rise of endogenous glucose levels. Conversely, when insulin levels decline in response to diminished circulating glucose levels, glucagon and epinephrine respond by increasing. These relationships are maintained when normal homeostasis is present. In patients with diabetes, there is a disruption of this homeostasis [20].

DIABETES RESEARCH

A strong focus has been placed on the area of prevention and treatment of type 2 diabetes with oral medications, lifestyle modification, and/or injectable medications. As the body of research grows, clinicians gain insights into possible treatment approaches and best practices.

THE DIABETES PREVENTION PROGRAM

The National Institute of Health's sponsored study, the Diabetes Prevention Program (DPP), was sanctioned to determine if diabetes could be prevented or delayed through the use of various interventions. The study was conducted in 27 centers throughout the United States, and the study participants were randomized into one of four treatment groups [21]. Treatment groups included lifestyle and behavior change or therapy with metformin, troglitazone, or placebo [21].

All 3,234 study participants were 25 years of age or older, overweight, and had IGT and elevated fasting plasma glucose, which are risk factors for the development of type 2 diabetes. In addition, 45% of the participants were from minority groups—African American, Alaskan Native, Native American, Asian American, Hispanic/Latino, or Pacific Islander—and 20% were 65 years of age or

older. The study lasted more than three years but was halted earlier than expected due to 25 of the 27 centers demonstrating remarkable findings proving the hypothesis [21].

The first group, referred to as the lifestyle intervention group, received intensive education and counseling pertaining to diet, physical activity, and behavior modification. For individuals in this group, the overall goal was to maintain a loss of 7% of total body weight by consuming a decreased amount of fat and fewer calories and engaging in 150 minutes of exercise per week. The metformin treatment group was prescribed 850 mg of metformin twice per day, while the placebo group received placebo pills twice per day. Both the metformin and placebo groups also received education regarding lifestyle interventions (e.g., diet, exercise) but not intensive counseling. The troglitazone group was prescribed 400 mg of the drug daily, but this arm of the study was discontinued due to concerns that troglitazone was associated with liver toxicity. Participants in the troglitazone group continued to be followed but were not included as one of the intervention groups [21]. Troglitazone was removed from the U.S. market in 2000 [22].

The researchers found that participants who lost a modest amount of weight through dietary changes and increased physical activity sharply reduced their chances of developing diabetes [21]. The metformin treatment group also displayed a reduced risk for the development of diabetes, but the decrease was less dramatic.

The DPP Outcomes Study (DPPOS) has continued to follow most DPP participants since 2002. To date, the DPPOS has shown that participants who took part in the DPP Lifestyle Change Program or who are taking metformin continue to prevent or delay type 2 diabetes for at least 15 years [21]. The DPPOS also has shown that the lifestyle change program is cost effective and that metformin is cost-saving after 10 years. DPPOS researchers also are following other health problems in participants (e.g., cancer, CVD, and kidney and eye disease) [21].

THE DIABETES COMPLICATION AND CONTROL TRIAL

Research has also proven that tight glycemic control can prevent the development of chronic microvascular complications in diabetic patients. Initial research in the Diabetes Complication and Control Trial (DCCT) focused on the benefits of conventional versus intensive therapy for the prevention of complications related to type 1 diabetes [14; 23]. The study involved 1441 individuals and demonstrated enough statistical power to unequivocally demonstrate the importance of glycemic control with utilization of multiple daily insulin injections [23; 24].

This randomized controlled trial found that the risk of microvascular complications was reduced by intensive glycemic control in patients with type 1 diabetes. Participants in the intensively treated group (goal glycosylated hemoglobin [HbA1c]: <6.05%; mean achieved HbA1c: approximately 7%) demonstrated an approximately 60% reduction in development or progression of diabetic retinopathy, nephropathy, and neuropathy compared to the standard group (mean achieved HbA1c: approximately 9%) over an average of 6.5 years. The relationship between glucose control and risk of complications was linear and extended down to the normal HbA1c range (<6%) with no threshold noted [25].

When the DCCT ended in 1993, researchers began a follow-up study called the Epidemiology of Diabetes Interventions and Complications (EDIC). The EDIC continues to follow more than 90% of DCCT participants, assessing the incidence and predictors of cardiovascular disease events (e.g., heart attack, stroke, needed heart surgery) and diabetic complications related to the eye, kidney, and nerves. For example, the EDIC has shown that an individualized eye exam schedule results in fewer eye exams, lower costs, and faster diagnosis and treatment of advanced diabetic eye disease [23]. The EDIC also is examining the impact of intensive versus standard control on participants' quality of life [23].

THE UNITED KINGDOM PROSPECTIVE DIABETES STUDY

Research from the DCCT trial was further substantiated in the United Kingdom Prospective Diabetes Study (UKPDS), a clinical trial of patients with newly diagnosed type 2 diabetes conducted between 1977 and 1997. Once more, the groups were separated into a conventional therapy study arm or an intensive therapy arm to determine the efficacy and outcomes of the differing treatments [14]. Intensive blood glucose control was achieved utilizing sulfonylurea medications or insulin in normal-weight people and metformin in participants who were overweight. The UKPDS aimed to treat patients using only a single medication even if blood glucose became quite high because, at the time, there were some concerns that utilizing multiple medications had the potential of being harmful. In the conventional therapy cohort, lifestyle alone was used to control blood glucose. This was the first study to establish the now well-known association between level of glucose control and the reduction of microvascular complications (i.e., retinopathy, nephropathy, neuropathy) in individuals with type 2 diabetes [26].

When researchers revisited the participants of the UKPDS after 10 years, it was found that those who had been in the tight glycemic control arm during the trial had a lower risk of myocardial infarction and death than those who participated in the conventional glycemic control arm [27]. This finding was somewhat surprising because within one year of UKPDS ending, differences in HbA1c levels between the intensive and conventional treatment groups had disappeared. However, 10 years later, the follow-up study reported that myocardial infarction risk was reduced 15% in the sulfonylurea/insulin group and 33% in the metformin group, while overall risk of death was reduced 13% and 27%, respectively [27]. With this knowledge, the goal for diabetes treatment is striving for euglycemia by utilizing behavior change, meal planning, and lifestyle change followed by medication management [7].

TREAT-TO-TARGET TRIAL

The Treat-to-Target Trial was designed to determine if the addition of basal insulin at bedtime to an existing oral therapy regimen could improve achievement of the recommended 7% HbA1c target. Its secondary goal was to assess the efficacy and safety of glargine compared to neutral protamine Hagedorn (NPH) insulin as the basal insulin of choice in this treatment approach [28].

Researchers found that the addition of bolus insulin at bedtime (either glargine or NPH) reduced the average HbA1c level from 8.6% to 7%, with almost 60% of patients reaching 7% or less [28]. This high success rate may be attributed to the fact that the average baseline HbA1c was lower than in most other studies, the majority of study participants had advanced diabetes (suggested by poor glucose control on two oral agents), and more than 90% of participants adhered to the treatment, indicating it was an easy regimen to follow. Researchers also systematically titrated the insulin dosage to target [28].

Although fasting glucose and HbA1c levels were similar with both types of insulin, glargine was associated with fewer symptoms of hypoglycemia and less variability in fasting glucose levels [28]. Rates of severe hypoglycemia were low for both insulins, but nocturnal hypoglycemia was significantly more likely with NPH insulin. Nocturnal hypoglycemia was reduced from 42% to 48% in the glargine group, indicating that this insulin's lower peak of action would make it a better choice for this treatment approach [28].

4-T TRIAL

The Treating to Target Type 2 Diabetes, or 4-T, Trial was established to determine the effects of adding biphasic, prandial, or basal insulin to oral therapy for type 2 diabetes [29]. Participants in the trial had suboptimally controlled diabetes (mean HbA1c: 8.5%) despite treatment with sulfonylurea plus metformin. Subjects were randomized into three treatment groups: biphasic insulin aspart (twice daily), prandial insulin aspart (three times daily),

or basal insulin detemir (once or twice daily, as required). All patients continued their established oral therapy, and dose titration, glucose monitoring, and follow-up visits were provided for all. After one year, the mean HbA1c level had decreased in all treatment groups, to 7.3% with biphasic insulin, 7.2% with prandial insulin, and 7.6% with basal insulin. However, no group met the goal of 6.5% or less; only 17%, 23.9%, and 8.1% of participants, respectively, met the goal. Although biphasic and prandial insulin more effectively lowered mean HbA1c levels, they were associated with greater risks of hypoglycemia and weight gain [29]. The authors concluded, based on a comparison of the risks and benefits of each approach, that the treatment of choice would be adding once-daily basal insulin to an established oral medication regimen for type 2 diabetes patients [29; 30]. Three years after the study concluded, the majority of patients in each group were receiving a second type of insulin (67.7% of the biphasic group, 81.6% of the prandial group, and 73.6% of the basal group) [29].

ORIGIN TRIAL

The Outcome Reduction with Initial Glargine Intervention (ORIGIN) Trial was a large study attempting to identify the advantages of insulin glargine therapy and omega-3 fatty acids (fish oil) in managing type 2 diabetes and associated cardiovascular risks. The trial was completed in 2013 [31]. Because the majority of individuals who experience a myocardial infarction have impaired fasting glucose and/or IGT, investigators believed that achieving lower blood glucose levels (using insulin) might reduce the risk of cardiovascular events. The ORIGIN Trial randomized participants into groups receiving standard insulin glargine or variable-dose glargine, and further into subgroups receiving 865 mg of omega-3 fatty acid or placebo. The trial followed 12,500 individuals to determine the effect on the incidence of cardiovascular events [31]. Results indicated no difference in the incidence of cardiovascular events between the insulin glargine and standard care groups. Additionally, there was no difference in the incidence of cardiovascular death between the omega-3 fatty acid supplement and placebo groups. Insulin glargine provided better glucose control and lower risk of new diabetes. Side effects included a small increase in risk of hypoglycemia and weight gain of approximately 1.6 kg over a period of more than six years [32].

CAROLINA TRIAL

The Cardiovascular Outcome Study of Linagliptin versus glimepiride (CAROLINA) trial was a randomized, noninferiority clinical trial that compared the effect of linagliptin with glimepiride on major cardiovascular events in more than 6,000 participants with type 2 diabetes and elevated cardiovascular risk [33]. Participants were randomized to receive 5 mg of linagliptin once daily or 1–4 mg of glimepiride once daily in addition to usual care. The primary outcomes were time to first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. The median duration of follow-up was 6.3 years. A cardiovascular event occurred in 356 (11.8%) participants in the linagliptin group and 362 (12%) participants in the glimepiride group. Results indicated that the use of linagliptin compared with glimepiride resulted in a noninferior risk of composite cardiovascular outcome [33].

DIAGNOSIS OF DIABETES

TYPES OF DIABETES

As discussed, the most common types of diabetes are type 1 and type 2. However, gestational diabetes is also relatively common and is a source of significant morbidity and mortality. Gestational diabetes complicates approximately 10% of all pregnancies [34; 35]. For many years, gestational diabetes has been defined as any degree of glucose intolerance first recognized during pregnancy, but this definition has limitations. Many cases of gestational diabetes represent pre-existing hyperglycemia that is first detected by routine screening in pregnancy (as routine screening is not widely performed in nonpregnant women of reproductive age) [35]. Ideally, women with risk factors who are planning pregnancy should be tested for undiagnosed diabetes prior to concep-

tion [35]. If not screened preconception, universal early screening before 15 weeks' gestation for undiagnosed diabetes may be considered, particularly in populations with a high prevalence of risk factors, including women of non-Hispanic Black, Hispanic/Latino, and Native American ethnicity, women who are obese, women with a personal history of gestational diabetes, and those with a family history of diabetes [35; 36]. Otherwise, testing should be done at between 24 and 28 weeks' gestation, usually with a glucose tolerance test [35]. Patients with gestational diabetes present special challenges, and the need for tight glycemic control often necessitates the use of insulin therapy. After conception and early in the first trimester, the risk of hypoglycemia is amplified as a result of increases in the peripheral utilization and storage of glucose. Late in the third trimester, overnight hypoglycemia can occur if a bedtime snack is insufficient to meet the intensified fetal demands for glucose. Lastly, during the postpartum period, the risk of hypoglycemia results from the loss of placental hormones [37].

Adequate glucose control should be maintained in order to prevent adverse effects to fetal health. Potential adverse effects include hyperbilirubinemia (jaundice), respiratory distress syndrome, hypocalcemia, polycythemia, macrosomia, and neonatal hypoglycemia [37; 38].

Macrosomia occurs when a high level of glucose in the maternal blood results in the elevated glucose to the fetus. Sensing this elevation, the fetal pancreas begins producing insulin to normalize the glucose levels. The result of this is increased adipose tissue in the organs, chest, and abdomen, leading to disproportionate size of the trunk and shoulders in relationship to the head. These infants are often large for gestational age, increasing likelihood of cesarean delivery, vaginal tearing, and other birth traumas, such as shoulder dystocia, brachial plexus injury, Erb palsy, and asphyxia [38].

If the fetal pancreas has been overproducing insulin in response to elevated maternal blood glucose levels, hypoglycemia will occur when the umbilical cord is clamped and glucose-rich maternal blood is no longer circulating in the neonate. Neonatal hypoglycemia occurs in the first 12 hours of life and resolves with infusions or oral administration of glucose until euglycemia is restored. The risks associated with neonatal hypoglycemia include seizure, cerebral damage, and death [38].

The first-line treatment for gestational diabetes is conventional therapy of diet, exercise, and other lifestyle changes [34]. The goals for blood glucose levels during this period of pregnancy are very strict [34]:

- Before meals and at bedtime: less than 95 mg/dL
- One-hour postprandial: less than 140 mg/dL
- Two-hour postprandial: less than 120 mg/dL

When these goals are not being met, insulin therapy should be initiated, if needed, to achieve glycemic targets [35]. Insulin is the preferred medication, as it does not cross the placenta to a measurable extent. Metformin and glyburide should not be used as first-line agents, as they do cross the placenta. All oral agents lack long-term safety data [35].

Other less common types of diabetes do occur, and it is important to have a basic understanding of these forms as well. Less common types of diabetes include [7; 14]:

- Maturity-onset diabetes of the young (MODY): A genetic, autosomal-dominant defect of the pancreatic beta cells that results in insulin deficiency and decreased insulin release without the presence of insulin resistance and obesity. This form of diabetes typically develops in patients younger than 25 years of age. This is a different clinical entity than type 2 diabetes of the adolescent, which presents with insulin resistance.
- Diabetes related to diseases of the exocrine pancreas, such as cystic fibrosis, and various endocrine diseases, such as Cushing syndrome, acromegaly, and chromocytoma
- Drug-induced diabetes resulting from the use of certain medications, particularly high-dose corticosteroids

DIAGNOSTIC CRITERIA FOR DIABETES			
Stage	**Fasting Plasma Glucose Levels**	**Two-Hour Postprandial Plasma Glucose Levels**	**A1c**
Prediabetes	100–125 mg/dL	140–199 mg/dL	5.7% to 6.4%
Diabetes	≥126 mg/dL	≥200 mg/dL	A1c ≥6.5% OR In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL

Source: [35] *Table 1*

SCREENING FOR DIABETES

Criteria for screening for diabetes or prediabetes in asymptomatic adults include [35]:

- Testing should be considered in adults with overweight or obesity (body mass index [BMI] ≥25 kg/m^2 [≥23 kg/m^2 in Asian Americans]) who have one or more of the following risk factors:
  - First-degree relative with diabetes
  - High-risk race/ethnicity (e.g., African American, Hispanic American, Native American, Alaskan Native, Pacific Islander, Asian American)
  - History of CVD
  - Hypertension (blood pressure ≥140/90 mm Hg or on therapy for hypertension)
  - HDL cholesterol level <35 mg/dL and/or a triglyceride level >250 mg/dL
  - Women with polycystic ovarian syndrome
  - Physical inactivity
  - Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
- Patients with prediabetes (A1c ≥5.7%, IGT, or IFG) should be tested yearly.
- Women who were diagnosed with gestational diabetes should have lifelong testing at least every three years.
- For all other patients, testing should begin at 35 years of age.
- If results are normal, testing should be repeated as a minimum of three-year intervals, with consideration of more frequent testing depending on initial results and risk status.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The U.S. Preventive Services Task Force recommends screening for prediabetes and diabetes as part of cardiovascular risk assessment in adults 40 to 70 years of age who are overweight or obese.

(https://jamanetwork.com/journals/jama/fullarticle/2783414. Last accessed October 28, 2022.)

Strength of Recommendation: B (There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.)

DIAGNOSTIC CRITERIA

The diagnostic criteria for type 2 diabetes are fairly straightforward and are based on fasting plasma glucose and plasma glucose levels (***Table 1***). After a diagnosis of type 2 diabetes has been definitively made, education on self-care management is necessary in order to obtain euglycemia and prevent complications related to the detrimental effects of hyperglycemia [3]. The healthcare team involved in providing care should include, at a minimum, the primary care physician, certified diabetes educator, dietitian, and support person/system. Education should focus on healthy eating habits, blood glucose monitoring, exercise planning, medication management, risk reduction, and healthy coping techniques [39]. As previously stated, it is estimated that as

SULFONYLUREAS						
Drug Name	**Trade Name**	**Dose Range**	**Maximum Daily Dose**	**Frequency**	**Onset of Action**	**Duration of Action**
First-Generation						
Chlorpropamide (no longer available in the United States)	APO-Chlorpropamide (Canadian)	100–500 mg daily	500 mg	Daily	1 hour	24 hours
Second-Generation						
Glimepiride	Amaryl	1–2 mg daily	8 mg	Once or twice daily	2 to 3 hours	24 hours
Glipizide	Glucotrol	2.5–5 mg daily	20 mg	Once daily	1 to 3 hours	12 to 24 hours
	Glucotrol XL (extended-release)	20 mg daily	20 mg	Daily	6 to 12 hours	12 to 24 hours
Glyburide	Glynase	1.25–5 mg daily	20 mg	Once or twice daily	2 to 4 hours	≤24 hours
Glyburide (micronized)	Glynase	0.75–3 mg daily	12 mg	Once or twice daily	2 to 4 hours	≤24 hours

Source: [42; 43] *Table 2*

many as 90% of patients with type 2 diabetes will require oral medications to achieve adequate glucose control within five years of diagnosis [15]. When glucose levels cannot be adequately controlled with oral medications, the use of injectable medications is necessary. If elevated blood glucose levels are untreated and continue to rise, the result can be hyperosmolar hyperglycemia syndrome (HHS) and ultimately death [2].

SULFONYLUREA THERAPY: FIRST AND SECOND GENERATIONS

Historically, there were few options to achieve control of blood glucose levels, and pharmacologic management was limited to the sulfonylureas [3]. Today, sulfonylurea medications are categorized as either first- or second-generation (***Table 2***). These medications are typically used as primary or secondary agents in the treatment of type 2 diabetes. Sulfonylureas can be rapid-acting, intermediate-acting, or long-acting based on their onset and duration of action. For sulfonylureas to be effective, the individual must have functioning pancreatic beta cells. Thus, they are not useful for patients with type 1 diabetes [40]. Some individuals will not respond to initial sulfonylurea therapy, and over time, most will experience failure with this therapy as the disease progresses. The ideal candidate for sulfonylurea therapy is a patient with [41]:

- Type 2 diabetes without dyslipidemia
- Normal weight
- Hyperglycemia despite following meal planning and an exercise program
- Ability and willingness to follow a reasonable dietary program
- Hyperglycemia for less than five years
- Age older than 30 years

Sulfonylurea preparations act to stimulate the release of insulin from functioning beta cells in the islets of Langerhans in the pancreas, which results in lowered blood glucose [40; 42; 44]. These agents close the energy-sensitive potassium channel in the cell membrane of the pancreatic beta cell. By accomplishing this, there is an increased amount of available insulin for action within the body [3]. It

is important to keep in mind that individuals with impaired first-phase insulin release will experience a diminished effect from sulfonylurea therapy [45]. Duration of action is generally rapid, fairly complete, and basically unaffected by food, with the exception of glipizide [42].

FIRST-GENERATION AGENTS

The original sulfonylurea agents are now known as the first-generation sulfonylureas. Although effective in controlling hyperglycemia, first-generation sulfonylureas were hindered by the frequency of hypoglycemia related to therapy and high dosage requirements. The second-generation sulfonylureas have improved on the effectiveness of the earlier agents by requiring smaller doses and demonstrating a lower incidence of side effects [3; 40]. Although no first-generation sulfonylurea agents are currently used in the United States, it is important to have an understanding of all medications within this category in the rare case a patient presents with a history of having taken one of these agents.

Discontinued Medications

Chlorpropamide

Chlorpropamide is typically prescribed at 100–250 mg/day for stable diabetics; those with more severe disease may take up to the maximum safe dose of 500 mg/day [42]. Adjusting doses up or down should be accomplished by increasing or decreasing by 50–125 mg/day over three to five days. Chlorpropamide has an onset of action of one hour, a half-life of less than 36 hours, and a duration of action of 24 hours [42]. Chlorpropamide is primarily metabolized in the liver and excreted via the kidneys. This medication does cross the placenta and has been found in breast milk, and women of childbearing age should be educated regarding possible effects to their fetus or infant [7; 42].

Acetohexamide

Acetohexamide has a prescribing dose range from 250–1,500 mg daily, with a maximum safe dosage of 1,500 mg/day [40]. Acetohexamide may be taken in two divided doses per day to obtain maximum efficacy of the medication. It has an onset of action of 1 hour, and the duration of action is anywhere from 12 to 24 hours [46].

Tolazamide

Tolazamide has a prescribing dose range of 100 mg to a maximum safe dose of 1,000 mg daily and may be given in divided doses [40]. The onset of action for tolazamide is four to six hours, with a half-life of seven hours. The duration of action ranges between 10 and 14 hours. This medication is metabolized in the liver with excretion via the kidneys. Like chlorpropamide, tolazamide crosses the placenta [42].

Tolbutamide

Tolbutamide has a prescribing dose range of 500 mg to a maximum 3,000 mg/day [42]. A prescribed dose of tolbutamide is given in three divided doses in order to reach maximum efficacy. A larger dose is typically required to be effective. The onset of action for tolbutamide is 1 hour, with a half-life of 6 to 8 hours; the duration of action ranges from 12 to 18 hours. Tolbutamide is metabolized in the liver with excretion via the renal system [42]. It is important to note that levels of tolbutamide are not reduced by hemodialysis [7].

SECOND-GENERATION AGENTS

The second generation of sulfonylureas was developed to include a shorter duration of action and shorter half-lives, which decrease the frequency and severity of side effects related to medication therapy [3]. These agents are most commonly used in the treatment of type 2 diabetes today.

Glimepiride

Glimepiride is typically prescribed at a maintenance dose of 1–4 mg/day, with a maximum safe dose of 8 mg daily [42]. Glimepiride is usually taken once daily with breakfast or the first main meal. The onset of action is two to three hours, with a half-life of five to nine hours. The maximum effect is experienced within 2 to 6 hours, but the duration of action is 24 hours.

After oral administration, glimepiride is completely metabolized by oxidative biotransformation into the major metabolites cyclohexyl hydroxy methyl derivative (M1) and carboxyl derivative (M2). Cytochrome P450 2C9 has been shown to be involved in the biotransformation of glimepiride to M1. M1 is about one-third as pharmacologically active as its parent; however, whether the glucose-lowering effect of M1 is clinically meaningful is not clear. When glimepiride is given orally, approximately 60% of the total radioactivity is recovered in the urine in seven days, and M1 (predominant) and M2 account for 80% to 90% of that recovered in the urine [42; 44]. Because this medication can pass through the placenta to the fetus, care should be taken when treating women of childbearing age [7; 42]. Agents other than glimepiride are currently recommended to treat diabetes in pregnant women [42]. Due to its different action and lack of effects on the coronary arteries, some have classified glimepiride as the first third-generation sulfonylurea.

Glipizide

Glipizide is initially prescribed at a dose of 2.5 mg/day, which may be titrated up in 2.5–5 mg increments until desired effects are achieved [42]. The maximum safe dose is 40 mg/day for the standard preparation and 20 mg/day for the extended-release formula [42]. The standard dose of glipizide is taken three times per day to obtain optimal effect; the extended-release formula is taken only once per day. The onset of action for both preparations is 3.5 to 6 hours, with the maximum effect obtained in 1 hour [7]. The duration of action for glipizide is 12 to 24 hours, and it has a half-life of approximately 2 to 5 hours [42]. Glipizide is extensively metabolized in the liver. The primary metabolites are inactive hydroxylation products and polar conjugates and are excreted mainly in the urine [47]. As with other sulfonylureas, the medication crosses the placenta and may affect the fetus [7; 42].

Glyburide

Glyburide is available in regular and micronized forms, and dosing will depend on the form prescribed [42]. The initial dose of the regular form is 1.25–5 mg/day, which may be increased weekly to desired effect or a maximum of 20 mg daily. The initial dose for the micronized tablets is 0.75–3 mg/day, which can also be titrated weekly. The maximum micronized dose is 12 mg/day [42].

The onset of action for glyburide is 90 minutes, with maximum effect noted at 60 minutes for micronized preparations and two to four hours for the nonmicronized formula. The half-life of glyburide is 10 hours regardless of micronization, and the drug has a duration of action of 12 to 24 hours (micronized) or 16 to 24 hours (nonmicronized) [42; 48]. Glyburide is excreted as metabolites in the bile and urine. This dual excretory pathway is different from that of other sulfonylureas, which are excreted primarily in the urine [42; 49]. Glyburide does cross the placenta, and precautions with women of childbearing age should be taken [7; 42].

POTENTIAL SIDE EFFECTS

As with any drug therapy, a hypersensitivity reaction can potentially occur with sulfonylurea therapy. However, hypersensitivity to one agent does not necessarily indicate a cross-sensitivity with other sulfonamide agents. Care should be taken when treating geriatric, malnourished, or debilitated patients, as these groups are at particular risk for hypoglycemia. Furthermore, any person with adrenal, pituitary, or hepatic insufficiency who is particularly susceptible to the hypoglycemic effects of glucose-lowering agents should be closely monitored while on a sulfonylurea therapy regimen [3]. Alteration in hepatic enzyme activity may also alter the clearance of sulfonylurea agents.

A secondary side effect of sulfonylurea therapy is weight gain as a result of a greater amount of circulating insulin [42]. This increase results in a greater amount of circulating glucose being stored as adipose tissue. Less commonly seen sulfonylurea side effects include [42]:

- Skin rash (2%)
- Gastrointestinal disturbances (5%)
- Metabolic disorders (e.g., syndrome of inappropriate antidiuretic hormone hypersecretion associated with chlorpropamide use) (4%)

It is important to mention that there is ongoing research regarding a possible correlation between sulfonylurea therapy and suspected deaths in patients with a past myocardial infarction [50; 51]. Although a causal relationship has not been established, it is important to understand this concept and to counsel patients to discuss any concerns with their primary care physician [52].

Sulfonylurea agents may also interact with a variety of other medications. These interactions have the potential to affect the action of the sulfonylurea agent, the other medication, or both. Drug-drug interactions are more commonly seen with the first-generation sulfonylurea agents [53]. One of the primary causes for drug interactions is a competition for protein binding sites, which results in a greater amount of circulating sulfonylurea agent in the bloodstream and can increase the hypoglycemic effect, seen more often with the longer acting agents (e.g., chlorpropamide, glibenclamide [i.e., glyburide]) [54]. Medications that may interact with sulfonylureas include beta blockers, corticosteroids, thiazide diuretics, cyclic antidepressants, and antifungals [42; 54].

CASE STUDY

Patient M is a white woman, 32 years of age, presenting to her primary care physician with complaints of polyuria for the past four weeks. Further assessment reveals an upcoming appointment with her optometrist for new onset blurred vision. The patient is 5 feet 5 inches tall and weighs 142 pounds; her calculated BMI is 23.6 kg/m^2. She confirms a family history of diabetes on her father's side and admits to a generally sedentary occupation and lifestyle. A random finger stick reveals a blood glucose level of 257 mg/dL.

***Rationale and comments**: Patient M's evaluation has resulted in adequate findings to diagnose diabetes. Any random blood glucose greater than 200 mg/dL with additional symptoms (in this case, polyuria and blurred vision) is considered diagnostic for diabetes.*

Patient M is referred for fasting blood work, which reveals the following results:

- HbA1c: 8.5% (estimated average glucose: 197 mg/dL)
- Fasting blood glucose: 147 mg/dL
- Two-hour glucose level (after 75 g oral glucose tolerance test): 240 mg/dL
- Triglycerides: 152 mg/dL
- Low-density lipoprotein (LDL): 97 mg/dL
- HDL: 35 mg/dL
- Liver function tests: Within normal limits
- Renal function: Within normal limits

Patient M is referred to an ADA-recognized diabetes education program for further education in diabetes self-management, self-monitoring of blood glucose (SMBG), and exercise and meal planning education [55].

Patient M returns to her primary care physician after three months. Her follow-up HbA1c demonstrates minimal change, with a result of 8.2% (estimated average glucose: 189 mg/dL) and a fasting blood glucose level of 156 mg/dL. SMBG records reveal blood glucose levels consistently between 135 mg/dL and 160 mg/dL fasting and between 230 mg/dL and 300 mg/dL postprandial. Patient M states that she is following her meal and exercise planning goals with little success.

The patient's physician evaluates all of her blood work and patient history information and determines that the best course of treatment would be to initiate sulfonylurea therapy. Patient M is started on glipizide 5 mg each morning, and continuation with her meal and exercise plans is emphasized.

***Rationale and comments**: This is an appropriate treatment plan for Patient M because, although she has a sedentary occupation, she is not considered obese. She has been adherent to her meal and exercise plan without success. Her fasting blood glucose levels are elevated, but it is the postprandial levels that have instigated the elevated HbA1c levels. The sulfonylurea secretagogue glipizide should improve the high postprandial levels resulting from loss of first-phase insulin release.*

NONSULFONYLUREA SECRETAGOGUES (GLINIDES)						
Drug Name	**Trade Name**	**Dose Range**	**Maximum Daily Dose**	**Frequency**	**Onset of Action**	**Duration of Action**
Repaglinide	Prandin (discontinued in the United States)	0.5–4.0 mg before meals	16 mg	Up to four times daily	25 to 30 minutes	4 to 6 hours
Nateglinide	Starlix, generic still available	60–120 mg before meals	360 mg	Three times daily	Within 20 minutes	4 hours

Source: [3; 42; 48; 56; 57] *Table 3*

NONSULFONYLUREA SECRETAGOGUE (GLINIDE) THERAPY

The nonsulfonylurea secretagogues, more commonly known as meglitinides or glinides, are hypoglycemic agents that predominantly affect postprandial glucose levels (***Table 3***). There are two medications considered to be within this classification of hypoglycemic agents: repaglinide, which is a meglitinide, and nateglinide, which is a D-phenylalanine derivative [7; 35; 42]. The ideal candidate for glinide therapy would have type 2 diabetes for which medical nutrition therapy and exercise has not achieved euglycemia, alone or in combination with other agents. In contrast, this therapy is not a viable option for patients with [3]:

- Type 1 diabetes
- Ketoacidosis
- Known hypersensitivity to either drug
- Severe infection
- Surgery
- Trauma

NATEGLINIDE

Nateglinide is a very rapid acting amino-acid derivative known as D-phenylalanine. Nateglinide interacts with the adenosine triphosphate (ATP)-sensitive potassium channel on pancreatic beta cells to produce calcium influx and insulin secretion. As with repaglinide, the extent of insulin release is glucose dependent and diminishes at low glucose levels [42; 58]. Nateglinide is rapidly absorbed, and the onset of action is approximately within 20 minutes of ingestion. This medication is taken just prior to a meal due to this mechanism of action [7; 42]. Due to the short half-life (1.5 hours), nateglinide stops acting on the pancreatic beta cells shortly after the meal, decreasing the possibility of hypoglycemia. This medication is excreted in the feces after it is metabolized in the intestinal tract [7]. Nateglinide can be used as monotherapy or in combination with metformin, TZD, or both. It is important to note that if adequate control is not achieved using a sulfonylurea agent, it is unlikely that nateglinide will be effective [42].

REPAGLINIDE

Repaglinide stimulates the release of insulin from functioning beta cells in the pancreatic islets. Repaglinide closes ATP-dependent potassium channels in the beta-cell membrane, which depolarizes the beta cell and leads to an opening of calcium channels. The resulting increased calcium influx induces insulin secretion [42]. This action is highly tissue selective, with low affinity for heart and skeletal muscle [59]. Results with repaglinide therapy are best achieved when taken within 15 to 30 minutes of a meal [7; 42]. This results in a greater insulin release from the pancreas during the first phase. The onset of action is rapid (usually within 15 to 60 minutes), and the drug possesses a short half-life (about one hour), resulting in a low plasma level of the medication [3; 42]. Excretion of repaglinide is completed via the intestinal system in the form of feces [7; 42].

Repaglinide can be utilized as a monotherapy agent or in conjunction with a biguanide, thiazolidinedione (TZD), or both [42; 56].

POTENTIAL SIDE EFFECTS

As with all medications, there are precautions when considering glinide therapy. These medications should not be used during pregnancy, in women who are breastfeeding, or in children [35]. Repaglinide should be used cautiously in persons with hepatic dysfunction, and routine, close monitoring of liver function is necessary. Individuals who are elderly, malnourished, debilitated, or have adrenal or pituitary dysfunction are particularly susceptible to hypoglycemia, the most common side effect related to this class of medication (<10%). The key measure for preventing hypoglycemia in patients taking glinides is patient education stressing the need to omit the medication if a meal is not going to be consumed [42].

Aside from hypoglycemia, there are less common side effects associated with glinides, including [3]:

- Bronchitis, sinusitis, rhinitis (<10%)
- Nausea/vomiting, diarrhea, constipation (2% to 5%)
- Headache, chest pain, urinary tract infection, back pain (2% to 9%)
- Dizziness (3.6%)

As with any pharmaceutical preparation, healthcare professionals should be aware of potential interactions between medications that an individual is prescribed. In the case of both sulfonylureas and nonsulfonylurea secretagogues, potential effects of drug-to-drug interactions include [56]:

- Drug level and/or effect decreased by: carbamazepine, charcoal, corticosteroids, estrogens, isoniazid, nicotinic acid, nonsteroidal anti-inflammatory drugs, oral contraceptives, phenobarbital, primidone, rifampin, sympathomimetics, thiazide and other diuretics, thyroid products, urinary alkalinizers
- Drug level and/or effect increased by: beta blockers, chloramphenicol, cimetidine, delavirdine, diclofenac, fibric acid derivatives, fluconazole, gemfibrozil, ketoconazole, nicardipine, salicylates, sulfonamides, telithromycin, tricyclic antidepressants

Herbs that may increase the effects of secretagogues include burdock, dandelion, eucalyptus, and marshmallow. As noted, it is imperative to understand these interactions and the impact they have on blood glucose levels. Rapid identification of hypoglycemic or hyperglycemic emergencies utilizing blood glucose monitoring and assessment skills is also critical [56].

CASE STUDY

Patient L is an African American man, 52 years of age, presenting to his primary care physician with complaints of frequent urination and excessive thirst, particularly in the late afternoon and early evening. He is a truck driver and works 12 hours each day. Patient L is 6 feet 1 inch tall and weighs 215 pounds, with a calculated BMI of 28.4 kg/m^2. He confirms a family history of diabetes on both his father's and mother's sides. A random finger stick results in a blood glucose level of 243 mg/dL.

***Rationale and comments**: The information gained from Patient L's initial examination indicates diabetes. Again, any random blood glucose greater than 200 mg/dL, accompanied by symptoms (polyuria and excessive thirst for this patient), is considered diagnostic for diabetes.*

Patient L is referred for fasting blood work, which reveals the following:

- HbA1c: 9.1% (estimated average glucose: 214 mg/dL)
- Fasting blood glucose: 132 mg/dL
- Two-hour glucose level (after 75 g oral glucose tolerance test): 310 mg/dL
- Triglycerides: 147 mg/dL
- LDL: 102 mg/dL
- HDL: 46 mg/dL
- Liver function tests: Within normal limits
- Renal function: Within normal limits

ALPHA-GLUCOSIDASE INHIBITORS						
Drug Name	**Trade Name**	**Dose Range**	**Maximum Daily Dose**	**Frequency**	**Onset of Action**	**Duration of Action**
Acarbose	Precose	25–100 mg before meals	300 mg	Three times daily	Immediate	6 hours
Miglitol	Glyset (discontinued) Generic	25–100 mg before meals	300 mg	Three times daily	Rapid	Less than 4 hours

Source: [3; 40; 41; 42; 48] *Table 4*

Patient L is diagnosed with type 2 diabetes and is referred to an ADA-recognized diabetes education program. A follow-up appointment in three months is scheduled.

Upon the follow-up primary care appointment, Patient L's HbA1c shows minimal change, with a result of 8.8% (estimated average glucose: 206 mg/dL) and a fasting blood glucose level of 148 mg/dL. The patient's SMBG records reveal fasting blood glucose levels consistently between 150 mg/dL and 165 mg/dL and postprandial levels steadily between 230 mg/dL and 290 mg/dL. Patient L states that he has difficulty eating meals at consistent times due to his profession and exercises when he is able. There has been little change in his weight since his last visit.

Patient L's physician determines that the best course of therapy would be to initiate nonsulfonylurea secretagogue therapy. The patient is started on repaglinide 2 mg 15 minutes prior to his first three main meals. He is advised not to take the medication if he does not eat the meal. He is strongly encouraged to continue with his meal and exercise plans.

***Rationale and comments**: This is an appropriate choice of medication for Patient L due to his inconsistent eating habits and continued postprandial hyperglycemia, his sedentary occupation, and his weight (not considered obese). His postprandial levels are the problematic factor, and repaglinide will allow Patient L the freedom to adjust his medication therapy to his eating schedule.*

ALPHA-GLUCOSIDASE INHIBITOR THERAPY

There are two available oral antihyperglycemic agents in the category of alpha-glucosidase inhibitors: acarbose and miglitol (***Table 4***). In contrast to sulfonylureas, alpha-glucosidase inhibitors do not enhance insulin secretion. The antihyperglycemic action of these agents is a result of a reversible inhibition of membrane-bound intestinal alpha-glucoside hydrolase enzymes. In addition, acarbose inhibits pancreatic alpha-amylase. Pancreatic alpha-amylase hydrolyzes complex starches to oligosaccharides in the lumen of the small intestine; membrane-bound intestinal alpha-glucosidases hydrolyze oligosaccharides, trisaccharides, and disaccharides to glucose and other monosaccharides in the brush border of the small intestine. When these factors are inhibited, glucose absorption is delayed and postprandial blood glucose levels remain within the normal range. Because their mechanism of action is different, alpha-glucosidase inhibitors enhance glycemic control achieved by sulfonylureas, insulin, or metformin when used in combination. In addition, alpha-glucosidase inhibitors diminish the insulinotropic and weight-increasing effects of sulfonylureas [60].

An ideal candidate for alpha-glucosidase therapy will have:

- Dyslipidemia
- Obesity
- Symptoms suggesting postprandial hyperglycemia

ACARBOSE

Acarbose is prescribed in doses of 25–100 mg, with a maximum daily dose of 300 mg [7; 42]. Acarbose should be taken in equal doses three times a day for maximum efficacy [7]. The onset of action of acarbose is immediate, with peak effect seen in one hour. Acarbose has a half-life of two hours and a duration of action of approximately six hours [42; 56]. Acarbose is excreted via the renal and fecal routes without being metabolized [7].

MIGLITOL

Miglitol has a dose range of 25 – 100 mg taken at the beginning of each meal, up to a maximum of 300 mg/day. Miglitol has a rapid onset of action, and peak effect is reached in about two to three hours. The half-life is roughly two hours, and the duration of action is believed to be less than four hours [42; 56]. No metabolites have been detected in plasma, urine, or feces, indicating a lack of either systemic or presystemic metabolism [42; 61]. The drug is excreted via the renal route [7; 42].

POTENTIAL SIDE EFFECTS

Due to the location and mechanism of action, alpha-glucosidase inhibitors are not well absorbed in the intestinal tract. Elevated plasma levels of acarbose have been found in persons with a creatinine clearance of less than 25 mL per minute, suggesting accumulation. With this in mind, caution should be used in these patients. In addition, use of alpha-glucosidase inhibitors is contraindicated in patients with [42]:

- Small bowel disease
- Colonic ulceration
- Obstructive bowel disorder
- Chronic intestinal disorders of digestion or absorption
- Cirrhosis of the liver
- Elevated creatinine levels >2.0 mg/mL

Furthermore, women who are pregnant or breast-feeding and children should not use these agents [42].

Side effects for alpha-glucosidase inhibitors are typically confined to the gastrointestinal system and usually occur during initiation of therapy or when adjustments to the dose are made [42]. Potential side effects of alpha-glucosidase inhibitors include [42]:

- Gastrointestinal effects
  - Abdominal pain: 12% to 21%
  - Diarrhea: 29% to 33%
  - Flatulence: 42% to 77%
- Increased plasma concentration relative to the degree of renal dysfunction
- Elevation in transaminases with acarbose (believed to be related to the use of higher-than-recommended dosages)

These side effects are generally self-limiting and transient and can be minimized by starting with a lower dosage and titrating up to desired effect or maximum therapeutic dose [42; 56]. When caring for a patient being treated with alpha-glucosidase inhibitors, two-hour postprandial blood glucose levels should be monitored to identify effectiveness of the therapy [3; 42]. Studies have demonstrated elevations in serum transaminases (aspartate aminotransferase [AST] or alanine aminotransferase [ALT]), so liver function should also be monitored periodically.

Lastly, alpha-glucosidase inhibitors' effects have the potential to be altered by charcoal products and may diminish the bioavailability of ranitidine, propranolol, and digoxin [42; 62].

Potential drug-drug interactions with the use of acarbose include decreased drug levels and/or efficacy when taken in combination with calcium channel blockers, corticosteroids, estrogens, fosphenytoin, hormonal contraceptives, isoniazid, nicotinic acid,

phenothiazine, phenytoin, sympathomimetics, thiazides and other diuretics, and thyroid products [42]. Digestive enzyme preparations containing carbohydrate-splitting enzymes (e.g., amylase, pancreatin) and intestinal absorbents (e.g., activated charcoal) may reduce the effects of acarbose [42]. As mentioned, digoxin levels may be reduced when taken in combination with acarbose.

Although in the same category as acarbose, miglitol has different drug interactions including [42; 56; 62]:

- Digoxin, propranolol, and ranitidine, which may decrease the bioavailability of miglitol
- Charcoal and digestive enzyme preparations such as amylase and pancreatin, which reduce the effect of miglitol

CASE STUDY

Patient V is a Hispanic man, 61 years of age, presenting to the primary care physician with complaints of polydipsia, polyphagia, and fatigue for the past month. Upon further assessment, he states that he has recently had his eyeglass prescription adjusted due to blurred vision. He is 5 feet 10 inches tall and weighs 245 pounds; his calculated BMI is 35.2 kg/m^2. The patient reveals a family history of diabetes on both sides. He works a physical job in a warehouse lifting 50-pound boxes. A random finger stick reveals a blood glucose level of 220 mg/dL. As previously discussed, this is sufficient information to diagnose diabetes.

Patient V's fasting blood work reveals the following:

- HbA1c: 8.7% (estimated average glucose: 203 mg/dL)
- Fasting blood glucose: 151 mg/dL
- Two-hour glucose level (after 75 g oral glucose tolerance test): 233 mg/dL
- Triglycerides: 210 mg/dL
- LDL: 112 mg/dL
- HDL: 35 mg/dL
- Liver function tests: Within normal limits
- Renal function: Within normal limits

Patient V is referred to an ADA-recognized diabetes education program and is instructed to return for follow-up in three months.

When the patient returns to his primary care physician, his follow-up HbA1c demonstrates minimal change with the result of 8.2% (estimated average glucose: 189 mg/dL) and a fasting blood glucose level of 156 mg/dL. SMBG records reveal fasting blood glucose levels consistently between 135 mg/dL and 160 mg/dL and postprandial levels steadily between 220 mg/dL and 248 mg/dL. His lipid levels remain greater than goal as well. Patient V indicates that he has been following his meal and exercise planning goals but has experienced minimal success.

After evaluation of the patient's blood work, history, and progress to date, the physician decides to utilize the alpha-glucosidase inhibitor, acarbose. Patient V is started on acarbose 25 mg with each meal, and adherence to his culturally specific meal and exercise plans is stressed.

***Rationale and comments**: Although not commonly utilized, acarbose is appropriate for Patient V due to his elevated lipid levels and postprandial hyperglycemia. His fasting blood glucose levels are above normal, and the physician has determined that his postprandial levels are the cause of the elevated HbA1c levels. Acarbose should improve the patient's postprandial glucose levels and his lipid levels.*

BIGUANIDE THERAPY

Biguanides are popular medications in diabetes treatment. Primitive versions of guanidines were used historically, in the form of extracts of *Galega officinalis* (goat's rue or French lilac), for blood glucose control [7]. The modern form was first introduced in Europe in the late 1950s. There is only one agent, metformin, available in this class of diabetes medications (***Table 5***) [42].

BIGUANIDES						
Drug Name	**Trade Name(s)**	**Dose Range**	**Maximum Daily Dose**	**Frequency**	**Onset of Action**	**Duration of Action**
Metformin	Glucophage, Fortamet	500 mg twice daily or 850 mg once daily	2,550 mg	Two or three times daily	Within days	6 hours
	Glucophage XL (extended-release)	500–2,000 mg daily with evening meal or 1,000 mg two times daily	2,500 mg	Once or twice daily	Within days	Up to 24 hours
Metformin liquid	Riomet	500 mg twice daily or 850 mg once daily	1,000 mg	Twice daily	–	–

Source: [3; 42; 48; 56; 57] *Table 5*

Metformin therapy is now frequently utilized due to the lack of hypoglycemia as a side effect [63]. If not contraindicated and if tolerated, metformin is the ADA-preferred initial pharmacologic agent for management of type 2 diabetes [35]. It is an antihyperglycemic agent that lowers both basal and postprandial plasma glucose and improves glucose tolerance. Metformin acts in several ways to achieve this effect, including inhibiting hepatic glucose production and intestinal absorption of glucose [63]. It also increases peripheral glucose uptake and utilization [42]. Unlike sulfonylureas, metformin does not increase the risk of hypoglycemia and does not cause hyperinsulinemia [64]. Insulin secretion remains unchanged using metformin, but fasting plasma insulin levels and day-long plasma insulin response may actually decrease [3].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The Institute for Clinical Systems Improvement recommends clinicians should initiate metformin as first-line pharmacotherapy for patients with type 2 diabetes, unless medically contraindicated.

(https://www.icsi.org/wp-content/uploads/2019/02/Diabetes.pdf. Last accessed October 28, 2022.)

Level of Evidence/Strength of Recommendation: High/Strong

Metformin therapy has been extensively studied, and a meta-analysis of randomized controlled trials supports the benefit of metformin use in comparison to sulfonylureas [7]. Patients on metformin therapy demonstrated greater fasting blood glucose reduction and improvement in weight [7]. Compared with treatment with a sulfonylurea, monotherapy treatment with metformin is associated with a lower risk of major adverse cardiovascular events among patients with diabetes and reduced kidney function [65]. Although the benefits are well-documented, metformin therapy may not be the treatment of choice in all cases. The optimal candidate would present with:

- Type 2 diabetes
- Dyslipidemia
- Obesity or a genetic factor increasing the potential for insulin resistance
- Elevated fasting blood glucose level
- Tendency for hypoglycemia with sulfonylurea therapy

Additionally, metformin is approved for use in children 10 years of age and older [42]. It is the only oral diabetes medication approved for children.

Metformin is available in both immediate-release and extended-release tablets. The initial recommended dose for adults is 500 mg once or twice daily or 850 mg once daily, which may be titrated up every one to two weeks to a maximum safe dose of 2,550 mg/day [42; 48]. In general, doses of at least 1,500 mg/day are necessary to produce clinically significant effects. Although the maximum safe dose is 2,250 mg/day, most preparations contain a maximum of 2,000 mg of active ingredient [66]. Metformin should be started in the evening and can be taken in two or three divided doses to improve efficacy [7; 42]. The extended-release formulation is initially prescribed at dosages of 500–1,000/day, which may be titrated weekly to a maximum dose of 2,000 mg daily [42].

The onset of action for metformin is within days, but the peak effect of the immediate-release form is typically seen in two to four hours [56]. Peak effect with the use of the extended-release form is in four to eight hours. The duration of action is approximately 6 hours for immediate-release metformin, while the extended-release preparation is up to 24 hours [48]. The drug has a plasma half-life of four to nine hours [42].

Metformin is not metabolized by the liver [42]. Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the unchanged drug is excreted in the urine [64].

Metformin is used both as a single agent and in combination with other therapies. It has been formulated into a multitude of combination preparations to increase the efficacy of both medications. The use of these combination formulations is cost effective and results in improvements in patient adherence to their medication regimen.

POTENTIAL SIDE EFFECTS

Although metformin is beneficial for many people, it should be used with caution in some populations. Women who are pregnant or breastfeeding should not utilize metformin therapy. There have been no formal studies to show benefit or risk analysis when metformin is used during pregnancy. Metformin use should also be temporarily halted in patients who are acutely ill or who are predisposed to acute renal failure or tissue hypoperfusion. Lastly, metformin should be withheld for a minimum of two days or until renal function has returned following any radiologic test utilizing iodinated contrast media [42]. Examples of such tests include urograms, angiography, intravenous cholangiography, and any scans using intravascular contrast media.

Metformin therapy is contraindicated in patients for whom the adverse effects may be life-threatening. This includes patients with elevated serum creatinine levels greater than 1.5 mg/dL for men or greater than 1.4 mg/dL for women, abnormal creatinine clearance from any cause, and patients with an eGFR <30 mL/minute/1.73 m^2 [7; 42; 67]. Because metformin is excreted through the kidneys, accumulation of the medication can occur in the presence of renal dysfunction. In 2016, the FDA issued a drug safety communication, new recommendations, and a label change requirement for metformin and metformin-containing medications for use in certain patients with mild-to-moderate renal impairment. The new FDA recommendations include [67]:

- Obtain eGFR prior to initiating metformin therapy.
- Initiate metformin in patients with an eGFR between 30–45 mL/minute/1.73 m^2 is not recommended. Metformin is contraindicated in patients with an eGFR less than 30 mL/minute/1.73 m^2.
- Obtain an eGFR at least annually in all patients taking metformin; assess renal function more frequently in patients at increased risk for renal impairment (e.g., the elderly).

- Assess the benefits of continuing metformin treatment in patients whose eGFR falls below 45 mL/minute/1.73 m^2; discontinue if the eGFR falls below 30/mL/minute/1.73 m^2.

Individuals with hepatic dysfunction who are receiving biguanide therapy can be predisposed to lactic acidosis [42]. Due to the potential damaging effects of alcohol on the liver, any individual with a history of alcohol abuse or binge drinking would not be a good candidate for metformin therapy. Finally, individuals with a history of chronic obstructive pulmonary disease or cardiac function impairment should not be prescribed metformin due to the potential of lactate accumulation in these hypoxic conditions [7; 42].

Side effects of metformin are relatively mild and self-limiting, with the exception of lactic acidosis. Typically, the side effects are gastrointestinal in nature and resolve within the first few weeks of therapy. Potential side effects include [42]:

- Lactic acidosis (0.03/1,000 patient years)
- Diarrhea, nausea/vomiting, flatulence, bloating, anorexia (>10% during initiation)
- Metallic taste (3% during initiation)
- Decrease of vitamin B12 to subnormal levels (7% in one study)
- Impaired hepatic function

Biguanide therapy rarely causes serious side effects, but lactic acidosis has occurred in some cases and is an important consideration for patients taking metformin [42]. Lactic acidosis, although rare, is a potentially fatal metabolic complication. Persons at risk include those with renal insufficiency and those with acute or unstable heart failure who are at risk for hypoperfusion and hypoxemia. Characteristics of lactic acidosis include:

- Serum lactate levels greater than 5 mmol/L
- Decreased blood pH
- Electrolyte abnormalities resulting in an elevated anion gap
- Increased lactate/pyruvate ratio

The onset of lactic acidosis symptoms are generally vague and subtle at presentation [3]. The person's symptoms may include malaise, myalgia, nonspecific abdominal pain, increased somnolence, and/or respiratory distress. Serum lactate levels should be monitored periodically or when a patient is at risk for lactate accumulation [62]. If a patient develops symptoms of lactic acidosis while taking metformin, the agent should be discontinued immediately [42; 62].

Metformin can interact with other medications and herbs. Knowledge of these interactions is necessary to ensure appropriate patient care. If taken with metformin, beta blockers may potentiate hypoglycemia. There are many medications that may potentiate hyperglycemia, including [56]:

- Calcium channel blockers
- Corticosteroids
- Estrogens
- Fosphenytoin
- Hormonal contraceptives
- Isoniazid
- Nicotinic acid
- Phenothiazines
- Phenytoin
- Sympathomimetics
- Thiazides and other diuretics
- Thyroid drugs

Several medications compete for the same renal tubular transport systems as metformin, which can increase the serum levels of both drugs. Medications with this effect include amiloride, cimetidine, digoxin, morphine, nifedipine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin [42]. In addition to these interactions, consumption of guar gum may decrease hypoglycemic effect of metformin.

CASE STUDY

Patient K is a white woman, 71 years of age, presenting to her primary care physician with complaints of fatigue, polyuria, polyphagia, and polydipsia for the past few months. She is 5 feet 4 inches tall and weighs 205 pounds, with a calculated BMI of 35.3 kg/m^2. She confirms a family history of diabetes on her mother's side, a personal history of having given birth to a child weighing more than 9 pounds, and arthritis of her bilateral knees. A finger stick reveals a blood glucose level of 198 mg/dL.

***Rationale and comments**: Based on the information gathered during the initial examination, Patient K cannot be definitively diagnosed with diabetes. Although symptoms of diabetes are present, a blood glucose level of 198 mg/dL is not diagnostic unless further laboratory testing is completed.*

In order to gain additional information, Patient K is referred for a complete blood work-up. The results of this work-up reveal:

- HbA1c: 8.0% (estimated average glucose: 183 mg/dL)
- Fasting blood glucose: 195 mg/dL
- Two-hour glucose level (after 75 g oral glucose tolerance test): 160 mg/dL
- Triglycerides: 167 mg/dL
- LDL: 123 mg/dL
- HDL: 29 mg/dL
- Liver function tests: Within normal limits
- Renal function: Within normal limits

Based on this additional information, Patient K is diagnosed with type 2 diabetes and is referred to an ADA-recognized diabetes education program. At her three-month follow-up appointment, the patient's HbA1c level has increased to 8.6% (estimated average glucose: 200 mg/dL) and her fasting blood glucose level is 205 mg/dL. Sporadic SMBG records reveal fasting levels consistently between 180 mg/dL and 210 mg/dL and postprandial levels between 150 mg/dL and 170 mg/dL. Patient K states she did not attend the education class as recommended but has attempted to limit her sugar intake. She denies starting an exercise program because of the pain she experiences in her knees when she tries to walk.

It is determined, taking into account Patient K's blood glucose level and failure to make lifestyle changes, that the best course of treatment is medication therapy utilizing metformin. The patient is prescribed metformin 500 mg each evening and water aerobics for exercise. Her physician again stresses the importance of SMBG and participation in diabetes self-management education.

***Rationale and comments**: The therapy prescribed is appropriate for Patient K for many reasons. Her fasting blood glucose levels are higher than normal, her postprandial levels are slightly elevated, and she is suspected to have insulin resistance. She is obese and has been non-adherent to her meal and exercise plans. Her SMBG has been erratic. Metformin will positively impact the patient's fasting blood glucose levels by decreasing the liver's production of endogenous glucose, decreasing insulin resistance, and decreasing the reabsorption of carbohydrates in the gut.*

THIAZOLIDINEDIONE THERAPY

The group of antihyperglycemic agents referred to as the thiazolidinediones, or TZDs, is one of the more modern classes of diabetes medications (***Table 6***). These agents improve blood glucose levels by increasing the body's sensitivity to insulin [3]. TZDs are not hypoglycemic agents and do not precipitate hypoglycemia, but when used in combination with a sulfonylurea, there is a synergistic effect to improve glucose tolerance by complimentary mechanisms [62].

THIAZOLIDINEDIONES						
Drug Name	**Trade Name**	**Dose Range**	**Maximum Daily Dose**	**Frequency**	**Onset of Action**	**Duration of Action**
Pioglitazone	Actos	15–45 mg daily	45 mg	Once daily	Days	Unknown
Rosiglitazone	Avandia (discontinued)	4–8 mg daily	8 mg	Once or twice daily	Days to weeks	Unknown

Source: [3; 42; 48; 56; 57] *Table 6*

TZDs depend on the presence of insulin to act. Insulin resistance is decreased in the periphery and in the liver when TZD therapy is utilized, resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output. TZDs are a potent agonist for peroxisome proliferator-activated receptor-gamma (PPARγ). PPAR receptors are found in tissues important for insulin action, such as adipose tissue, skeletal muscle, and the liver, and also in the vascular endothelium, macrophages and other cell types [7; 42; 62]. Activation of PPARγ nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism [42; 62].

TZDs have been found to reduce the hyperglycemia, hyperinsulinemia, and hypertriglyceridemia characteristic of insulin-resistant states such as type 2 diabetes. The metabolic changes produced by TZDs result in increased responsiveness of insulin-dependent tissues [62; 68]. TZDs enhance the action of insulin at the receptor or post-receptor level in the peripheral hepatic tissues, reversing or partially reversing insulin resistance [69]. In addition, TZDs improve insulin sensitivity within the muscle and adipose tissues, further improving blood glucose levels [56].

In addition to their blood glucose-regulating effects, TZDs can improve the efficiency of the cardiac workload [3]. Adipose tissue expression of adiponectin is lowered in the presence of insulin resistance. As a result, lower plasma levels have been documented in humans with obesity, type 2 diabetes, and/or coronary artery disease. Research and trials have also demonstrated a close correlation between changes in adiponectin plasma levels after TZD treatment and measures of insulin-mediated glucose metabolism and adipose tissue distribution [7].

TZDs can be utilized as a monotherapy or in combination with metformin, a sulfonylurea, a secretagogue, and/or insulin. They should be used as monotherapy agents only when insulin production appears to be adequate [3]. Due to the adiponectin relationship, this is an ideal medication regimen for patients with type 2 diabetes complicated by obesity and/or coronary artery disease. However, TZD therapy is contraindicated in some cases, including for patients with [42; 62]:

- Acute liver disease or ALT levels greater than 2.5 times the upper limit
- Symptomatic class III or IV heart failure (black box warning)
- Jaundice
- Hypersensitivity to the medication
- Type 1 diabetes
- Diabetic ketoacidosis

TZDs are not recommended for patients who plan to become pregnant [42]. Although TZDs are contraindicated for the treatment of type 1 diabetes, research is being done to identify the risks and benefits associated with TZD therapy in type 1 diabetics with a BMI greater than 27 kg/m^2 [7].

PIOGLITAZONE

Pioglitazone is initially prescribed at a dose of 15 – 30 mg once daily, which may be increased to the desired response up to a maximum of 45 mg/day [42]. The exact onset of action of pioglitazone is unknown, but peak effect is reached in approximately two hours, a time that may be delayed with food. The half-life of pioglitazone is 16 to 24 hours [42; 56]. Pioglitazone is extensively metabolized by hydroxylation and oxidation; the metabolites also partly convert to glucuronide or sulfate conjugates. Following oral administration, approximately 15% to 30% of the dose is excreted in the urine. Renal elimination of pioglitazone is negligible, and the drug is excreted primarily as metabolites and their conjugates. It is presumed that most of the oral dose is excreted into the bile either unchanged or as metabolites and eliminated in the feces [68].

ROSIGLITAZONE (DISCONTINUED)

Rosiglitazone should be started at an initial daily dose of 4 mg, regardless of whether it is being used as monotherapy or as part of combination therapy [42]. After several weeks, the dose may be titrated up, if necessary, to a maximum of 8 mg/day. Rosiglitazone may be taken in two divided doses [42; 48]. The onset of action for rosiglitazone is unknown; maximum effects may not be present for up to 12 weeks. The drug has a peak action time of about one hour with a half-life of three to four hours [42; 56]. Rosiglitazone is extensively metabolized, and the major routes of metabolism are *N*-demethylation and hydroxylation, followed by conjugation with sulfate and glucuronic acid. All the circulating metabolites are considerably less potent than the parent drug and, therefore, are not expected to contribute to the insulin-sensitizing activity of rosiglitazone. The majority of rosiglitazone metabolites are eliminated in the urine (64%) and the feces (23%) [42; 70].

POTENTIAL SIDE EFFECTS

Weight gain is the most recognized side effect with TZD therapy and is thought to be a result of plasma volume expansion leading to edema [42]. As a result of this plasma volume expansion, there is also a small reduction in hemoglobin, hematocrit, and neutrophil counts [7]. Other notable side effects include [3; 42]:

- Increased total serum cholesterol
- Fluid retention (5% with monotherapy and 15% with insulin therapy)
- Headache, arthralgia, back pain (5% to 14%)
- Nausea and diarrhea (4% to 6%)
- Small decrease in hemoglobin, hematocrit, and neutrophil counts (5%)
- Elevation in ALT levels (1.9%)

In addition, rosiglitazone is associated with specific adverse effect risks, such as [3; 42]:

- Bone fracture in women
- Decreased efficacy of oral contraceptives
- Resumption of ovulation in premenopausal anovulatory women
- Increased risk of heart failure (resulting in black-box warning and eventual removal from market)

TZD therapy has several known drug-drug interactions, including [56; 62]:

- Atorvastatin: may decrease atorvastatin and pioglitazone levels
- Hormonal contraceptives in conjunction with pioglitazone may decrease the level of hormonal contraceptives, reducing the effectiveness of the contraceptive
- Ketoconazole may inhibit pioglitazone metabolism

The concurrent administration of certain herbs, such as burdock, dandelion, eucalyptus, and marshmallow, can result in potentiation of TZDs' hypoglycemic effects.

CASE STUDY

Patient H is an African American woman, 38 years of age, presenting to her primary care physician for a routine physical with complaints of fatigue and constant hunger. She is 5 feet 7 inches tall and weighs 235 pounds, with a calculated BMI of 36.9 kg/m^2. She has a strong history of diabetes and coronary artery disease on both sides of her family, a personal history of gestational diabetes with her last two children, and is employed as a legal secretary. A finger stick reveals a blood glucose level of 213 mg/dL. A diagnosis of diabetes is made, and the patient is referred for fasting blood work, which reveals:

- HbA1c: 7.8% (estimated average glucose: 177 mg/dL)
- Fasting blood glucose: 137 mg/dL
- Two-hour glucose level (after 75 g oral glucose tolerance test): 187 mg/dL
- Triglycerides: 178 mg/dL
- LDL: 131 mg/dL
- HDL: 21 mg/dL

The physician refers Patient H to an ADA-recognized diabetes education program so she may receive information regarding blood glucose monitoring and exercise and meal planning. At her follow-up appointment, the patient's HbA1c has not significantly changed, with a result of 7.7% (estimated average glucose: 174 mg/dL) and a fasting blood glucose level of 172 mg/dL. SMBG records reveal fasting blood glucose levels consistently between 155 mg/dL and 190 mg/dL and postprandial levels steadily between 190 mg/dL and 213 mg/dL. Patient H claims to be adherent to her meal and exercise planning goals but is struggling with weight loss and hunger. As a result, her physician initiates her on TZD therapy. The patient is prescribed pioglitazone 15 mg each morning, and she is advised to continue with her meal and exercise plans. Patient H is also given instructions to report any signs of sudden weight gain, shortness of breath, or chest pains, as these could be signs of excessive fluid retention related to TZD therapy.

***Rationale and comments**: Patient H has been adherent to her meal and exercise plan with little success and growing frustration. Her morning and postprandial blood glucose levels are above normal, and both contribute to the elevated HbA1c levels. TZD therapy is indicated for Patient H because of her family history of coronary heart disease, obesity, and suspected insulin resistance.*

DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITOR THERAPY

A more recent addition to the available treatments for type 2 diabetes is the dipeptidyl peptidase-4 (DPP-4) inhibitor, of which there are four approved medications: sitagliptin, linagliptin, saxagliptin, and alogliptin (***Table 7***). This discovery has launched a new era in the management of hyperglycemia. The two well-characterized incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), both cause an increase in insulin synthesis and release from pancreatic beta cells in response to normal or increased blood glucose levels [71; 72]. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by intracellular signaling pathways involving cyclic adenosine monophosphate. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production [57]. DPP-4 inhibitors are believed to exert their action in patients with type 2 diabetes by slowing the inactivation of incretin hormones. Concentrations of the active intact hormones are increased by these agents, thereby strengthening and prolonging their action. GLP-1 and GIP are released by the intestine throughout the day, and levels are increased in response to a meal. These hormones are rapidly inactivated by the enzyme DPP-4.

DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITORS						
Drug Name	**Trade Name**	**Dose Range**	**Maximum Daily Dose**	**Frequency**	**Onset of Action**	**Duration of Action**
Sitagliptin	Januvia	25–100 mg daily	100 mg	Once daily	1 to 4 hours	24 hours
Linagliptin	Tradjenta	5 mg daily	5 mg	Once daily	1.5 hours	24 hours
Saxagliptin	Onglyza	2.5–5 mg daily	5 mg	Once daily	2 hours	24 hours
Alogliptin	Nesina	12.5–25 mg daily	25 mg	Once daily	—	24 hours

Source: [3; 42; 48; 56; 57; 73] *Table 7*

SITAGLIPTIN

Sitagliptin is generally dosed at 100 mg/day, with decreased doses necessary for patients with renal impairment [42]. It is given once daily and may be used alone or with other medications to obtain the best results. The drug is rapidly absorbed, with time to peak action within one to four hours after ingestion. Sitagliptin has a half-life of 12 hours, with a duration of action equaling 24 hours. Metabolism is a minor pathway of elimination [42]. Six metabolites have been detected at trace levels and are not expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin. Following administration of sitagliptin, approximately all of the active drug was eliminated in feces (13%) or urine (87%) within one week of dosing, and renal clearance is approximately 350 mL/minute [57]. An estimated 79% of sitagliptin that is excreted in the urine is unchanged drug [42].

Sitagliptin is indicated for patients with type 2 diabetes who are not achieving adequate blood glucose control with medical nutrition therapy and exercise alone. It can be utilized as a monotherapy or in combination with metformin, a secretagogue, or a TZD [7; 42]. Sitagliptin may be used for a person with mild renal insufficiency at the full dosage. For patients with moderate renal insufficiency (creatinine clearance of 30–50 mL/minute), the dose should be 50 mg, and for those with a creatinine clearance of less than 30 mL/minute or end-stage renal disease and hemodialysis, the dosage should be 25 mg [42; 48].

Side Effects

The most common adverse effect associated with sitagliptin monotherapy is nasopharyngitis, which occurs in 5% of patients [42]. Additional adverse effects include [62]:

- Upper respiratory infection (6.2% in combination therapy)
- Headache (5.9%)
- Abdominal pain (2.2%)
- Diarrhea (2.4%)
- Nausea (1.3%)

When caring for an individual receiving sitagliptin therapy, it is also important to be aware of reports to the U.S. Food and Drug Administration (FDA) regarding 88 post-marketing cases of pancreatitis, 2 of which were hemorrhagic or necrotizing, in patients receiving sitagliptin therapy. These cases of pancreatitis were reported to the FDA between October 2006 and February 2009 [74]. In 2009, the FDA issued a special alert regarding the possible association of sitagliptin/metformin combination with acute pancreatitis [74]. A study that examined insurance records found that the use of sitagliptin could double the risk of developing acute pancreatitis [75]. Additionally, in 2013 the FDA announced that it is evaluating unpublished findings that suggest precancerous cellular changes (i.e., pancreatic duct metaplasia) in patients with type 2 diabetes treated with sitagliptin. The findings are based on examination of a small number of pancreatic tissue specimens taken from patients after they died from

unspecified causes [76]. Patients taking sitagliptin should be advised regarding symptoms of pancreatitis (i.e., persistent severe abdominal pain, anorexia, nausea, vomiting) and instructed to contact their physician should they experience these symptoms. In the case of sitagliptin, there are no known significant drug-herb interactions [56].

SAXAGLIPTIN

Saxagliptin is dosed at 2.5–5mg/day, with a lower dose used in patients with moderate or severe renal impairment or when the agent is prescribed in conjunction with a strong cytochrome P450 3A4 inhibitor [42; 77]. This agent is approved for use with other drugs or as monotherapy for the treatment of type 2 diabetes in adults. The time to peak action for saxagliptin is approximately two hours, and the drug is metabolized hepatically to 5-hydroxy saxagliptin, an active metabolite [77]. The majority of the drug and the metabolite are excreted in the urine (75%) and the feces (22%) [42].

Saxagliptin may be initiated as a single therapy or in conjunction with metformin, under the brand name Kombiglyze XR [42]. It may also be added on to an ongoing metformin, sulfonylurea, or TZD regimen. No adjustment of dosage is necessary for BMI, gender, or age. For patients with a creatinine clearance of 50 mL/minute or less, the recommended dosage is 2.5 mg once daily; for those with end-stage renal disease, a dose of 2.5 mg should be given once daily after dialysis [42].

Side Effects

The most common adverse reactions associated with saxagliptin are upper respiratory tract infection (7.7%), headache (6.5%), nasopharyngitis (6.9%), and urinary tract infection (6.8%) [62; 78]. Anyone with a hypersensitivity reaction should discontinue the drug immediately. There have been postmarketing reports of acute pancreatitis in patients taking saxagliptin [62; 78]. After initiating treatment, observe patients carefully for signs and symptoms of pancreatitis. An FDA safety review also has found that saxagliptin may increase the risk of heart failure, particularly in patients with heart or kidney disease [79]. As a result, the agency has added new warnings to drug labels.

LINAGLIPTIN

Linagliptin was approved by the FDA in 2011 for the treatment of patients with type 2 diabetes that is uncontrolled by diet modification and exercise [77]. In addition to monotherapy, it has also been studied as add-on therapy with metformin, pioglitazone, and a sulfonylurea. When used with a secretagogue, the dose of the secretagogue should be lowered in order to reduce the risk of hypoglycemia [62; 80]. Linagliptin is absorbed rapidly, with an onset of action of about 1.5 hours [42]. It is primarily excreted as unchanged drug in the feces (80%) and urine (5%) [42].

No dosage adjustment is necessary for patients with renal or hepatic impairment. Concurrent use of linagliptin with either insulin or a secretagogue is associated with an increased risk for hypoglycemia [42]. The medication may be taken with or without food, and the only significant contraindication is allergy or hypersensitivity to linagliptin [42; 77].

Side Effects

Side effects most commonly associated with linagliptin include headache (6%), nasopharyngitis (6% to 7%), arthralgia (6%), and back pain (6%) [42]. Drug interactions are also possible. Clinicians should consider using an alternative to any strong cytochrome P450 3A4 inducer in patients who are being treated with linagliptin, as the combination can reduce the effectiveness of linagliptin [42]. The FDA has advised of postmarketing reports of acute pancreatitis, including fatal pancreatitis, in patients taking linagliptin [80; 81]. If pancreatitis is suspected, the drug should be promptly discontinued.

ALOGLIPTIN

Approved by the FDA in 2013, alogliptin is now available in the United States. It is usually dosed at 12.5–25 mg/day and is available in fixed-dose formulations with metformin (brand name Kazano) and with pioglitazone (brand name Oseni) [42; 73]. Alogliptin is approved for use with diet and exercise to improve blood sugar control in adult patients with type 2 diabetes.

Alogliptin or its combination formulations may be added to an ongoing regimen. It has been shown to be safe and effective in reducing HbA1c in 14 clinical trials involving more than 8,500 patients [73]. The most common side effects are nasal congestion, headache, and upper respiratory tract infection [42]. In 2013, the FDA requested that the manufacturer complete postmarking studies related to the safety of the drug, including a cardiovascular outcomes trial, a study monitoring for liver abnormalities, and three pediatric studies [73]. A safety review published by the agency in 2016 found that alogliptin may increase the risk of heart failure, particularly in patients with heart or kidney disease [79]. As a result, the agency has added new warnings to drug labels.

CASE STUDY

Patient B is a Pacific Islander woman, 64 years of age, presenting to the primary care physician with complaints of a urinary tract infection (UTI) and fatigue. She attributes the fatigue to waking frequently at night due to the UTI. The patient denies any recent history of febrile states or pain with urination. She is 5 feet 1 inch tall and weighs 170 pounds, with a calculated BMI of 32.2 kg/m^2. She confirms a family history of diabetes on her mother's side and admits to a sedentary lifestyle.

Patient B's urine sample is negative for infection. A random finger stick reveals a blood glucose level of 207 mg/dL. She is diagnosed with type 2 diabetes based on her blood glucose level and the characteristic symptoms (polyuria and fatigue).

In order to gain additional information, Patient B is referred for fasting blood work. The results of this blood work indicate:

- HbA1c: 7.8% (estimated average glucose: 177 mg/dL)
- Fasting blood glucose: 147 mg/dL
- Triglycerides: 167 mg/dL
- LDL: 199 mg/dL
- HDL: 32 mg/dL

Patient B is referred to an ADA-recognized diabetes education program and is initiated on treatment for dyslipidemia based on her very high LDL level and borderline high triglycerides.

When Patient B returns for her three-month follow-up appointment, she acknowledges compliance to her meal and exercise planning goals with very little success. Her repeat HbA1c demonstrates minimal change with a result of 7.6% (estimated average glucose: 171 mg/dL) and a fasting blood glucose level of 165 mg/dL. Her fasting levels during SMBG are generally between 145 mg/dL and 170 mg/dL; her postprandial levels are between 170 mg/dL and 190 mg/dL.

DPP-4 therapy is determined to be the best treatment choice to control Patient B's diabetes. She is started on sitagliptin 100 mg each morning and continues her meal plan and exercise program.

***Rationale and comments**: Patient B's higher than normal fasting and postprandial blood glucose levels are contributing to the elevated HbA1c levels, and she has been adherent to her meal plan and exercise program with minimal success. This treatment is appropriate for Patient B because DPP-4 therapy assists in weight loss while impacting blood glucose levels.*

SODIUM-GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS						
Drug Name	**Trade Name**	**Dose Range**	**Maximum Daily Dose**	**Frequency**	**Time to Peak Action**	**Duration of Action**
Bexagliflozin	Brenzavvy	20 mg daily	20 mg	Daily	2–5 hours	24 hours
Canagliflozin	Invokana	100–300 mg daily	300 mg	Daily	1–2 hours	24 hours
Dapagliflozin	Farxiga	5–10 mg daily	10 mg	Daily	2 hours	24 hours
Empagliflozin	Jardiance	10–25 mg daily	25 mg	Daily	1.5 hours	24 hours
Ertugliflozin	Steglatro	5–15 mg daily	15 mg	Daily	1–2 hours	24 hours

Source: [42; 82; 83; 84] *Table 8*

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 dapaglifozin and empagliflozin, approved in 2014, ertugliflozin, approved in 2017, and bexagliflozin approved in 2023 (***Table 8***) [82; 83; 84]. This class of drugs acts by inhibiting sodium-glucose cotransporter 2 (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 concentrations [42].

The recommended initial dose of canagliflozin is 100 mg once daily prior to the first meal of the day [42; 82]. 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 [42; 83; 84]. Ertugliflozin is started at a dose of 5 mg daily, with possible titration up to 15 mg/day [42]. The daily dose of bexagliflozin is 20 mg [42]. These agents are approved for use with diet and exercise to improve the control of type 2 diabetes in adult patients. They have been studied for use as monotherapy and in combination with other antidiabetics, including metformin, sulfonylureas, pioglitazone, and insulin [82].

POTENTIAL SIDE EFFECTS

The most common side effects associated with SGLT2 inhibitors are vulvovaginal candidiasis and urinary tract infection [82]. Other possible adverse effects include increased serum potassium, renal insufficiency, and hypoglycemia [42]. In 2013, the FDA requested that the manufacturer of canagliflozin complete postmarking studies, including a cardiovascular outcomes trial; an enhanced pharmacovigilance program to monitor for malignancies, liver abnormalities, pancreatitis, hypersensitivity reactions, photosensitivity reactions, and adverse pregnancy outcomes; a bone safety trial; and two pediatric studies [82].

In 2015, the FDA issued a warning that canagliflozin, dapagliflozin, and empagliflozin may lead to ketoacidosis. The warning was based on the identification of 20 cases of diabetic ketoacidosis requiring hospitalization in patients treated with SGLT2 inhibitors between March 2013 and June 2014. Later in the year, the FDA revised the labels of SGLT2 inhibitors, warning about the risks of ketoacidosis as well as serious urinary tract infections.

Additionally, the FDA is requiring manufacturers of the drugs to conduct enhanced pharmacovigilance studies to evaluate spontaneous reports of ketoacidosis in patients treated with SGLT2 inhibitors. The enhanced studies include a five-year period of specialized follow-up to collect additional information [85; 86; 87].

In 2022, the FDA approved changes to the prescribing information for SGLT2 inhibitors. To lessen the risk of ketoacidosis following surgery, the agency recommends that healthcare professionals consider stopping canagliflozin, dapagliflozin, and empagliflozin at least three days prior to surgery and ertugliflozin at least four days prior to surgery [88]. Patients are advised to stop taking their SGLT2 inhibitor and to seek medical attention immediately if they have any symptoms of ketoacidosis (e.g., nausea, vomiting, abdominal pain, fatigue, trouble breathing) or signs or symptoms of a urinary tract infection [88].

In 2016, the FDA alerted the public about interim safety results from an ongoing clinical trial that found an increase in leg and foot amputations, mostly affecting the toes, in patients treated with canagliflozin. Also in 2016, the FDA strengthened the existing warning about the risk of acute kidney injury with canagliflozin and dapagliflozin. The warning was based on reports of 101 confirmable cases of acute kidney injury, some requiring hospitalization and dialysis, with canagliflozin or dapagliflozin use [89].

In 2017, based on data from two large clinical trials, the FDA confirmed the increased risk of leg and foot amputations with canagliflozin and issued requirements for a new boxed warning [90]. In 2020, the FDA removed the boxed warning about amputation risk with canagliflozin after review of new data from three clinical trials [91]. In 2018, the FDA issued a warning about rare but serious necrotizing fasciitis of the perineum associated with SGLT2 inhibitor therapy [92].

GLUCOSE-DEPENDENT INSULINOTROPIC POLYPEPTIDE (GIP)/GLUCAGON-LIKE PEPTIDE (GLP-1) RECEPTOR AGONISTS

In May 2022, the FDA approved tirzepatide (Mounjaro) injection, a first-in-class diabetes medication that activates both GLP-1 and GIP receptors [93]. It is approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes [42]. The efficacy of tirzepatide was compared to placebo, to a GLP-1 receptor agonist (semaglutide), and to two long-acting insulin analogs. On average, patients who received the maximum recommended dose (15 mg) of tirzepatide had lowering of their A1c level by 1.6% more than placebo when used as stand-alone therapy, and by 1.5% more than placebo when used in combination with a long-acting insulin [93]. In trials comparing tirzepatide with other diabetes medications, patients who received the maximum recommended dose had lowering of the A1c by 0.5% more than semaglutide, 0.9% more than insulin degludec, and 1.0% more than insulin glargine [93].

The recommended initial dose of tirzepatide is 2.5 mg once weekly for four weeks, which may then be increased to 5 mg once weekly. The dose may be increased in 2.5 mg/week increments every four weeks if needed to achieve glycemic goals. The maximum recommended weekly dose is 15 mg [42].

POTENTIAL SIDE EFFECTS

Common side effects include nausea, vomiting, diarrhea, decreased appetite, abdominal discomfort, and abdominal pain [42]. Tirzepatide is contraindicated in patients with a personal or family history of medullary thyroid cancer or in patients with multiple endocrine neoplasia syndrome type 2 [42; 93]. Tirzepatide is not approved for use in patients with type 1 diabetes nor for patients who are planning to become pregnant [42].

COMBINATION PREPARATIONS OF ORAL DIABETES MEDICATIONS		
Agents	**Brand Name**	**Available Dosages**
Pioglitazone and metformin	Actoplus Met	15 mg/500 mg 15 mg/850 mg
Pioglitazone and metformin	Actoplus Met XR	15 mg/1,000 mg 30 mg/1,000 mg
Pioglitazone and glimepiride	Duetact	30 mg/2 mg 30 mg/4 mg
Glyburide and metformin	Glucovance	1.25mg/250 mg 2.5 mg/500 mg 5 mg/500 mg
Sitagliptin and metformin	Janumet	50 mg/500 mg 50 mg/1,000 mg
Sitagliptin and metformin	Janumet XR	50 mg/500 mg 50 mg/1,000 mg 100 mg/1,000 mg
Glipizide and metformin	Metaglip	2.5 mg/250 mg 2.5 mg/500 mg 5 mg/500 mg
Alogliptin and metformin	Kazano	12.5 mg/500 mg 12.5 mg/1,000 mg
Alogliptin and pioglitazone	Oseni	12.5 mg/15 mg 12.5 mg/30 mg 12.5 mg/45 mg 25 mg/15 mg 25 mg/30 mg 25 mg/45 mg
Dapagliflozin and metformin	Xigduo	5 mg/500 mg 5 mg/1,000 mg 10 mg/500 mg 10 mg/1,000 mg
Canagliflozin and metformin	Invokamet	50 mg/500 mg 50 mg/1,000 mg 150 mg/500 mg 150 mg/1,000 mg
Linagliptin and metformin	Jentadueto	2.5 mg/500 mg 2.5 mg/1 g
Linagliptin and metformin	Jentadueto XR	5 mg/1 g 5 mg/2 g
Saxagliptin and metformin	Kombiglyze XR	5 mg/500 mg 5 mg/1,000 mg 2.5 mg/1,000 mg
Empagliflozin and metformin	Synjardy	5 mg/500 mg 5mg/1,000 mg 12.5 mg/500 mg 12.5 mg/1,000 mg

Table 9 continues on next page.

COMBINATION PREPARATIONS OF ORAL DIABETES MEDICATIONS *(Continued)*		
Empagliflozin and metformin	Synjardy XR	5 mg/1,000 mg 10 mg/1,000 mg 12.5 mg/1,000 mg 25 mg/1,000 mg
Ertugliflozin and metformin	Segluromet	2.5 mg/500 mg 2.5 mg/1,000 mg 7 mg/500 mg 7 mg/1,000 mg
Dapagliflozin and saxagliptin	Qtern	10 mg/5 mg
Ertugliflozin and sitagliptin	Steglujan	5 mg/100 mg 15 mg/100 mg
Empagliflozin and linagliptin	Glyxambi	10 mg/5 mg 25 mg/5 mg
Empagliflozin, linagliptin, and metformin	Trijardy XR	5 mg/2.5 mg/1,000 mg 10 mg/5 mg/1,000 mg 12.5 mg/2.5 mg/1,000 mg 25 mg/5 mg/1,000 mg
Source: [3; 42; 48; 56; 57; 73; 95]		*Table 9*

COMBINATION ORAL MEDICATION PREPARATIONS

Traditional recommendations have been to use stepwise addition of medications to metformin to maintain A1c at target. The advantage of this is to provide a clear assessment of the positive and negative effects of new drugs and to reduce potential side effects and expense. However, there are data to support initial combination therapy for more rapid attainment of glycemic goals and later combination therapy for longer durability of glycemic effect [35]. Due to the success of using multiple agents concurrently to combat diabetes, many medications have been combined into one preparation to provide the benefits of both drugs and lessen the number of pills necessary (***Table 9***) [7]. Research has demonstrated a greater level of success utilizing combination therapy as opposed to separate prescriptions [94]. The ideal candidate for combination preparations is being treated with separate classifications of antihyperglycemic agents for which a single, combination form is available. However, combination therapy is not without risks. When formulations are combined, the adverse effects and contraindications associated with both must be taken into consideration [42]. Combination medications are only available in fixed dosages and may not meet the needs of every individual. Furthermore, in some instances, these combined formulas may be more expensive than the separate agents [3]. In all cases, treatment regimens should be continuously reviewed for efficacy, side effects, and patient burden [35].

CASE STUDY

Let us revisit Patient K, who has been taking metformin to control her type 2 diabetes. One year ago, Patient K was started on metformin 500 mg each evening with recommendations to attend diabetes self-management education. Since then, her dosage has been titrated up, and she currently takes metformin 1,000 mg twice per day. At her scheduled appointment, Patient K has an HbA1c level of 8.8% (estimated average glucose: 206 mg/dL) and claims to be adherent with her meal and exercise plan the majority of the time. Occasional SMBG indicates fasting levels between 145 mg/dL and 170 mg/dL and postprandial levels between 180 mg/dL and 230 mg/dL. Although the metformin achieved a small

decrease in Patient K's blood glucose levels, she has not obtained satisfactory results. More intensive therapy, with a second antihyperglycemic agent, is necessary, and the physician prescribes glyburide 2.5 mg daily. Upon hearing this, the patient becomes teary-eyed and expresses concerns about the cost of the new medication. She states she is on a fixed income and can barely make ends meet. The physician offers to prescribe a combination medication that is less expensive than the two agents separately. Patient K agrees and is prescribed Glucovance 2.5 mg/500 mg in the morning and continues with metformin 1,000 mg in the evening.

Patient K returns for a three-month follow-up. Her HbA1c demonstrates a decrease, with the result of 8.1% (estimated average glucose: 186 mg/dL) and a fasting blood glucose level of 110 mg/dL. SMBG records show fasting blood glucose levels consistently between 98 mg/dL and 120 mg/dL and postprandial levels between 160 mg/dL and 200 mg/dL. The patient has also made great improvements in adhering to meal plans, exercise goals, and SMBG. However, the physician stresses the need for Patient K's HbA1c level to be less than 7.0%, and they agree to change therapy to Glucovance 2.5 mg/500 mg twice per day. The patient agrees to wake at 3 a.m. at least twice in the first week to test her morning blood glucose level to assess for nocturnal hypoglycemia.

***Rationale and comments**: Patient K's morning blood glucose levels are close to optimal, but her postprandial levels remain elevated and her HbA1c level remains suboptimal. She has demonstrated greater adherence to her meal, exercise, and SMBG plans. Metformin will continue to impact her fasting and mid-day blood glucose levels by decreasing the liver's production of endogenous glucose, decreasing insulin resistance, and decreasing the reabsorption of carbohydrates in the gut. In addition, glyburide will assist the pancreas in the production of insulin. Patient K will require education regarding the importance of determining the presence of nocturnal hypoglycemia, signs and symptoms of hypoglycemia, and conditions that require communication with her primary care physician.*

BOLUS INSULIN THERAPY

A bolus of insulin refers to the administration of insulin over a short period of time, usually after ingestion of carbohydrates (meal bolus) or in reaction to an elevated glucose level (correction bolus) [96]. Bolus insulin therapy can be administered via a single injection, an insulin pump, or inhaled mist and is used in the treatment of both type 1 and type 2 diabetes [2]. In 2016, the FDA approved the first automated insulin delivery device for individuals 14 years of age and older with type 1 diabetes. Medtronic's MiniMed 670G is a hybrid closed-loop system that automatically monitors glucose and provides appropriate basal insulin doses [97]. Medtronic's newest iteration, the MiniMed 770G, offers the ability to track glucose levels via a smartphone; the ability for friends and family to view the patient's glucose trends on enabled smartphones; access to future innovations via remote software updates; and patient access to personalized educational content [98].

Meal bolus therapy provides more flexibility to individuals with diabetes, but it requires competency in carbohydrate counting and a working knowledge of the rapid-acting insulin analog's impact within the body [99]. When administering a meal bolus, the dosage of insulin is determined by the amount of carbohydrates to be ingested. This amount is divided by the insulin-to-carbohydrate ratio (the number of grams of carbohydrate that one unit of insulin covers). The ratio must be individualized and will vary among patients [96]. For example, a patient may have an insulin-to-carbohydrate ratio requiring 1 unit of insulin for every 15 g of carbohydrate. If this patient consumed a meal containing 60 g carbohydrates, 4 units of insulin would be needed. Alternatively, if this patient attends a party and chooses to consume a piece of cake with ice cream for a total of 120 g carbohydrate, the flexibility provided by meal bolus insulin therapy will allow the patient to administer the insulin needed (8 units).

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the Institute for Clinical Systems Improvement, insulin dosing schedules must be individualized based on a variety of factors, including the severity of diabetes, oral intake, severity of illness, and other concurrent diabetic medication. It is not feasible to design a single algorithm for determining an insulin regimen in every patient.

(https://www.icsi.org/wp-content/uploads/2019/02/Diabetes.pdf. Last accessed October 28, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

Correction bolus is an infusion or injection of insulin delivered quickly to bring high blood glucose levels back within a goal range [100]. The dose of insulin administered for a correction bolus is determined by the sensitivity factor (the amount the blood glucose level will decrease with 1 unit of insulin). As with the meal bolus, the correction bolus will vary depending on certain factors, including an individual's weight. The sensitivity factor is calculated by dividing 2,000 (2,200 for less tight control, 1,800 for tighter control) by the individual's total daily dose of insulin [96]. For example, if a patient takes an average of 100 units of insulin each day, his or her sensitivity factor would be 20, meaning 1 unit of insulin would decrease the blood glucose level by 20 mg/dL. If this same patient has a target blood glucose level of 110 mg/dL and a blood glucose test indicating a current blood glucose level of 240 mg/dL, he or she could utilize a correction bolus to lower the blood glucose level by 130 mg/dL to the target. The necessary dose is calculated by dividing the difference (130 mg/dL) by the correction factor of 20 to determine the amount of insulin needed—6.5 units of insulin in this case.

Several insulin preparations may be administered via bolus for use in meal or correction bolus therapy. The most commonly used types will be discussed in length in the following sections.

INSULIN ASPART

One available insulin analog that may be administered in bolus therapy is insulin aspart (recombinant DNA [rDNA] origin). This type of insulin is rapid-acting and is nearly homologous with regular human insulin. It is produced using *Pichia pastoris* or *Saccharomyces cerevisiae*, also known as baker's yeast [101]. A slight change in the insulin chain makes insulin aspart more rapidly absorbed than regular insulin. Insulin aspart is available in a concentration of 100 units/mL (U100). Its onset of action is 5 to 15 minutes, and the peak of action is one to three hours. The effective duration of action for insulin aspart is less than five hours [42; 48]. Unlike oral antihyperglycemic agents, insulin aspart does not have a maximum dosage, but is specific to the individual [102].

Insulin aspart is available in 10 mL vials containing U100 insulin aspart and in prefilled and cartridge pens containing 3 mL of U100 insulin. These preparations can be stored unopened until the expiration date; however, once opened or punctured, insulin aspart will expire in 28 days regardless of storage location [42; 56]. If stored in a refrigerator, it is important to allow the insulin aspart to warm to room temperature before administration for greater absorption rates and comfort [101]. It is important to note that although refrigeration is permissible, cartridges should not be refrigerated after they are punctured [56; 101]. Although cartridge pens have been available for several years, in 2010 and 2011 the manufacturer began to discontinue these pens in favor of the prefilled types.

AFREZZA

Afrezza (insulin human) inhalation powder is indicated to improve glycemic control in adult patients with type 1 and type 2 diabetes [42; 103]. Inhaled insulin can be useful for patients who have an aversion to injection [35]. Afrezza inhalation powder is available in three strengths: 4-U, 8-U, and 12-U single-use cartridges that are color-coded for patient ease of use. The inhaler is individually packaged. It

must be discarded after 15 days of use and replaced with a new inhaler [103]. The initial dose in insulin-naïve patients is 4 U at each meal. A conversion scale is available to guide replacement of prandial or premixed insulin with inhaled insulin [42; 103]. Dosage adjustments may be needed based on the patient's metabolic needs, blood glucose monitoring results, glycemic control goal, changes in physical activity, or changes in meal patterns [103]. Afrezza is contraindicated during episodes of hypoglycemia and in patients with chronic lung disease (e.g., asthma, COPD). The agent contains a boxed warning of risk of acute bronchospasm in patients with chronic lung disease [103]. Hypoglycemia is the most common adverse reaction [42; 103].

INSULIN LISPRO

Insulin lispro (rDNA origin) is also a rapid-acting human insulin analog. This type of insulin is created from a non-pathogenic strain of *Escherichia coli* that has been genetically altered by the addition of the gene for insulin lispro [104]. Insulin lispro is available in U100 or U200 concentration and has no labeled maximum dose [102]. Its onset of action is 15 to 30 minutes, and peak effect is experienced in 30 minutes to 2.5 hours. Insulin lispro has an effective duration of action of less than five hours [42; 48].

Insulin lispro is available in pens, cartridges, and vials for subcutaneous injection, intravenous injection, or infusion via insulin pump. It can be stored refrigerated unopened until the expiration date [42; 56]. After the vial has been opened, it must be used within 28 days. If the vial is stored in the refrigerator, it should be allowed to warm to room temperature prior to use [104].

INSULIN GLULISINE

Insulin glulisine (rDNA origin) is another rapid-acting insulin analog. As with insulin lispro, insulin glulisine is synthesized from non-pathogenic *E. coli*. It is available in U100 concentration in 10 mL vials or 3 mL pens [42; 48; 56]. The onset of action for insulin glulisine is 15 to 30 minutes, with peak action reached within approximately 1.5 to 2.5 and a duration of action of three to four hours [42].

Insulin glulisine may be administered via subcutaneous injection, intravenous injection, or insulin pump. Like other insulin analogs, opened vials of insulin glulisine must be used within 28 days and may be stored at room temperature or refrigerated. Refrigerated vials should be brought to room temperature before use [42]. Preparations mixed for intravenous use are stable at room temperature for 48 hours [42].

REGULAR INSULIN

There are two preparations of regular human insulin on the market: Humulin R and Novolin R. Both preparations are similar in action but differ in chemical make-up. Both have an onset of action of 15 to 30 minutes, and peak action is noted at 2.5 to 5 hours. The effective duration of action is between 2 to 12 hours [42]. Regular insulin can be utilized as a subcutaneous injection, intravenous infusion, insulin pump infusion, or inhaled mist, although insulin analogs are now more widely used [96; 105].

Humulin R is created in a non-pathogenic strain of *E. coli* and consists of zinc-insulin crystals dissolved in a clear fluid. It is a sterile solution and is for subcutaneous, not intramuscular, injection [104]. The concentration of Humulin R is U100 or U500 [42; 56].

Novolin R (rDNA origin) is structurally identical to natural human insulin and is produced utilizing *S. cerevisiae* [106]. Novolin R is only available in the U100 concentration [56]. Humulin R and Novolin R may be stored in the refrigerator until expiration or at room temperature for up to 31 days (Humulin R U100), 40 days (Humulin R U500), or 42 days (Novolin R) after the vial is opened [42].

HYPERGLYCEMIC CRISES

In addition to their use in the everyday management of diabetes, the action and short half-life of these insulins, both regular and analogs, makes them well suited for use in the treatment of hyperglycemic states resulting from metabolic changes in response to system stresses, such as surgery, trauma, and sepsis. Hyperglycemia and insulin resistance are common in critically ill patients, even when glucose

homeostasis has previously been normal. This effect is amplified in diabetics because diabetic patients cannot increase insulin production to counteract the effect of the increase in catabolic hormones. In some patients, the insulin requirements may increase more than 10-fold [107]. Many critically ill patients are also receiving high-carbohydrate feedings in the form of hyperalimentation or enteral feeding, which can contribute to increased blood glucose levels. Therefore, providing adequate amounts of insulin to promote euglycemia and enough nutrition to avoid hypoglycemia, proteolysis, and lipolysis is a challenge in critically ill patients [108]. When this balance is not maintained, either due to poor diabetes control or illness/trauma, hyperglycemic crises, such as diabetic ketoacidosis or HHS, may develop.

Diabetic Ketoacidosis

Diabetic ketoacidosis is caused by the body's inability to utilize glucose due to a lack of insulin. Because glucose is unavailable for energy needs, fat is used as a fuel source. The byproducts of this fat metabolism (i.e., ketones) accumulate, and electrolyte disturbances, acidosis, and severe dehydration result [109]. It occurs most often in persons with type 1 diabetes, but it can occur in patients with type 2 diabetes as well [110]. Children younger than 5 years of age and those without ready access to health care are at the greatest risk to develop diabetic ketoacidosis [111]. Factors that can precipitate the development of this disorder include [96; 110; 112]:

- Severe infection
- Serious illness, such as myocardial infarction
- Inappropriate dosing or skipped or missed doses of insulin
- Continuous subcutaneous insulin infusion failure
- Leaving insulin pump infusion sets intact for longer than the manufacturer recommendation
- Growth spurts in children and adolescents
- Steroid therapy
- Alcohol or illicit drug use
- Stress

The diagnostic criteria for diabetic ketoacidosis includes a plasma glucose level greater than 250 mg/dL and an arterial pH less than 7.3 [110; 113]. It is further classified based on arterial pH level and mental status as mild (pH 7.25–7.3, alert), moderate (pH 7–7.24, alert/drowsy), or severe (pH <7, stupor/coma). Conditions associated with diabetic ketoacidosis requiring prompt treatment and correction include [2; 110]:

- Chronic hyperglycemia and glucotoxicity
- Acidosis
- Low blood volume
- Hyperosmolality and associated potassium loss

Diabetic ketoacidosis is considered a medical emergency, and if left untreated, it can result in death. Healthcare professionals require the knowledge and critical thinking skills to swiftly recognize the signs and symptoms of diabetic ketoacidosis and provide rapid treatment [110].

In critically ill patients, symptoms of diabetic ketoacidosis can prevent the treatment of the triggering condition. The early signs of ketoacidosis, such as unexplained hyperglycemia, nausea, weakness, fatigue, and confusion, can prevent the individual from partaking in SMBG and insulin administration [96; 110].

A successful outcome is based on the recognition and prompt treatment of this medical emergency, initiation of intensive therapy, and careful clinical follow-up. Goals for treatment include rehydration, providing adequate insulin to restore normal glucose metabolism, and correction of electrolyte deficiencies and acidosis [110; 112; 114].

The Institute for Clinical Systems Improvement recommends that for insulin-deficient patients, despite reductions or the absence of caloric intake, basal insulin must be provided to prevent diabetic ketoacidosis.

(https://www.icsi.org/wp-content/uploads/2019/02/Diabetes.pdf. Last accessed October 28, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

Fluid Replacement

The partial correction of dehydration within the first few hours of therapy is necessary to significantly reduce hyperglycemia and ketonemia. This is accomplished by fluid replacement [110; 113]. Adults with diabetic ketoacidosis may present with a deficit of more than 6 liters of fluid [115]. Initial fluid replacement consists of 50% normal saline or 100% normal saline, depending on serum sodium levels, urine output, and the individual's state of dehydration [112; 113; 114].

Phosphate concentration decreases with insulin therapy. Although studies have failed to show any beneficial effect of phosphate replacement on the clinical outcome in diabetic ketoacidosis, the ADA states that phosphate replacement may be indicated in patients with cardiac dysfunction, anemia, or respiratory depression, or in patients whose serum phosphate concentration is less than 1.0 mg/dL. The ADA recommends that 20–30 mEq/L potassium phosphate be added to replacement fluids when needed [113].

Insulin Replacement

All individuals with diabetic ketoacidosis require insulin therapy, which should be started soon after initiation of fluid replacement therapy. Insulin therapy is best accomplished by a continuous insulin infusion of rapid- or short-acting insulin [110; 114]. Intravenous insulin is the most effective route in this case because it can be adjusted rapidly and is not dependent on tissue perfusion for absorption, as is subcutaneous delivery [110; 113]. The initial intravenous bolus of regular insulin or insulin analog is 0.1–0.15 units/kg. This is followed by an infusion of 0.1 units/kg/hour, which is titrated to lower blood glucose 50–75 mg/dL/hour. A decrease in blood glucose greater than 75 mg/dL/hour is associated with the potential complication of cerebral edema [110; 114]. Insulin therapy should continue until metabolic control is achieved [110].

Correction of Electrolyte Imbalances

It is necessary to provide aggressive potassium supplementation for all individuals with diabetic ketoacidosis, as depletion of potassium can lead to cardiac dysrhythmias. However, renal function must be replaced prior to the administration of potassium [115]. If the potassium level is 4.5 – 6 mEq/L, administer 10 mEq/h of potassium chloride. If the level is 3 – 4.5 mEq/L, administer 20 mEq/h of potassium chloride. Supplementation is not needed if the potassium level is greater than 6 mEq/L. Monitor serum potassium levels hourly and stop if the level is greater than 5 mEq/L [110].

The use of bicarbonate for the treatment of acidosis is no longer routine unless the metabolic acidosis is severe [110; 113; 114; 115]. If bicarbonate therapy is utilized, 1–2 mEq/kg should be administered over two hours followed by an assessment of plasma bicarbonate levels until the venous pH is >7.0 [113]. Total bicarbonate treatment should not exceed 5 mEq/kg in a 12-hour period [116].

Prevention

The prevention of diabetic ketoacidosis can often be accomplished with patient education regarding the condition and recognition of the initial signs and symptoms. Patients with type 1 diabetes or ketosis-prone type 2 diabetes should be educated and assessed for understanding regarding the recognition of the early warning signs. Individuals with infections or who are on injection or infusion insulin therapy may benefit from regularly measuring urine ketones and adjusting insulin doses and diet in accordance with findings [117].

Hyperosmolar Hyperglycemic Syndrome

HHS is an acute metabolic complication characterized by insulin deficiency. The condition was formerly referred to as hyperosmolar hyperglycemic nonketotic syndrome, but the terminology was changed because coma is found in fewer than 20% of patients with HHS. It is a life-threatening crisis with a high rate of mortality [118; 119]. The syndrome

is typically seen in individuals with undiagnosed diabetes, patients who are diagnosed after a long period of hyperglycemia, and elderly patients with type 2 diabetes, especially those who reside in long-term care facilities [2]. Blood glucose levels increase in response to a precipitating stressful situation or event. As the stress continues, the hyperglycemia is exacerbated and the evolution of HHS begins [118]. If untreated, blood glucose levels will exceed 180 mg/dL, the level at which the kidneys are no longer able to reabsorb glucose. At the same time, water loss reduces renal perfusion and causes further dehydration. This cascade of events results in more extreme levels of hyperglycemia and osmolarity with HHS than those found with diabetic ketoacidosis [114; 118]. As the patient becomes increasingly dehydrated and hyperosmolar, mental status will be impaired. Like diabetic ketoacidosis, HHS will result in death if left untreated [118].

Patients experiencing HHS may present to the emergency department with seizures or symptoms that mimic a cerebrovascular accident. In most cases, physical examination will demonstrate evidence of extreme dehydration, orthostatic hypotension, and a frank hypovolemic shock. The plasma glucose level is typically greater than 600 mg/dL, with a serum osmolality level greater than 320 mOsm/kg [118]. Anything that elevates blood glucose levels or reduces hydration can contribute to the development of HHS, including [114; 118]:

- Infection (the precipitating factor in 60% of cases)
- Surgery
- Myocardial infarction
- Gastrointestinal hemorrhage
- Pancreatitis
- Pulmonary embolism
- Medications that impact carbohydrate metabolism (e.g., glucocorticoids, thiazides, phenytoin, beta blockers)

Fluid and Electrolyte Replacement

The main goal in the treatment of HHS is providing adequate fluids for rehydration [114]. Aggressive fluid replacement is crucial, as patients have an average fluid loss of 9 liters [118]. The guideline for fluid replacement is to infuse half of the fluid deficit over the initial 12 hours and the remainder during the subsequent 12 to 24 hours [114; 118]. When administering hypertonic solutions, it is important to be alert to the potential of cerebral edema due to the rapid decrease in serum osmolality [118].

Laboratory values provide critical information to guide electrolyte replacement decisions. The potassium replacement strategy is similar to that with diabetic ketoacidosis, and evidence of the deficit may be initially evident by an electrocardiogram [114]. The total body potassium loss is significant and can equal 4 – 6 mEq/kg. Furthermore, after insulin therapy is initiated, the potassium level may drop even further [118]. For this reason, insulin therapy should be withheld if the serum potassium is less than 3.3 mEq/L [114].

Insulin Therapy

After hydration is re-established, insulin therapy is usually, but not always, required to obtain euglycemia. The treatment of acidosis is not a part of the treatment plan of HHS; therefore, insulin requirements are not as high [114]. The initial insulin intravenous bolus should be 0.1 units/kg of rapid- or short-acting insulin followed by a consistent infusion at the same rate. When glucose levels reach 300 mg/dL, the infusion may be decreased to 0.05 units/kg. The infusion should be maintained to keep the glucose level between 250–300 mg/dL until the osmolality is less than 315 mOsm/kg and the individual is alert [118].

Prevention

The most important tactic in the prevention of hyperglycemic crises is patient and family education regarding the early identification, treatment, and management of illnesses. Patients with a history of HHS are at risk for further episodes [118]. Patients with type 1 diabetes should be taught about urine ketone testing and appropriate steps should the test return a positive result, including communication with a physician, increased non-caloric fluid intake, and insulin therapy [118]. Additionally, increasing the frequency of SMBG can help prevent the progression and potential complications related to diabetic ketoacidosis and HHS. Key patient and family teaching points include [120]:

- Always take diabetes medications as prescribed. Patients having trouble tolerating the medication due to vomiting should notify their primary care provider.
- Monitor blood glucose levels at least four times a day. If a patient is too sick to self-test, a family member, caregiver, or trusted support person should provide assistance.
- Maintain a blood glucose log and keep it readily available in case the primary care provider is called.
- Monitor for ketones any time blood glucose levels are 250 mg/dL or greater. Levels should be recorded.
- Maintain adherence to the normal meal plan whenever possible.
- Drink plenty of sugar-free liquids to prevent dehydration.

Conditions that require the immediate notification of a physician include [120]:

- A fever greater than 38 degrees Celsius (100.5 degrees Fahrenheit)
- Vomiting or diarrhea for more than two hours
- Blood glucose levels of 250 mg/dL or greater after two checks or after additional insulin injections
- Moderate or large urine ketones

Case Study

Patient A is a white man, 19 years of age, with a history of type 1 diabetes. He is currently in the end of his first year of college and studying for his final examinations. He has been unable to exercise due to the amount of time devoted to studying. His eating has been erratic, and he has forgotten to cover his meals with insulin aspart. He presents to the emergency department with a six-hour history of abdominal pain, nausea, and confusion as reported by his roommate. The roommate also recalls a fruity odor to Patient A's breath and knows he has not been consuming alcohol. When asked questions regarding his blood glucose levels, Patient A is confused and unable to recall any past history of testing. The roommate states he did not witness the patient assessing any glucose levels. The patient's laboratory evaluation reveals:

- Blood glucose: 531 mg/dL
- Strong serum ketones
- Bicarbonate: 3 mEq/L
- Arterial pH: 7.1
- Potassium: 5.3
- CO_2: 10 mmol/L
- Liver function tests: Within normal limits
- Renal function: Within normal limits

***Rationale and Comments**: Diabetic ketoacidosis should be the expected diagnosis. Signs and symptoms that support this diagnosis include:*

- *History of type 1 diabetes*
- *High level of stress related to upcoming examinations*
- *Erratic eating patterns*
- *Not covering carbohydrates with insulin*
- *Acetone breath, confusion, nausea*
- *Laboratory glucose, bicarbonate, pH, CO_2, and serum ketone levels*

Based on the laboratory values and patient history, the attending physician diagnoses diabetic ketoacidosis and orders insulin therapy: a bolus of regular insulin at 0.1 units/kg followed by an insulin infusion of 0.1 units/kg/hour. An infusion of 0.9% sodium chloride at 20 mL/kg/hour is administered for the first hour. Blood glucose levels are monitored hourly, and adjustments to the infusion are made based on hospital policy.

Eighteen hours after admission, Patient A awakes. His blood glucose is well controlled on the insulin infusion, and his acidosis is resolved. One hour prior to discontinuation of the insulin infusion, he is started on his home dose of insulin glargine, as his HbA1c level was assessed to be 7.1%. The next morning, the patient remains stable and his glucose status is controlled.

Before Patient A is discharged, important patient education points are reviewed and reinforced. The nurse assesses the patient's insulin administration technique by allowing him to demonstrate drawing up and administering his insulin injections. An overview of the onset, peak action times, and duration of all prescribed insulin preparations is provided. The need for injection site rotation and appropriate storage of insulin vials are stressed. The nurse also provides Patient A with information on stress management techniques. Finally, the nurse gives the patient written information regarding sick day management and encourages him to share the handout with his roommate or anyone else who will be involved with his care or well-being.

BASAL INSULIN

Basal insulin refers to the steady background insulin that controls blood glucose levels in the fasting state (overnight and between meals). In nondiabetic individuals, healthy beta cells release insulin into the circulatory system throughout the day [5]. This basal or background insulin enables stored fat and glucose to be released in the appropriate amounts to sustain metabolism during times when fuel is not being consumed and metabolized. A consistent insulin level throughout the day regulates glucose production from the hepatic system, the breakdown and production of fat as fuel, and the entry of amino acids into the cells for the creation of enzymes and structural proteins [96]. Basal insulin can be utilized to successfully control blood glucose levels in individuals with either type 1 or type 2 diabetes, but it is one of the cornerstones of therapy for those with type 1 diabetes [5].

Basal insulin therapy may be administered via an injection or with a continuous subcutaneous insulin infusion. For patients with type 2 diabetes with a less than optimal blood glucose level, basal insulin may be added to oral agents to achieve the most advantageous level of metabolic control [2]. A patient's basal insulin needs can be met using a variety of preparations and routes, including intermediate-acting insulin, long-acting insulin, basal/bolus combination in multiple daily dosages, or continuous subcutaneous insulin infusions via an insulin pump.

NPH (INTERMEDIATE-ACTING) INSULIN

NPH insulin is manufactured by two companies and marketed in the United States as Novolin N or Humulin N [42]. NPH is a zinc insulin suspension that includes the polypeptide protamine. It is produced in a concentration of 100 units/mL and generally appears cloudy or milky [121]. As with some insulin analogs, the insulin in NPH is synthesized using noninfectious *E. coli* bacteria.

NPH is available only in U100 concentration vials or pre-filled pen preparations [56]. The onset of action is within 1 to 2 hours, with peak effect to be expected within 4 to 12 hours [42]. NPH is considered an intermediate-acting insulin as its effective duration is longer than regular insulin or insulin aspart but not as long as insulin glargine or detemir [42; 48]. Due to its wide variation in effective action time, this insulin may be prescribed once or twice per day [2]. As with most insulin preparations, NPH can be stored at room temperature or refrigerated until it expires or for 31 to 42 days (depending on preparation) after it is opened. As with any injectable insulin, it should be room temperature prior to injection [56].

INSULIN GLARGINE

Insulin glargine is a long-acting recombinant human insulin analog. It is available in U100 concentration vials, 3-mL pens, and U300 pens [56; 62]. The onset of action is three to four hours, and glargine is considered to be peakless in terms of action [42]. Insulin glargine was the first insulin to be truly long acting, with an effective duration of action of 20 to 24 hours [48]. The rate of absorption does not differ among various sites of injection, and the pharmacokinetics within various individuals is fairly consistent [2].

In 2021, the first biosimilar insulin (insulin glargine-yfgn) was approved by the FDA [122]. As an agent that is readily interchangeable with insulin glargine, it is hoped that this approval will improve availability and affordability of insulin therapy.

INSULIN DETEMIR

Like insulin glargine, insulin detemir is a long-acting basal insulin analog with up to 24 hours duration of action [62; 123]. It was approved in 2005 by the FDA for use in maintaining background insulin in patients with type 1 or type 2 diabetes [124].

Insulin detemir is available in U100 concentration vials and 3-mL prefilled pens [42; 56]. The onset of action for insulin detemir ranges from three to eight hours, and it is also considered a peakless insulin. The effective duration of action of insulin detemir is dose-dependent and varies from just under 6 hours to 23 hours [42; 48]. The duration is mediated by slow absorption from the injection site and slow distribution to target tissues due to a strong self-association and albumin binding [2].

In 2009, the FDA issued a public health advisory regarding stolen vials of insulin detemir [125]. Stolen vials had reappeared on the market, and because handling and storage of these vials (lots XZF0036, XZF0037, and XZF0038) was unknown, patients were advised to avoid them. It is unlikely that these vials are still in circulation.

Insulin glargine, insulin detemir, and NPH preparations are not appropriate for continuous subcutaneous insulin infusion or intravenous infusions and should only be considered for basal insulin therapy [2]. According to the ADA, subcutaneous basal insulin is a preferred treatment option to correct hyperglycemia in noncritically ill hospitalized patients as part of a basal-bolus or basal-plus-correction insulin regimen [35]. Subcutaneous injection sites for intermediate- or long-acting insulins include the abdomen, buttocks, posterior-lateral area of the arm, and lateral area of the thigh [126].

INSULIN DEGLUDEC

Insulin degludec is another long-acting insulin with "peakless" action over a 24-hour period. It is preferred in patients with symptomatic hyperglycemia or ketonuria. The initial dose is 10 units once daily or 0.1 – 0.2 units/kg once daily. A dose of 0.2-0.3 units/kg/day is recommended for insulin resistance [42]. Insulin degludec should not be administered IV or IM or in an insulin infusion pump and should not be used if the solution is viscous or cloudy. The onset of action for degludec is about one hour [17].

POTENTIAL SIDE EFFECTS

As with any other insulin therapy, the greatest side effect risk is hypoglycemia [42]. Hypoglycemia is a result of one of two different issues: hyperinsulinemia (resulting from too much exogenous insulin, an insulin-secreting pancreatic tumor, or excessive diabetes medication) or iatrogenic (alteration in glucose counter-regulation) [127]. In the case of exogenous insulin therapy, hypoglycemia is due to the effects of hyperinsulinemia [100].

The benefits of the intermediate- and long-acting insulins include the benefit of improved blood glucose control with a minimized risk of hypoglycemia [128]. For many patients, the greatest benefit of basal therapy is achieved when used in combination with bolus insulin to more effectively mimic the normal physiology of the pancreas [128].

COMBINATION INSULIN PREPARATIONS

Many insulin preparations can be utilized in combination to achieve greater efficacy, coverage, and accuracy [42; 62]. Most insulin combinations can be mixed in the same syringe, requiring only one injection rather than two [129]. However, insulins glargine and detemir and injectables exenatide and pramlintide cannot be mixed in the same syringe with additional insulin formulations [56].

Multiple combination insulin preparations are available in premixed solutions in vial or pen form [42; 62]. These combinations provide the benefit of NPH and a rapid- or short-acting insulin for greater glycemic control and management [56]. All of the fixed combinations are only available in U100 concentration to prevent potential hypoglycemia. Available fixed combinations include [42; 48; 62; 130]:

- Humulin or Novolin 70/30 (70% NPH and 30% regular insulin)
- Humalog 75/25 (75% NPH and 25% insulin lispro)
- NovoLog 70/30 (70% NPH and 30% insulin aspart)
- Soliqua 100/33 (100 units insulin glargine and 33 mcg lixisenatide)
- Xultophy 100/3.6 (100 units insulin degludec and 3.6 mg liraglutide)

INCRETIN MIMETICS

The first agent in this category of antihyperglycemics, exenatide, was approved for the adjunctive treatment of diabetes in 2005 [131]. Exendin-4 is a naturally occurring incretin mimetic originally isolated from the salivary secretions of the *Heloderma suspectum* lizard [2]. The action of exenatide differs from other available diabetes medications. It enhances insulin secretion by pancreatic beta cells, slows gastric emptying, and suppresses glucagon secretion [42]. Exenatide has been shown to bind and activate the GLP-1 receptor, which increases both synthesis and secretion of insulin [132].

As it primarily acts to stimulate insulin secretion, exenatide is approved for patients with type 2 diabetes [42]. For these patients, use of this agent results in improved glycemic control. It is important to note that exenatide does not impair the normal glucagon response to hypoglycemia. Though mainly used for patients with type 2 diabetes, studies have shown exenatide to be a useful adjunctive therapy for patients with type 1 diabetes, although this is an off-label use. Its effect of delaying gastric emptying has been found to reduce postprandial hyperglycemia in adults and adolescents with type 1 diabetes [133].

Exenatide is available in prefilled injection pens (immediate-release) and as a kit containing 2 mg of the drug (extended-release) and a diluent [56; 62]. The recommended initial dosage for the immediate-release pen preparation is 5 mcg twice daily within one hour prior to a meal [42]. The dose may be increased to a maximum of 10 mcg twice per day. The recommended dosage for the extended-release 2-mg kit is once every seven days (weekly); it can be administered at any time of day, with or without meals [62]. Exenatide has an onset of action of 30 minutes and effective duration of action of approximately 10 hours [48]. The greatest side effect risk and disadvantage with exenatide is nausea, which is reported by 44% of patients who take the drug [129]. Other possible side effects include vomiting, diarrhea, dizziness, headache, and dyspepsia [129]. However, the drug has the beneficial effects of beta cell rejuvenation, decreased glucagon production, and weight loss [102]. Exenatide is best indicated for individuals who have not achieved adequate control on combination medication therapy [2].

In 2010, a second incretin mimetic, liraglutide (Victoza), was approved by the FDA [134]. Liraglutide is a long-acting GLP-1 analog that acts by suppressing glucagon secretion, stimulating insulin secretion, and inhibiting gastric motility [42; 135].

Like exenatide, it has also been linked to weight loss and improvements in beta-cell function and mass. However, because liraglutide has a longer action than exenatide, it may be administered only once per day.

Liraglutide is started at a dose of 0.6 mg/day for one week, administered subcutaneously via a prefilled injectable pen, after which the dose is increased to 1.2 mg/day [42]. The dose may be titrated to a maximum of 1.8 mg/day if necessary. Its peak serum concentration is generally reached within 8 to 12 hours, with a half-life of approximately 13 hours [42].

The most common side effects observed with liraglutide are headache, nausea, vomiting, and diarrhea [42; 136]. Other side effects include allergic-like injection site reactions, such as hives. Albiglutide is administered at a dose of 30 mg once weekly, though the dose may be titrated to 50 mg once weekly to effect [137]. The initial dose of dulaglutide is 0.75 – 1.5 mg once weekly [138]. These weekly medications should be administered on the same day each week. Common side effects include hypoglycemia, diarrhea, nausea, and local site reactions [42]. As with exenatide, these drugs are approved for monotherapy or as an addition to an existing regimen. However, albiglutide, dulaglutide, and liraglutide are considered second-line therapies [35]. Further, albiglutide was discontinued in 2018.

Another GLP-1 receptor agonist, lixisenatide, received FDA approval in 2016 [42]. Lixisenatide is administered at a dose of 10 mcg once daily. Lixisenatide is available as a kit containing 10 mcg of the drug and a diluent. Common side effects include nausea, vomiting, and headache [42].

In 2019, the FDA approved semaglutide, the first oral treatment for type 2 diabetes [139]. It is not recommended as first-line therapy and is contraindicated in patients with type 1 diabetes or diabetic ketoacidosis [139]. Semaglutide is administered at a dose of 0.25 mg once per week for four weeks via a prefilled injectable pen, then increased to 0.5 mg once weekly for four weeks. The maximum dose is 1 mg once weekly. Gastrointestinal adverse effects are common [42].

GLP-1 receptor agonists, with or without metformin based on glycemic needs, are an appropriate initial therapy for individuals with type 2 diabetes who are either with or at high risk for atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease. Among these patients, GLP-1 receptor agonists have demonstrated cardiovascular disease benefit. A GLP-1 receptor agonist is preferred to insulin, when possible, in patients with type 2 diabetes. If insulin is used, combination therapy with a GLP-1 receptor agonist is recommended for greater efficacy and durability of treatment effect [35].

Clinical studies have indicated that the incretin mimetics are associated with an increased risk for the development of thyroid tumors, and their labeling includes a black-box warning regarding the increased risk of thyroid C-cell tumors. Therefore, these patients should be assessed for elevated calcitonin concentrations and should be counseled on the risk and symptoms (e.g., neck mass, dysphagia, dyspnea, persistent hoarseness) of thyroid tumors [42]. Patients with a personal or family history of medullary thyroid cancer or with multiple endocrine neoplasia syndrome type 2 should not take liraglutide. In 2013, the FDA began investigating unpublished new findings by a group of researchers that suggest an increased risk of pancreatitis and pancreatic duct metaplasia in patients with type 2 diabetes treated with incretin mimetics [76].

CASE STUDY

Patient T is a defense attorney in a busy prestigious law firm. She has dealt with type 1 diabetes since the age of 13 years. She was started on an insulin pump in order to improve her blood glucose control and her overall health. Patient T has been happy with the results achieved with the pump, with the exception of a recent weight gain of 10 pounds and increases in her postprandial blood glucose levels. She confers with her endocrinologist regarding options to decrease the postprandial levels and alleviate any further weight gain.

The endocrinologist suggests treatment with exenatide. However, Patient T is concerned with returning to a twice-daily injection, which is one reason she appreciates insulin pump therapy. The patient and her endocrinologist discuss this option, and although she is hesitant to return to daily injections, the patient chooses to attempt the therapy. The endocrinologist prescribes exenatide 5 mcg twice daily.

After four weeks of therapy with exenatide, Patient T returns for follow-up. She states that although she initially experienced nausea, her weight is starting to trend down and her postprandial levels are improving. Patient T indicates she would like to continue with the exenatide therapy based on seen benefits.

AMYLIN ANALOGS

Like exenatide, pramlintide is another relatively new antihyperglycemic medication available to help obtain and maintain glycemic control [129]. FDA approved in 2005, pramlintide is utilized in combination with insulin therapy for patients with type 1 or type 2 diabetes [42; 140]. Pramlintide mimics the human hormone amylin, a neuroendocrine hormone that contributes to glucose control during the postprandial period. As a synthetic analog of amylin, pramlintide primarily acts by promoting satiety, slowing gastric emptying, and decreasing postprandial glucagon secretion. Because use of pramlintide is associated with feelings of fullness and a reduction in caloric intake, one benefit of use is potential weight loss. Slowed gastric emptying, an effect that lasts for approximately three hours following administration, reduces the initial postprandial increase in plasma glucose, but it does not alter absorption of carbohydrates, fats, or other nutrients.

Pramlintide is contraindicated for patients with gastroparesis or who are prescribed medications that affect gastrointestinal motility or slow the absorption of nutrients [42; 129]. Potential side effects include nausea, anorexia, dizziness, and pharyngitis, but the greatest risk is the development of hypoglycemia [56]. Particularly among individuals with type 1 diabetes, pramlintide taken in addition to insulin is associated with an increased risk of severe hypoglycemia [42]. When it does occur, severe hypoglycemia usually develops within three hours of administration of pramlintide injection. Complete patient education and monitoring insulin dose response can help prevent this untoward effect [141].

A patient with type 1 diabetes who uses bolus insulin at mealtime and has not achieved optimum glycemic control is a prime candidate for the addition of pramlintide [42; 56]. In addition, pramlintide is indicated for patients with type 2 diabetes who utilize bolus insulin at mealtimes and have failed to achieve adequate glycemic control, with or without a concurrent sulfonylurea and/or metformin therapy [42; 102].

For the management of type 1 diabetes, pramlintide is started at a dose of 15 mcg before each meal [42]. This can be titrated up every three days in 15 mcg increments to a maximum of 60 mcg. If pramlintide is prescribed for type 2 diabetes, the initial dose is 60 mcg immediately before eating [42]. Again, this can be titrated up to 120 mcg after three to seven days, if necessary [42]. The onset of action for this medication is 30 minutes, with a duration of action of three hours [42; 48]. Pramlintide is primarily metabolized in the kidneys to an active metabolite with a short half-life [42; 129].

IMMUNOTHERAPY

In 2022, the FDA approved teplizumab injection to delay the progression to symptomatic type 1 diabetes in adults and pediatric patients 8 years and older who currently have presymptomatic type 1 diabetes [155]. Teplizumab binds to certain immune system cells and may deactivate the immune cells that attack beta cells. It is administered by intravenous infusion once daily for 14 consecutive days. The dosage is roughly doubled each day for five days, then continued at the final dosage for the remaining days [42].

Teplizumab's safety and efficacy were evaluated in a randomized, double-blind, event-driven, placebo-controlled trial with 76 patients with stage 2 (presymptomatic) type 1 diabetes. In the trial, patients randomly received teplizumab or a placebo once daily via intravenous infusion for 14 days. The primary measure of efficacy was the time from randomization to development of stage 3 (symptomatic) type 1 diabetes diagnosis. After 51 months, 45% of the patients who received teplizumab were diagnosed with symptomatic type 1 diabetes, compared to 72% of the patients who received a placebo [155].

The most common side effects of teplizumab include leukopenia, lymphocytopenia, rash, and headache. However, the FDA-approved dose does not reflect the dose used in the premarket clinical trial due to pharmacokinetic differences between the product used in the clinical trial and the product that was FDA approved; therefore, adverse reactions and incidences reported in the product labeling may differ from the product that was FDA approved [42]. The use of teplizumab requires premedicating and monitoring for symptoms of cytokine release syndrome; serious infections; leukopenia/lymphocytopenia; and hypersensitivity reactions. All age-appropriate vaccinations should be administered prior to starting teplizumab, and concurrent use of live, inactivated and mRNA vaccines should be avoided [155].

PATIENT EDUCATION

ORAL DIABETES MEDICATIONS

Patient education is of the utmost importance when it comes to prevention of adverse effects and detrimental outcomes related to diabetes medication therapy. Each class of diabetes medication requires specific instructions and education. Many healthcare providers leave diabetes self-management education to a certified diabetes educator prepared to provide this type of formal education, which is optimal. However, consistent reinforcement is needed and is best done at every patient interaction in the form of teachable moments [14]. It is important to consider each individual's specific comprehension and comfort level. Encompassing a variety of theories and teaching styles is paramount [3].

Fundamental topics for all individuals taking a medication to prevent and correct hyperglycemia include [3; 56]:

- Adherence to the medication regimen
- Adherence to the meal and exercise regimen
- Importance of wearing medical identification at all times
- Symptoms of hypoglycemia and necessary treatment
- Consultation with physician regarding the use of over-the-counter medications and herbal medications

According to the Institute for Clinical Systems Improvement, nonadherence with diabetes medications can limit the success of therapy and help to explain why a patient is not achieving treatment goals. To screen for nonadherence, clinicians can ask patients open-ended, non-threatening questions at each office visit.

(https://www.icsi.org/wp-content/uploads/2019/02/Diabetes.pdf. Last accessed October 28, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

HYPOGLYCEMIA

Any person receiving medication therapy for diabetes should be educated regarding the prevention, signs and symptoms, and treatment of hypoglycemia. Overmedication, meal skipping, alcohol consumption, excessive exercise, drug interactions, illness or infection, and trauma can all precipitate hypoglycemia in patients taking certain medications, particularly insulin secretagogues.

Prevention of hypoglycemia includes not skipping meals and eating prior to exercise. Additionally, patients should be advised regarding what to do in the event of a missed medication dose. Most medication preparations should be taken as soon as the missed dose is realized, with a few exceptions. If the medication is repaglinide or nateglinide, or if it is too close to the time of the next dose, the dose should be skipped altogether [56]. Patients should also know the signs and symptoms of hypoglycemia, which include [142]:

- Dizziness or lightheadedness
- Weakness
- Hunger
- Numbness or tingling around the mouth
- Headache
- Palpitations
- Confusion
- Shakiness
- Sweating
- Irritability or nervousness

In general, patients can manage instances of hypoglycemia using the 15:15 rule. According to this rule, patients should treat low blood glucose with 15 grams of carbohydrate and recheck their blood glucose level in 15 minutes. Fifteen grams of carbohydrate would consist of three to four glucose tablets, 4 ounces of fruit juice, one-half can of regular soda, or one tube of glucose gel. In cases of severe hypoglycemia, when the individual is unable to swallow or has a potential of choking, the treatment includes dextrose 50% intravenously or, if intravenous access is unavailable, an intramuscular injection of glucagon [2].

TIMING OF MEDICATIONS AND OTHER CONSIDERATIONS

Sulfonylureas

Sulfonylurea medications should be taken with breakfast or with the first main meal of the day to maximize effect and safety [56]. In addition, there is a risk for hypoglycemia, and steps should be taken to prevent this complication. This includes spacing meals no more than four hours apart and avoiding situations when meals may be missed [5]. The elderly are particularly susceptible to hypoglycemic reactions, largely due to the age-related decline in renal function that slows the excretion of these drugs. Individuals taking a sulfonylurea should carry a rapid-acting glucose source, such as glucose tablets or gel, in order to swiftly treat the onset of hypoglycemia at the initial signs of low blood glucose [56]. Finally, it is essential to advise these patients regarding safe alcohol practices [3].

Nonsulfonylurea Secretagogues

Timing is essential for the prevention of hypoglycemia while utilizing the nonsulfonylurea secretagogues repaglinide and nateglinide. Patients should be instructed to take the medication no more than 30 minutes prior to the meal [56]. Often, patients are advised to take this medication with the first bite of a meal [3]. If a meal is not going to be consumed, the prescribed doses of the medication should also be skipped [56].

Alpha-Glucosidase Inhibitors

Patients prescribed acarbose or miglitol should be instructed to take the medication immediately before the three main meals of the day [56]. Instruction regarding the action of alpha-glucosidase inhibitors and the need to treat incidents of hypoglycemia with simple sugar sources is imperative. These patients should carry glucose tablets or gel with them at all times to prevent severe hypoglycemia [3].

Biguanides

Metformin should be given with a meal, taking into consideration that maximum doses will be better tolerated if divided into three doses and taken with each main meal [56]. Additional education regarding metformin therapy should include the discontinuation of the medication for 48 hours or until appropriate renal function has been verified following procedures involving iodized contrast media [42]. As stated, the FDA has issued a drug safety communication for metformin and metformin-containing medications for use in certain patients with mild-to-moderate renal impairment [67]. Some individuals may experience a metallic taste, but this should subside in time [3]. Lastly, patients should be instructed to avoid excessive alcohol consumption while utilizing this medication [56].

TZDs

Education regarding TZD therapy should be centered on identification of developing or worsening heart failure. It is essential that patients monitor weight daily and report any weight gain of 5 pounds or more over a two-day period to their physician immediately [56]. Moreover, monitoring liver function to evaluate safe levels is critical [3]. Patients should be instructed to notify their healthcare provider immediately if unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine occurs, as these symptoms may indicate liver problems [56].

DPP-4 Inhibitors

Sitagliptin can be taken during the day regardless of food intake. Patient education regarding sitagliptin should include the nasopharyngeal and upper respiratory side effects discussed previously [42]. Because weight loss is a benefit of DPP-4 therapy, it is imperative to stress that the medication is not a substitute for a healthy diet and exercise, and that the prescribed medical nutrition and exercise therapy should be followed [56]. As discussed, the FDA is evaluating findings that suggest pancreatic duct metaplasia in patients with type 2 diabetes treated with sitagliptin [76]. Other gliptins include saxagliptin, linagliptin, and alogliptin [42]. All the gliptins are oral agents taken once daily with or without food. They are unlikely to cause hypoglycemia because they do not work well when blood glucose is low.

INSULIN AND NONINSULIN INJECTABLES

Patient selection is critical to the successful use of insulin or noninsulin injectable therapy. The ideal candidate would be motivated, compliant, educable, and without any other medical condition or physical limitations that preclude accurate and reliable SMBG and insulin administration [2]. Caution is required in the elderly population or for any individual who could have difficulty with the identification of signs and symptoms of hypoglycemia. For patients with type 2 diabetes, insulin therapy is most commonly reserved for individuals in whom a sufficient trial of diet, exercise, and oral medication therapy has proven ineffective [2].

Any individual initiating injectable therapy to control diabetes requires specific instructions to safely administer the medications. Necessary education related to injectable therapy includes injection techniques, site rotation, needle disposal, and identification of signs and symptoms of hypoglycemia [143].

Injection Techniques

If insulin is being used, it may be available in a prepared pen or cartridge or the patient may be required to prepare a syringe. Steps to correct syringe preparation for a single type of insulin are:

- Wash hands with soap and water.
- Clean the top of the vial with an alcohol wipe.
- Pull enough air into the syringe to replace the prescribed amount of insulin to be taken from the vacuum-sealed vial.
- Insert the air into the vial, and invert the vial.
- Pull back the total amount of insulin prescribed.
- Assess the syringe for any air pockets.

- If air pockets are present, lightly tap the syringe to elevate the air to the top of the syringe and release the bubble back into the vial.
- Remove the needle from the vial

Vials of suspension preparations, such as NPH, should be rolled gently to mix the components prior to administration. In cases of mixed insulins, most commonly when a rapid- or short-acting insulin is utilized in tandem with NPH insulin, additional steps are required. For example, a patient administering NPH and insulin lispro would complete the following steps [144]:

- Wash hands with soap and water.
- Clean the top of the vial with an alcohol wipe.
- Roll the vial of NPH 10 times on its side to thoroughly combine the active components.
- Pull 10 units of air into the syringe to replace the prescribed amount of NPH insulin to be taken from the vacuum-sealed vial.
- Insert the air into the vial, and invert the vial.
- Remove the needle from the vial of NPH.
- Pull 7 units of air into the syringe to replace the 7 units of insulin lispro to be removed from the vacuum-sealed vial.
- Insert the air, and invert the vial.
- Pull back 7 units of insulin lispro.
- Assess the syringe for any air pockets.
- If air pockets are present, lightly tap the syringe to elevate the air to the top of the syringe and release the bubble back into the vial.
- Remove the needle from the vial.
- Insert the needle into the vial of NPH. Do not insert the insulin lispro into the NPH.
- Pull back 10 units of NPH into the syringe containing the insulin lispro.
- Assess for the presence of air pockets. If present, tap the syringe lightly and release only the air back into the vial.
- Remove the needle.

It is important to note that insulin glargine, insulin detemir, and insulin degludec cannot be mixed with any other insulin or fluid. Therefore, if glargine, detemir, or degludec is prescribed with rapid- or short-acting insulin, this will require two separate injections [56]. Furthermore, pramlintide and exenatide should not be combined with any other injectable medication due to the chemical composition [145].

Preparation of the site requires cleaning the area of injection with soap and water. Alcohol can be an alternative when soap and water are unavailable. After the site has dried completely, the patient will pinch the skin into a tent with the non-dominate hand and insert the needle at a 90-degree angle. He or she should then count to three; this will allow time for the insulin to start to disperse. It will also decrease the chance of removing the needle too rapidly, allowing the medication to back out of the subcutaneous tissue along with the needle [144]. The needle should then be disposed of in adherence with local requirements. The patient may utilize a commercial container or something as simple as a detergent bottle. When the container is full to within one inch of the top, recap the container and place strong tape around the top or follow the manufacturer's specific instructions [144].

It is important for patients to not reuse the needle due to the risk of infection and contamination of the medication vial. Patients should also be advised to assess needles prior to use and discard any that appear dull or bent to prevent injury [144]. A new needle should be used with each injection regardless of delivery method (e.g., syringe, pen device). This is a crucial topic of education [129].

Site Selection and Rotation

Injectables should be administered into specific locations to allow for the greatest absorption [129]. The first choice is usually the abdomen, which is considered the most consistent and rapid; the posterior upper arm is the second choice and is considered fast absorbing. The anterior thigh is appropriate, but the absorption is considered slow. Lastly, the buttocks can be utilized but will result in the slowest route of absorption [143].

Injection site rotation is of significant importance due to the potential development of a scar tissue related to overuse of a particular site of injection [143]. Insulin does not absorb into scar tissue; therefore, sites with overuse injuries will be ineffective [143]. For this same reason, it is important for patients to avoid areas where there are surgical or trauma scars. No one particular site-rotation technique is preferred as long as the chosen method is performed consistently by the person responsible for the injections [129].

Hypoglycemia

The development of hypoglycemia is a concern for all individuals on an injectable therapy regimen. Education should include information regarding oral and injectable combination medication management, insulin and injectable medication management, exercise considerations, and specific patient-centered issues to maintain safe use of medications in daily life [5].

Injectable medications alone or in combination with another antihyperglycemic agent increase the potential for an adverse hypoglycemia reaction [56]. Preventative measures include not skipping meals, eating prior to exercise, and appropriately timing insulin bolus therapy [56; 96].

With the greater potential for hypoglycemia reactions, caregivers or significant others will require specialized training in the preparation and administration of glucagon. The caregiver should receive instruction on how to prepare the solution. He or she should inject saline from the prefilled syringe into the vial of powdered hormone and shake to assure the complete mixing of the solution. Then the preparation may be drawn back into the syringe for injection into the upper arm, leg, or buttock [96].

Accurate and frequent SMBG is vital. Patients should report frequent blood glucose levels below 70 mg/dL to their primary care provider [146]. Communication among the entire team, including the patient, the certified diabetes educator, and the primary care provider, is an optimal approach to patient education regarding the prevention of hypoglycemia [129]. Individuals should communicate frequent and multiple episodes of hypoglycemia to their primary care provider for adjustments in basal insulin, bolus insulin, or a combination, depending on the timing of the hypoglycemic event(s). This will allow for the fine tuning of the insulin regimen, which should result in optimized glycemic control and reduction of adverse outcomes [147].

For patients on an insulin regimen, exercise can significantly increase the potential for hypoglycemia [35; 148]. Education related to exercise should focus on the assessment of pre-exercise blood glucose levels and determination if additional carbohydrates are needed. The patient should have a carbohydrate source available for treatment if signs or symptoms of hypoglycemia develop. Longstanding guidelines recommend consuming 10–15 grams of carbohydrate to prevent exercise-induced hypoglycemia [149]. However, subsequent research has illustrated that carbohydrate supplementation should be individualized to the patient's type of insulin and absorptive state [150; 151]. Patient education should include information about how different therapies affect timing of peak insulin levels and duration of insulin action [152]. Patients should not exercise during periods of hypoglycemia and should be advised to avoid exercise for 24 hours after an episode of hypoglycemia [153]. The risk for hypoglycemia increases as the duration or intensity of the activity increases. Patients should be advised to avoid exercise when their insulin is at peak effect. Lastly, patients should avoid injection into the muscle on which exercise will be focused. This is because as a muscle is exercised, blood flow increases the utilization of glucose transport into the skeletal muscle, leading to greater decreases in blood glucose levels [153].

Patients who have or who are suspected to have nocturnal hypoglycemia as a result of insulin therapy should monitor blood glucose levels prior to going to bed. When the blood glucose level is less than 90 mg/dL, the individual should be instructed to consume a snack that includes a carbohydrate and a protein. Specific signs and/or symptoms of nocturnal hypoglycemia should be provided, and patients should be instructed to notify the primary care provider of suspected episodes. When nocturnal hypoglycemia is suspected, patients will be required to test blood glucose levels at 3 a.m.; this will provide vital information for the primary care provider [154].

Storage Issues

As discussed, insulin and injectables should be stored in a cool place or refrigerated until the preparation is used or has expired. If the preparation becomes frozen, it should be discarded [42]. After they are opened and in use, vials and pens can usually be stored at room temperature but should be discarded after the amount of time specified by the manufacturer.

CASE STUDIES

CASE STUDY 1

Patient W is a Native American woman, 48 years of age, who is admitted to the hospital with complaints of chest pain. She is 5 feet 6 inches tall and weighs 256 pounds; her BMI is 41.4 kg/m^2. Her vital signs are assessed; her heart rate is 122 beats per minute, regular rate and rhythm, blood pressure is 198/101 mm Hg, and oral temperature is 37.4 degrees Celsius. Her past medical history is positive for gestational diabetes with her fourth child (five years previous), bilateral arthritis of the knees, and tobacco use. Patient W denies use of recreational drugs and homeopathic pharmaceuticals, but she does admit to occasional alcohol usage, generally two beers per day on the weekend. Her family history includes diabetes, heart disease, stroke, lung cancer, and alcohol abuse. Although her electrocardiogram is negative for myocardial infarction, her stress test reveals left coronary artery ischemia. Her cardiac enzymes are negative, but other significant laboratory results include:

- Triglycerides: 250 mg/dL
- LDL: 141 mg/dL
- HDL: 22 mg/dL
- Blood urea nitrogen (BUN): 35 mg/dL
- Creatinine: 1.5 mg/dL
- Random blood glucose: 310 mg/dL
- HbA1c: 9.5% (estimated average glucose: 226 mg/dL)
- Liver function tests: Within normal limits
- eGFR: 43 mL/min/1.73 m^2

Patient W is admitted for a cardiac catheterization and further cardiac work-up. She is started on blood glucose monitoring before meals and at bedtime with weight-based insulin correction with analog (rapid-acting) insulin, a calorie-controlled cardiac diet, antihypertensive medication, a statin for lipid management, an angiotensin-converting enzyme inhibitor, and pain medications as needed for chest pain or discomfort.

On hospital day 2, Patient W has a fasting blood glucose of 210 mg/dL. She receives rapid-acting insulin coverage per weight-based protocol even though she is being prepared for cardiac catheterization in the late morning and has not eaten. At approximately 10 a.m., the patient is taken for a cardiac catheterization, which reveals a 90% blockage of the left coronary artery, and subsequently undergoes percutaneous coronary intervention (PCI). A drug-eluting stent is placed. Postprocedure, Patient W returns to her room mildly sedated with an arterial line in place and a blood glucose level of 201 mg/dL, for which she receives weight-based coverage. At 5 p.m., the patient is alert and hungry. Her arterial line is discontinued, and her blood glucose is 220 mg/dL, for which she again receives weight-based coverage.

At 9 p.m., Patient W has been pain free throughout the day and is ready to sleep. Her blood glucose level is 201 mg/dL. She is given insulin and is instructed to notify the nurse of any pain, palpitations, sweating, shakiness, and/or dizziness.

On hospital day 3, Patient W awakens with a blood glucose level of 248 mg/dL. Her physician initiates basal insulin to obtain better glucose control. She is cleared for discharge by her cardiologist, but her primary care physician would prefer to monitor her glucose levels for one more day, including her two-hour postprandial level after her evening meal. Throughout the day, the following blood glucose levels are documented:

- 7 a.m.: 248 mg/dL
- 11 a.m.: 121 mg/dL
- 5 p.m.: 118 mg/dL
- 7 p.m. (two-hour postprandial): 210 mg/dL
- 9 p.m.: 178 mg/dL

The following morning, Patient W is discharged to home with a prescription for glyburide 2.5 mg twice a day for her newly diagnosed type 2 diabetes. She is also referred to an ADA-recognized education program. She receives survival skills education prior to leaving the hospital and is encouraged to contact the outpatient education center within the first week after discharge. Patient W agrees with her discharge plan and states understanding of all instructions given.

Rationale and comments: *The treatment approach appears appropriate to manage Patient W's diabetes. Patient education will be extensive for this patient given the many new medications and changes associated with the PCI and her various conditions. Education specific to the glyburide should include instructions to eat meals at a consistent time (not skipping meals) and information regarding the signs, symptoms, and treatment of hypoglycemia.*

At her follow-up appointment, Patient W has completed her self-management education and set personal behavior change goals for meal planning and exercise. She is demonstrating competent SMBG assessment; her fasting levels are between 140 mg/dL and 170 mg/dL, and her postprandial levels range from 160 mg/dL to 200 mg/dL. The patient's occasional two-hour postprandial readings range from 190 mg/dL to 230 mg/dL. Her fasting laboratory results are as follows:

- Fasting blood glucose: 167 mg/dL
- HbA1c: 8.6% (estimated average glucose: 200 mg/dL)
- Triglycerides: 220 mg/dL
- LDL: 110 mg/dL
- HDL: 33 mg/dL
- BUN: 35 mg/dL
- Creatinine: 1.5 mg/dL
- Liver function tests: Within normal limits

In order to improve Patient W's blood glucose control, her physician chooses to increase her glyburide to 5 mg twice a day with instruction to return for follow-up in one month to assess the efficacy of treatment. In one month, Patient W continues to have difficulties achieving optimal control on monotherapy. The decision is made to start combination therapy with pioglitazone, a TZD.

Rationale and comments: *Combination therapy with a TZD is the correct choice for Patient W because her BUN and creatinine levels are too high to safely utilize metformin. Furthermore, her casual use of alcohol on the weekends can be an area of concern with the potential for liver dysfunction. Pioglitazone will address the issue of insulin resistance in the presence of the metabolic syndrome and has beneficial effects on coronary artery disease in the presence of type 2 diabetes.*

Prior to leaving the physician's office, the nurse reviews the signs and symptoms of hypoglycemia with Patient W. The patient is instructed to alert her primary care physician of frequent episodes of hypoglycemia. She is also counseled regarding the need to eat meals at spaced intervals throughout the day to decrease the chances of developing hypoglycemia.

The heart failure risks associated with TZD use are discussed as well as the need to report any weight increase of 3 to 5 pounds over a two-day period to her primary care physician. Patient W is also advised to contact her primary care physician if she experiences any symptoms related to liver dysfunction/failure, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine. Finally, the patient is reminded of the need to monitor her liver function by venipuncture periodically while on pioglitazone.

CASE STUDY 2

Patient O is a Hispanic male, 48 years of age, with a seven-year history of type 2 diabetes. He presents to his primary care physician's office for a routine follow-up appointment to assess his diabetes control. His only complaint at the time of his appointment is an occasional burning sensation in his bilateral lower extremities.

Patient O's past medical history is positive for type 2 diabetes diagnosed at 41 years of age, hypertension for the past two years, and new onset of hyperlipidemia within the past six months. He is negative for renal disease, retinopathy, and peripheral vascular disease. The patient's family history is positive for type 2 diabetes, coronary artery disease, cerebral vascular accident, hyperlipidemia, and obesity.

During the physical assessment, Patient O is alert and oriented. His height (5 feet 10 inches), weight (239 pounds), and BMI (34.4 kg/m^2) are measured and documented. Blood pressure is 128/68 mm Hg on medications, pulse is 74 beats per minute, and oral temperature is 37 degrees Celsius. Lungs are clear to auscultation, and heart sounds are clear without rubs or murmurs. The patient's abdomen is soft and nontender at all quadrants. Peripheral pulses are present at +2 at all extremities, and feet are free from lesions with a positive Babinski reflex. All extremities are warm to touch and responsive to monofilament test.

Patient O's laboratory results include:

- HbA1c: 8.1% (estimated average glucose: 186 mg/dL)
- Fasting blood glucose: 155 mg/dL
- BUN: 24 mg/dL
- Creatinine: 1.3 mg/dL
- ALT: 16 U/L
- HDL: 31 mg/dL
- LDL: 122 mg/dL
- Triglycerides: 201 mg/dL
- Microalbuminuria: 312 mcg/mg

The patient is currently prescribed captopril 25 mg twice a day, simvastatin 40 mg daily at bedtime, metformin 1,000 mg twice per day, and glipizide extended-release 20 mg daily. He has previously met with a registered nurse certified diabetes educator and registered dietitian certified diabetes educator regarding self-care management, blood glucose monitoring, behavior change, meal planning, and goal setting. He tests his blood glucose levels twice a day at various times.

At this visit, Patient O receives the results of his blood work and has expressed concerns regarding his recent SMBG numbers and new onset of burning in his lower extremities. He presents verbalizing frustration and feeling like a failure. It is vital to actively listen to the patient regarding his frustrations and fears related to his diabetes. It is also important to educate him regarding the progressive nature of diabetes, regardless of the attentiveness a person gives to the care of the disease [2].

The nurse reviews Patient O's eating and exercise habits to see if any changes could be made to optimize control. Furthermore, sources of stress are discussed. Patient O is told that worrying about the progression of his diabetes and having anxiety regarding adherence to his meal or exercise plan is normal, but it is possible for this additional stress and anxiety to result in increased blood glucose levels [7]. Patient O states that he was unaware of the impact stress was having on his body.

Due to the continued elevated blood glucose levels, the primary care physician wants to maximize oral medication therapy, most likely by adding a DPP-4 inhibitor, an alpha-glucosidase inhibitor, or a TZD [2]. In order to make a decision regarding the most appropriate agent, each of the classes' benefits and risks should be considered with Patient O in mind. The addition of a DPP-4 inhibitor has been shown to be weight neutral, occasionally demonstrating a reduction in weight. The dose can be decreased for safe use in those individuals who have some renal impairment, such as Patient O [57]. The greatest drawback of DPP-4 inhibitor therapy is the cost.

The addition of an alpha-glucosidase inhibitor is a less expensive option and would benefit Patient O by decreasing the absorption of complex carbohydrates in the intestinal tract. The alpha-glucosidase inhibitors do have objectionable side effects, such as recurrent flatulence, that some patients are unable to tolerate [56]. Patient education needs for those taking alpha-glucosidase inhibitors include timing of medication with meals, gastrointestinal side effects, and the treatment of hypoglycemia [42; 56; 60].

The addition of a TZD would reduce insulin resistance and reduce cardiovascular risk factors, including markers of vascular inflammation [2]. However, precautions should be taken when this therapy is prescribed. Weight gain and liver damage are possible, and laboratory levels should be regularly monitored. Patient education regarding weight gain and shortness of breath is necessary as these are signs of impending heart failure.

The final option for Patient O would be to continue current therapy and add basal insulin. This would provide long-acting coverage to allow the metformin and extended-release glipizide to have a greater effect. This also has obstacles to acceptance, including fear of injection, fear of acute hypoglycemia, and misconceptions about insulin therapy. All therapy choices would be viable options for Patient O, and as a healthcare provider, understanding of all available agents is needed to support the final decision.

CASE STUDY 3

Patient F is a black female resident of a local long-term care facility. She is 87 years of age and has had type 2 diabetes for the past 25 years. In addition to diabetes, Patient F has a past medical history of hypertension, cardiovascular disease, peripheral neuropathy, and mild Alzheimer disease. Her son and daughter-in-law came to visit and found the patient confused, wet with foul urine, and begging for water. She had a temperature of 38.5 degrees Celsius. The family requested her transfer to the emergency department for evaluation and treatment.

Upon admission to the emergency department, Patient F is increasingly confused and combative, with a body temperature of 38.8 degrees Celsius. She is started on oxygen at 2 liters for an oxygen saturation of 88%. Laboratory samples are obtained, and an infusion of 0.9% sodium chloride is initiated at 75 mL/hour for observed signs of dehydration. The laboratory results indicate:

- Blood glucose: 1179 mg/dL
- Potassium: 5.2 mEq/L
- Phosphorus: 3.4 mmol/L
- Ketones: Minimal
- Serum osmolality: 420 mOsm/kg
- HbA1c: 11.9%
- White blood cell count: 46,000
- Urinalysis: Positive for bacteria

Based on this information, a diagnosis of HHS is made. Because HHS is characterized by profound dehydration, management is initially focused on rehydration. The physician orders an increase in the current 0.9% sodium chloride infusion to 100 mL/hour. Because there are no dysrhythmias noted on the telemetry monitor, the physician continues to monitor the potassium level with subsequent laboratory assessments. Patient F is also started on empirical antibiotic therapy for a suspected UTI until the results of urine and blood culture are known. An additional intravenous access is initiated in order to administer insulin. A regular insulin bolus of 0.1 units/kg followed by an infusion of regular insulin is ordered to run at a rate of 0.1 units/kg/hour.

Patient F's blood glucose levels slowly drop to 275 mg/dL, but her osmolality is 365 mOsm/kg and she remains confused. Because the patient's osmolality remains greater than 350 mOsm/kg and her confusion is unresolved, her blood glucose levels should be maintained between 250 mg/dL and 300 mg/dL. Her potassium level stabilizes without intravenous therapy and is currently 4.2 mEq/L. Her telemetry readings remain in sinus rhythm.

After 36 hours of therapy, Patient F has an osmolality of less than 315 mOsm/kg, and she is back to her baseline mentation. Her blood glucose level is 225 mg/dL, and she is getting prepared to transfer off of the insulin infusion.

***Rationale and comments**: Several considerations should be made in order to continue to achieve optimal glycemic control. The patient's HbA1c is 11.9%, which is considered uncontrolled. If a long-acting insulin is not started, the glucose levels will rebound. Also, it is vital that hydration status is maintained. Basal insulin should be given at least one hour prior to the discontinuation of the insulin infusion in order to prevent rebound hyperglycemia, which is a risk due to Patient F's continuing UTI and high HbA1c.*

Patient F is maintained on 0.9% sodium chloride 75 mL/hour until adequate oral intake is established. She also starts insulin detemir 0.2 units/kg (total dose: 15 units) to be given once per day at night, which should provide weight-based coverage for correction of glucose elevations.

After three days, Patient F's HHS has been resolved, and the team is preparing the patient for discharge. However, she continues to have blood glucose levels between 280 mg/dL and 400 mg/dL.

***Rationale and comments**: There are several available options for Patient F. Insulin detemir may be continuously increased to desired effect and/or split to a twice daily schedule. If glycemic control is not achieved on the long-acting insulin preparation, addition of bolus insulin therapy may be necessary. Because the patient is a resident of a long-term care facility and has a history of cognitive impairment, the better option for her may be combination therapy.*

To combat the consistently high blood glucose levels, Patient F's insulin detemir dose is increased to 15 units twice a day. The next day, the patient has the following glucose results: 146 mg/dL, 175 mg/dL, 188 mg/dL, and 136 mg/dL. Her primary care provider is satisfied with these readings and plans to discharge her the following day.

CONCLUSION

As the prevalence of diabetes increases, it is important to have a general understanding of the many options for treatment. Each of the various drug classes has specific contraindications and potential side effects, and all members of the interdisciplinary team should be involved with assessing the efficacy of the treatments and patients' quality of life. This approach is best to ensure optimal outcomes and prevention of long- and short-term complications. With the constant evolutions and advances being made in the management of diabetes, healthcare professionals should frequently review and rene w their professional knowledge to ensure the care provided to diabetic patients is the most accurate and up-to-date possible.

FACULTY BIOGRAPHY

Diane Thompson, RN, MSN, CDE, CLNC, has an extensive history in nursing and nursing education. She possesses a strong background in diabetes and cardiac care, starting her professional career at the cardiac care area of the Cleveland Clinic in Cleveland, Ohio. Ms. Thompson took the knowledge and experience she learned from the Cleveland Clinic and transferred it into the home health arena in rural Ohio, after which she moved to Florida and obtained further knowledge while working as a PRN nurse in all areas, including medical/surgical, intensive care, emergency, critical care, and cardiology. With a desire to have a specific area to concentrate her profession, Ms. Thompson accepted a position as a pneumonia case manager, which led into a diabetes case manager career.

Ms. Thompson has been employed in diabetes care since 2001, when she was hired as a diabetes case manager. After the completion of 1,000 hours of education to diabetes patients, Ms. Thompson earned her certification as a diabetes educator in 2003. From 2006 to 2018, Ms. Thompson was the Director of Diabetes Healthways at Munroe Regional Medical Center in Ocala, Florida. As the director of the diabetes center, Ms. Thompson was responsible for the hospital diabetes clinicians, hospital wound care clinicians, and out-patient education program. Today, she is the nurse manager of a heart, vascular, and pulmonary ambulatory clinic at Metro Health System in Cleveland, Ohio. Ms. Thompson has also lectured at the local, state, and national level regarding diabetes and the hospital management of hyperglycemia. Ms. Thompson is a member of the ADA, AADE, Florida Nurses Association, and the National Alliance of Certified Legal Nurse Consultants.

Ms. Thompson acknowledges her family as her greatest accomplishment. She is a wife of more than 30 years and a mother of a daughter and son, of which she is very proud. Ms. Thompson credits her husband for the support needed to set a goal and achieve it. He has been by her side through nursing school and completion of her Bachelor's degree and Master's degree, which she was awarded in 2015 from Jacksonville University in Florida.

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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