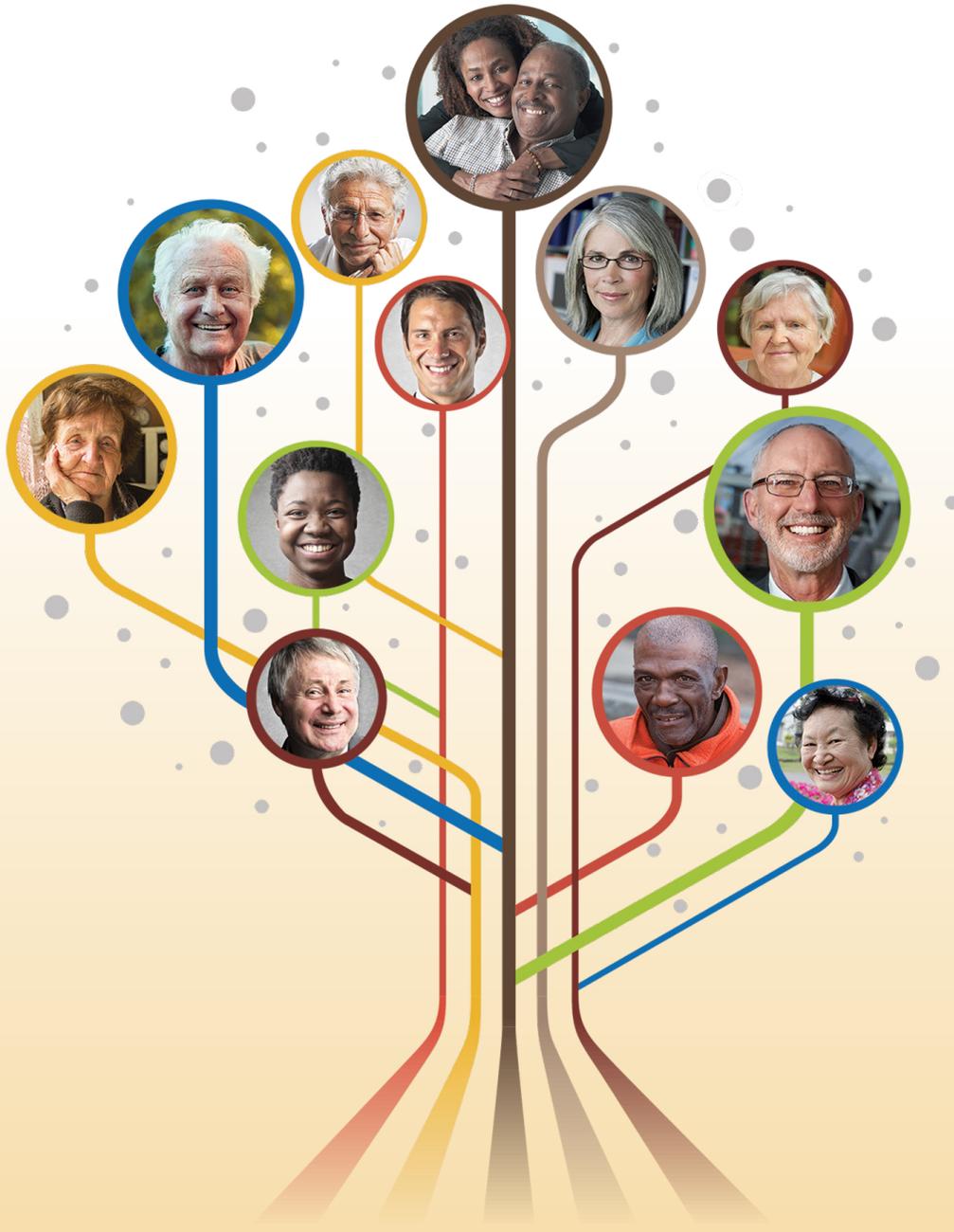


Use of Insulin Therapy in Managing Type 2 Diabetes Mellitus



Planned and coordinated by ASHP Advantage
Supported by an educational grant from Novo Nordisk Inc.

Use of Insulin Therapy in Managing Type 2 Diabetes Mellitus

Target Audience

This continuing pharmacy education activity was planned to meet the needs of pharmacists with an interest in diabetes management and new drug therapies who practice in hospitals, ambulatory care clinics, specialty pharmacies, and community pharmacies.

Learning Objectives

After studying this discussion guide, readers should be able to

1. Describe the clinical impact of type 2 diabetes mellitus.
2. Explain the role of insulin in managing type 2 diabetes mellitus taking into account current treatment guidelines and available insulin products.
3. Outline a plan for addressing adverse effects and safety issues in insulin-treated patients.

CONTINUING PHARMACY EDUCATION

This continuing pharmacy education discussion guide is part of the educational initiative, “Individualization of Insulin Therapy for Type 2 Diabetes Mellitus: What You Need to Know.” The initiative focuses on individualized insulin therapy with an emphasis on new insulin options. The activities are designed to build upon each other to facilitate application of concepts to clinical practice.

To access other educational opportunities in the initiative, visit www.ashpadvantage.com/go/type2.



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This discussion guide provides 1.5 hours (0.15 CEUs—no partial credit) of continuing pharmacy education credit. See page 17 for CE information and instructions for processing CE.

Reviewers and Disclosures

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SYSTEM REQUIREMENTS

Web Browser: Microsoft Internet Explorer 8 or above, Mozilla Firefox, Apple Safari or Google Chrome. Note: Please disable any “pop-up blocker” features. **Software:** Adobe Acrobat Reader version 7 or above to view PDF files (If you do not have Acrobat Reader, you can download it for free from <http://get.adobe.com/reader>). **Connection Speed:** Cable, DSL, or better of at least 300 kbps.

Executive Summary

Type 2 diabetes mellitus is a serious chronic disease involving dysfunction of numerous organs. Macrovascular and microvascular complications often are present at the time of diagnosis. Early, aggressive intervention with lifestyle modification and pharmacotherapy can delay or prevent disease progression. An individualized approach with combination pharmacotherapy often is needed to target multiple dysfunctional organs for optimal glucose control. Most adults with diabetes do not use insulin despite recommendations in authoritative treatment guidelines and failure to achieve their glycemic goals. Hypoglycemia and weight gain are common concerns and barriers to the use of insulin therapy. Insulins vary in their time to onset, peak, and duration of action, and these differences are taken into consideration in selecting insulin therapy.

New types, concentrations, and delivery systems for insulin were recently introduced that may improve glycemic control, convenience, and adherence in patients with type 2 diabetes. Concentrated insulins offer advantages to patients with large insulin dosing requirements, but dosing conversion may be required and error could occur. The new concentrated insulins are available only as insulin pens, except for U-500 regular human, which has been available in vials. Insulin pens have been associated with greater dose accuracy, convenience, ease of use, and adherence than conventional vials and syringes, but potential safety risks associated with the use of insulin pens have been reported. Various strategies may be used to ensure the safe use of insulin pens and to avoid or minimize adverse effects and overcome safety concerns associated with insulin therapy to improve long-term outcomes in patients with type 2 diabetes.

Introduction

Diabetes mellitus is a common and deadly disease. One person on our planet dies from the disease every 6 seconds.¹ Five million deaths were attributed to diabetes worldwide in 2015. In the United States, 29.1 million people have diabetes.² The prevalence of prediabetes—a condition characterized by insulin resistance and hyperglycemia that often leads to diabetes and its complications—is nearly threefold higher, affecting an estimated 86 million adults. Type 2 diabetes accounts for 90-95% of adults with diabetes. Three in five patients with type 2 diabetes develop one or more macrovascular or microvascular complications (e.g., ischemic heart and peripheral vascular disease, microalbuminemia, retinopathy).³

Natural History

The metabolic changes that result in the macrovascular and microvascular complications of diabetes begin long before the time of diagnosis in most patients with type 2 diabetes (Figure 1). There is an estimated 9- to 12-year

gap between the onset of these changes and a clinical diagnosis.⁶ Type 2 diabetes is the result of insulin resistance and a progressive loss of pancreatic β -cell insulin-secreting function.⁷ Insulin promotes glucose uptake by liver and muscle tissues and suppresses hepatic glucose production and lipolysis. To maintain glucose homeostasis, the effects of insulin ordinarily are opposed by glucagon secreted by

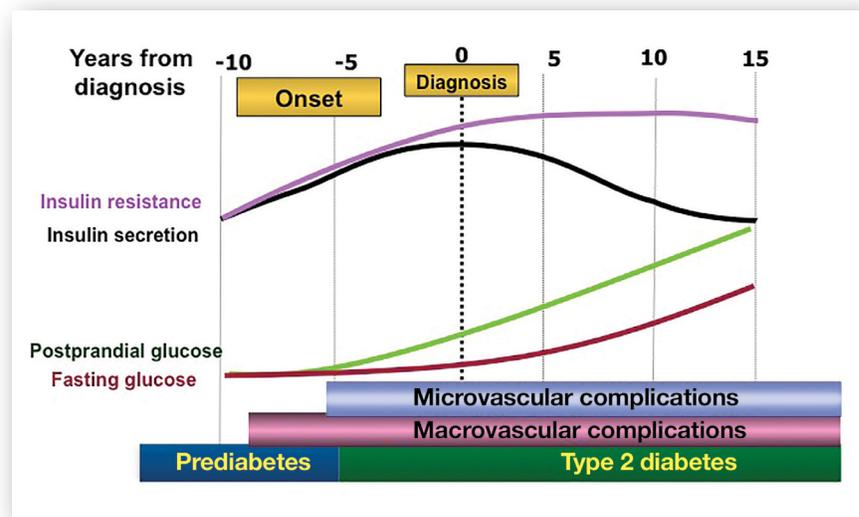


FIGURE 1. Natural history of type 2 diabetes.^{4,5}

pancreatic α cells. Type 2 diabetes often does not manifest until insulin secretion decreases to such an extent that it fails to compensate for insulin resistance, and the patient becomes symptomatic as a result of hyperglycemia.⁸ The majority of β -cell function (80% to 85%) is lost by the time of diagnosis.⁷

Type 2 diabetes has been attributed to insulin resistance in the liver, which increases hepatic glucose production, and muscle tissue, which decreases glucose uptake by muscle cells; it has also been attributed to β -cell dysfunction, which reduces insulin secretion.⁷ All of these effects contribute to hyperglycemia. The pathogenesis of type 2 diabetes also involves dysfunction in multiple other organ systems, including adipose tissues (increased lipolysis by fat cells), the gastrointestinal tract (deficiency of incretins, which are hormones that promote insulin secretion and suppress glucagon release after the ingestion of food), kidneys (increased glucose reabsorption), brain (insulin resistance leading to appetite dysregulation and weight gain), and pancreatic α cells (increased release of glucagon, which promotes hepatic glucose production).⁹ In healthy persons, β cells outnumber α cells. However, as type 2 diabetes progresses, the α -cell mass is unchanged while the β -cell mass decreases, so the ratio of α cells to β cells increases, resulting in hyperglucagonemia.⁹

Lipotoxicity plays an important role in the pathogenesis of type 2 diabetes. Accelerated lipolysis by fat cells increases circulating free fatty acids, and deposition of free fatty acids in β cells impairs insulin secretion, worsening hyperglycemia. Excess deposition of fats in the liver and muscle cells contributes to insulin resistance.

Recent evidence suggests a role for the immune system (i.e., dysregulation or inflammation) and colon or microbiome (i.e., abnormal gastrointestinal microflora) in type 2 diabetes.¹⁰

Current Treatment Guidelines

The American Diabetes Association (ADA) recommends less than 7% as a reasonable goal A1c for many nonpregnant adults with type 2 diabetes, although individualization of treatment goals and strategies is recommended.^{11,12} Less than two thirds of American adults with type 2 diabetes (57%) achieve an A1c less than 7%.¹³ The rates of achievement of this target A1c value are lower among black non-Hispanic and Mexican Americans than white non-Hispanics. There is room for improvement in glycemic control among most Americans with type 2 diabetes.

Treating type 2 diabetes involves dietary modification (i.e., reduced consumption of simple carbohydrates and if overweight, calories), increased physical activity, and drug therapy.¹¹ Drug therapy aims to improve or replace insulin secretion, reduce hepatic glucose production, reduce insulin resistance, reduce glucagon secretion, increase urinary glucose excretion, increase satiety, delay gastric emptying, or provide a combination of these effects.^{11,12} Specific medication options and their mechanism of action include the following¹²:

- Exogenously administered insulin and sulfonylureas augment inadequate endogenous insulin secretion;
- Metformin reduces hepatic glucose production;
- Thiazolidinediones (TZDs) reduce insulin resistance;
- Glucagon-like peptide (GLP)-1 receptor agonists and dipeptidyl peptidase (DPP)-4 inhibitors promote glucose-dependent insulin secretion and suppression of glucagon release after the ingestion of food, and GLP-1 agonists also delay gastric emptying, thereby increasing satiety; and
- Sodium glucose cotransporter (SGLT)-2 inhibitors reduce renal reabsorption of glucose.

Achieving glycemic control and A1c goals often requires combination drug therapy that targets dysfunction in multiple organs.⁷ Early aggressive therapy may prevent or slow β -cell loss and disease onset or progression.

Currently available glucose-lowering agents vary in their mechanism of action, primary target organ(s), usefulness for patients with prediabetes, effects on insulin resistance and fasting and postprandial plasma glucose, A1c-lowering effect, and adverse effects (Table 1). The A1c reduction provided by oral and noninsulin injectable diabetes medications is limited. By contrast, insulin therapy can be used to provide whatever reduction in A1c is needed to achieve the target value.

Current (2015) guidelines for the management of hyperglycemia in patients with type 2 diabetes from ADA and the European Association for the Study of Diabetes (EASD) call for the use of metformin monotherapy as first-line therapy in conjunction with lifestyle modification unless the drug is contraindicated or not tolerated (Figure 2).¹² If the target A1c is not achieved after approximately 3 months of metformin monotherapy, basal insulin is an option as part of second-line dual therapy or third-line triple therapy in combination with metformin with or without a TZD, DPP-4 inhibitor, SGLT-2 inhibitor, or GLP-1 agonist. Combination

TABLE 1

Pharmacology and Pharmacodynamics of Commonly Used Drug Therapies for Type 2 Diabetes Mellitus^{12,14-16, a}

Drug or Drug Class	Target Organ	Useful in Prediabetes	Targets Insulin Resistance	Plasma Glucose Affected	Typical A1c Reduction (%) ^b
Sulfonylureas	Pancreas	No	No	FPG and PPG	1.5-2.0
Metformin	Liver	Yes	Possibly	FPG	1.5
Thiazolidinediones	Liver, peripheral tissues (e.g., muscle), fat	Yes	Yes	FPG and PPG	1.0-1.5
Dipeptidyl peptidase-4 inhibitors	Liver and pancreas	No	No	PPG	0.7
Glucagon-like peptide-1 agonists	GI tract, liver, pancreas, and brain	Yes	No	Short-acting: PPG Long-acting: FPG and PPG	0.8-2.0
Sodium glucose cotransporter-2 inhibitors	Kidneys	No	Possibly	FPG	0.5-1.0
Insulin	Pancreas, liver, muscle, and fat	No	Yes (to some extent)	Basal: FPG Bolus: PPG	As much as needed

^aFPG = fasting plasma glucose, GI = gastrointestinal, PPG = postprandial plasma glucose.

^bA1c-lowering effect may vary for individual patients. The A1c data in this table were not obtained from head-to-head comparative studies.

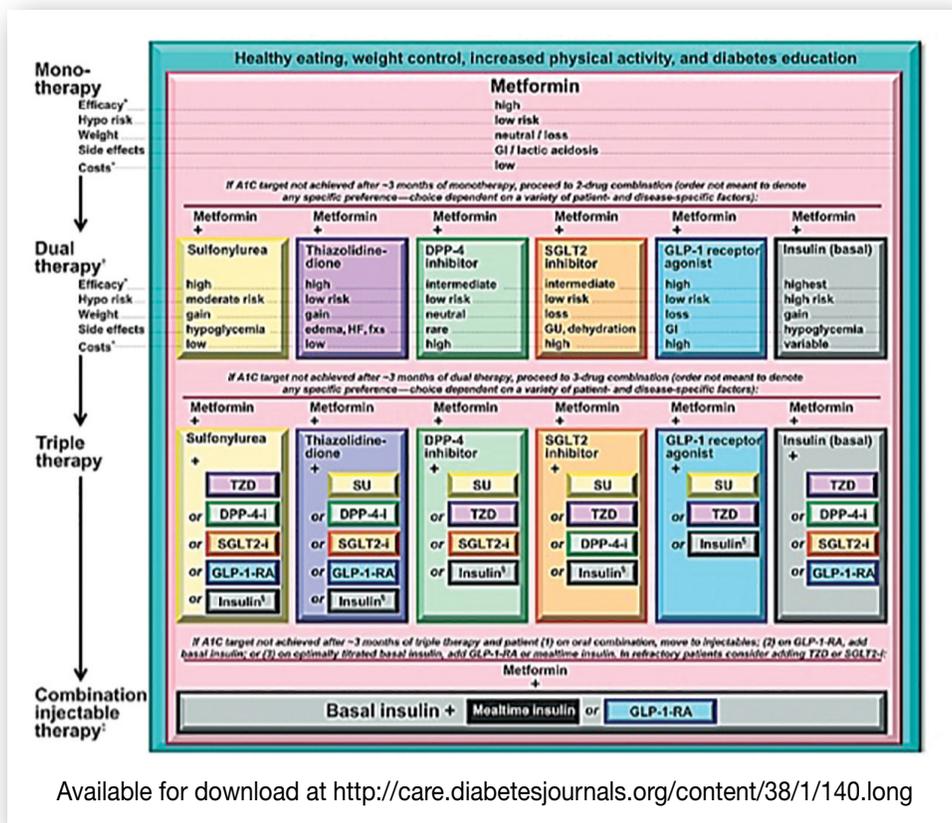


FIGURE 2. Guidelines of the American Diabetes Association and European Association for the Study of Diabetes for the management of hyperglycemia in patients with type 2 diabetes.¹²

Available for download at <http://care.diabetesjournals.org/content/38/1/140.long>

injectable therapy with basal insulin and either a GLP-1 agonist or mealtime (i.e., bolus) insulin is recommended if triple therapy is ineffective, the blood glucose concentration is 300 mg/dL or higher, or the A1c is 10% or higher, especially if the patient is symptomatic or exhibits catabolic features (e.g., weight loss, ketosis). An individualized approach is recommended based on the risk for hypoglycemia and other adverse effects, duration of disease, life expectancy, and the presence of comorbidities and vascular complications.¹² Hypoglycemia is a concern with the use of insulin and sulfonylureas. Weight gain is a concern with insulin, sulfonylureas, and TZDs.

An individualized approach with patients stratified by A1c is used in a comprehensive type 2 diabetes management algorithm from the American Association of Clinical Endocrinologists and American College of Endocrinology (Table 2).¹⁶ Basal insulin may be used as part of first-line dual therapy (i.e., with metformin or another first-line agent, such

as a GLP-1 agonist, SGLT-2 inhibitor, or DPP-4 inhibitor) or second-line triple therapy (i.e., in combination with metformin and another first-line agent if the A1c goal is not achieved with dual therapy for 3 months) in conjunction with lifestyle modification for patients with an A1c of 7.5% to 9.0%. The same is recommended for asymptomatic patients with an A1c greater than 9.0%. Insulin is indicated earlier (with or without other agents) for symptomatic patients with an A1c exceeding 9.0%.

The majority of adults with diabetes (71%) do not use insulin despite evidence-based guidelines recommending the early use of basal insulin.² Only 14% of adults with diabetes use insulin alone, and another 15% use insulin in combination with oral diabetes medications. Delays in intensification of insulin and other diabetes drug therapies and suboptimal glycemic control in patients with type 2 diabetes have been attributed to clinical inertia (i.e., reluctance to intensify therapy for a chronic disease).¹⁷

TABLE 2

Approach to Type 2 Diabetes Mellitus Management Based on Entry Level A1c and Symptoms^{a,b,16}

Approach Based on Entry-level A1c	Recommended Options^c
<i>Entry level A1c < 7.5%</i>	
Monotherapy is appropriate	Metformin, GLP-1 agonist, SGLT-2 inhibitor, DPP-4 inhibitor, TZD, AGI, sulfonylurea/glinide (order represents suggested hierarchy of use)
<i>Entry level A1c ≥ 7.5%</i>	
Combination (dual) therapy is appropriate	Metformin + one of the following (order represents suggested hierarchy of use) GLP-1 agonist, SGLT-2 inhibitor, DPP-4 inhibitor, TZD, basal insulin, BAS, dopamine agonist, AGI, sulfonylurea/glinide
Combination (triple) therapy is appropriate	1st + 2nd line agents + one of the following (order represents suggested hierarchy of use) GLP-1 agonist, SGLT-2 inhibitor, TZD, basal insulin, DPP-4 inhibitor, BAS, dopamine agonist, AGI, sulfonylurea/glinide
<i>Entry level A1c > 9.0%</i>	
No symptoms	Combination (dual or triple) therapy
Symptoms	Insulin +/- other agents

^aAdapted from American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive type 2 diabetes management algorithm.¹⁶ Algorithm is available for download at <http://journals.aace.com/doi/pdf/10.4158/EP151126.CS>.

^bAGI = α -glucosidase inhibitor, BAS = bile acid sequestrant, DPP = dipeptidyl peptidase, GLP = glucagon-like peptide, SGLT = sodium glucose cotransporter, TZD = thiazolidinedione.

^cMedications in GREEN = few or minimal adverse effects with possible benefits, and medications in RED = use with caution.

Insulin Therapy

The goal of insulin therapy in patients with type 2 diabetes is to mimic the endogenous secretion of insulin in healthy persons, with continuous basal secretion and meal-stimulated secretion.¹⁸ Endogenous basal insulin maintains glucose homeostasis by regulating hepatic glucose production. The ideal strategy for managing insulin therapy in patients with type 2 diabetes involves a basal-bolus approach using a combination of a long-acting basal insulin and bolus doses of a rapid- or short-acting insulin prior to meals. Administering approximately 50% of the total daily insulin requirement as a basal insulin once or twice daily maintains consistent blood glucose concentrations at night and between meals.¹⁹ Giving the other 50% of the daily insulin requirement in divided bolus doses before meals prevents postprandial hyperglycemia. Supplemental correction doses of a rapid- or short-acting insulin may be used to address excursions in blood glucose, with dosing guided by blood glucose measurements and insulin sensitivity, which hinges on patient-specific factors (e.g., ability to eat meals, age, renal impairment).

The approach to initiating and adjusting insulin therapy in patients with type 2 diabetes recommended by ADA and EASD is illustrated in Figure 3 (next page).¹² Strategies for addressing an inadequate A1c response to basal insulin in combination with metformin with or without another noninsulin agent include the addition of a rapid-acting insulin analog before meals (i.e., bolus insulin) or a GLP-1 agonist (i.e., the GLP-1 agonist may be used instead of a bolus insulin). The use of a premixed formulation of an intermediate-acting insulin and a short- or rapid-acting insulin is an alternative. The number of daily injections and complexity

What patients in your practice with type 2 diabetes mellitus could potentially benefit from insulin therapy?



and flexibility of these regimens vary, with implications for adherence. The effects on fasting and postprandial plasma glucose, risk for hypoglycemia, and effect on weight also vary among different combinations (Table 3).

Development of Insulin

Insulin was discovered and first administered to humans as a product derived from cows in the early 1920s.²⁰ Isophane NPH (neutral protamine Hagedorn), zinc insulin (Lente), and extended zinc insulin (Ultralente) with a prolonged duration of action were introduced in the early 1950s.²¹ Allergic reactions and immune-mediated lipodystrophy were associated with impurities in insulins obtained from animal sources. Human insulin was first synthesized in a laboratory in the 1960s, although synthesis through recombinant DNA technology was not achieved until 1978, with approval from the Food and Drug Administration (FDA) in 1982. Since that time various insulin analogs have become available, including lispro (1996), aspart (2000), glargine (2000), glulisine (2004), and detemir (2005). The pharmacokinetics and pharmacodynamics of these insulins vary, with a rapid onset and short duration of action from insulin lispro, aspart, and glulisine and a long duration of action from insulin glargine and

TABLE 3

Pharmacodynamics of Insulin Strategies in Patients with Type 2 Diabetes Mellitus^{12,a}

Combination	Plasma Glucose Affected	Risk for Hypoglycemia	Effect on Weight
Basal insulin + metformin	FPG	Low (from basal insulin) but higher if NPH used	Gain or neutral
Basal + bolus insulin (with or without metformin)	FPG and PPG	High (primarily from bolus insulin)	Gain
Basal insulin + a GLP-1 receptor agonist (with or without metformin)	FPG and PPG	Low (from basal insulin)	Neutral or loss

^aFPG = fasting plasma glucose, GLP = glucagon-like peptide, NPH = neutral protamine Hagedorn, PPG = postprandial plasma glucose.

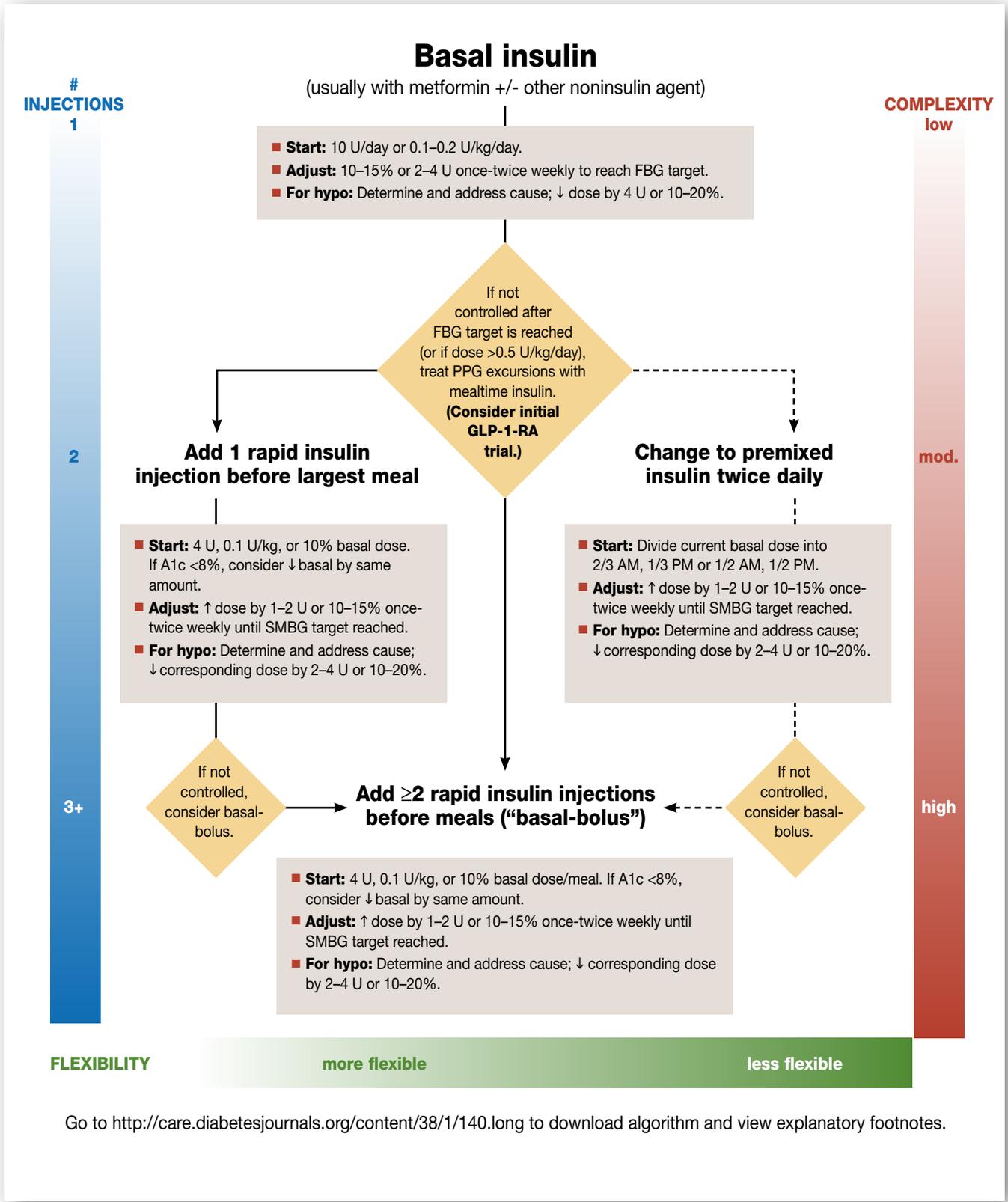


FIGURE 3. Approach of the American Diabetes Association and European Association for the Study of Diabetes to starting and adjusting insulin in patients with type 2 diabetes mellitus.¹²

detemir (Table 4 and Figure 4). A rapid onset and prolonged duration of action can be obtained from the use of the insulin mixtures in Table 4, which may reduce the number of daily injections and promote adherence. However, use of these mixtures may promote weight gain and compromise glycemic control (i.e., increase the risk of hyperglycemia and hypoglycemia) because of the lack of flexibility in tailoring insulin therapy.

Orally inhaled human insulin was introduced in 2011, but it was withdrawn from the market by the manufacturer

because of poor acceptance of the cumbersome delivery device. In 2014, a new formulation of regular human insulin inhalation powder was approved by FDA for use in patients with type 1 or 2 diabetes.²⁵ It is a rapid-acting insulin provided in 4- and 8-unit cartridges for use with an oral inhaler at mealtimes. The cartridges are provided in sealed packages containing blister cards with five strips of three cartridges per strip. The packages must be used within 10 days after opening (stored at room temperature), and the strips must be used within 3 days after opening.

TABLE 4

Insulin Pharmacodynamic Comparison^{19,21-38,a}

Type of Insulin (concentration)	Time to Onset of Action (hr)	Time to Peak Action (hr)	Duration of Action (hr)
<i>Single-agent products</i>			
Lispro (U-100, U-200)	<0.25	0.5-1.5	4-6
Aspart	<0.25	0.5-1.5	4-6
Glulisine	<0.25	0.5-2	4-6
Inhaled regular human	<0.25	1	3
Regular human (U-100)	0.5	3	8
Regular human (U-500)	0.25	4-8	13-24
NPH	2-4	4-10	12-18
Detemir	3-4	6-8, although relatively flat	Up to 24
Glargine (U-100)	2-4	Flat (no peak)	20-24
Glargine (U-300)	6	Flat (no peak)	Up to 36
Degludec (U-100, U-200)	1	Flat (no peak)	>42 hr
<i>Mixtures</i>			
Lispro 50/50 ^b	<0.25	0.5-1.5	Up to 24
Lispro 75/25 ^c	<0.25	0.5-1.5	18-24
Aspart 70/30 ^d	<0.25	1.5-2.5	Up to 24
Degludec/aspart 70/30 ^e	<0.25	1-2.5	>24

^aAll times are after subcutaneous injection, except inhaled regular human insulin. The time course of action of insulin and insulin analogs may vary considerably in different individuals or within the same individual. The onset of activity is known to be affected by the site of injection, exercise, and other variables.

^bLispro 50/50 is 50% insulin lispro protamine suspension and 50% insulin lispro injection, [rDNA origin].

^cLispro 75/25 is 75% insulin lispro protamine suspension and 25% insulin lispro injection, [rDNA origin].

^dAspart 70/30 is 70% insulin aspart protamine suspension and 30% insulin aspart injection, [rDNA origin].

^eDegludec/aspart 70/30 is 70% insulin degludec and 30% insulin aspart injection.

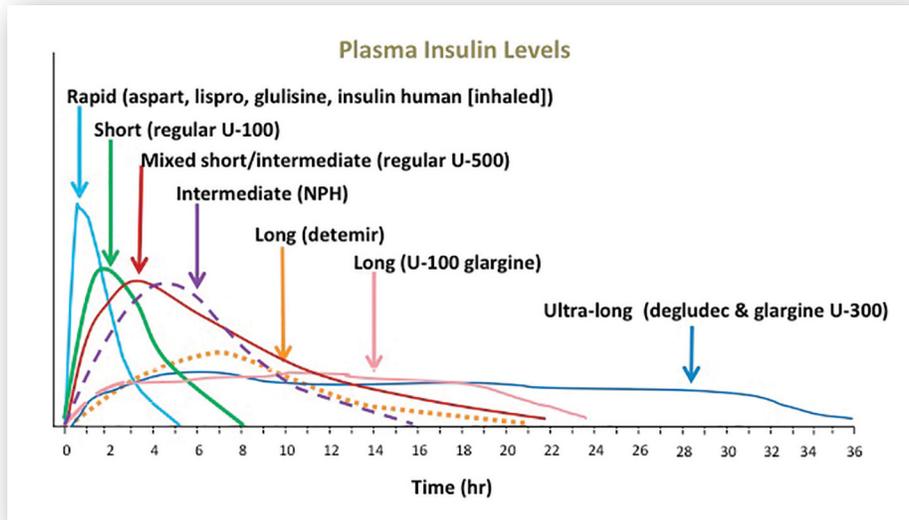


FIGURE 4. Pharmacokinetic profile of currently available insulins.

The use of inhaled regular human insulin is contraindicated in patients with chronic lung disease (e.g., asthma, chronic obstructive pulmonary disease) because of the risk of acute bronchospasm.

The year 2015 might be considered the “golden age” of insulins because of the introduction of insulin degludec and concentrated forms of this and several established insulins in pen form (Table 5). The smaller injection volume of concentrated insulins is a potential advantage over

conventional U-100 (i.e., 100 units/mL) insulin for obese or other severely insulin-resistant patients with large insulin dosing requirements (e.g., 200 units/day or more, or 2 units/kg/day or more, for U-500 insulin, which contains 500 units/mL).^{39,40} Many of these patients require multiple injections of U-100 insulin to deliver a single dose or divided daily doses if they use a 1-mL syringe (which accommodates only 100 units) or a U-100 insulin pen (the maximum dose delivered using U-100 pens is 60-80 units). Injection of a smaller volume of U-500 insulin, for example, creates a smaller subcutaneous (s.c.) depot

for absorption that may be less painful and provides more reliable absorption than a large volume.⁴⁰ Use of single injections of concentrated insulin instead of multiple injections of U-100 insulin to deliver a dose may improve adherence. It also may reduce the frequency of prescription refills, which improves convenience.

A longer duration of action and a flatter, more consistent pharmacokinetic/pharmacodynamic profile is a potential advantage of concentrated basal insulins. The long duration

TABLE 5

Recently Introduced Insulin Pens^{22,27,31,32}

Characteristic	Degludec U-100	Degludec U-200	Glargine U-300	Regular U-500 ^a	Lispro U-200 ^b
Concentration (units/mL)	100	200	300	500	200
Volume (mL)/pen	3	3	1.5	3	3
Units/pen	300	600	450	1500	600
Dial increments (units/click)	1	2	1	5	1
Maximum units/injection	80	160	80	300	60
Pens per box	5	3	3 or 5	2 or 5	2
Storage requirements and expiration after first use ^c	56 days under refrigeration or at room temperature	56 days under refrigeration or at room temperature	42 days at room temperature	28 days at room temperature	28 days at room temperature

^aRegular U-500 insulin also is available as multiple-dose vials.

^bInsulin lispro also is available as U-100 pens, multiple-dose vials, and cartridges.

^cPlease consult the prescribing information for details about storage requirements for pens prior to first use.

of action and lack of fluctuation in plasma concentrations may prevent nocturnal hypoglycemia, which is a concern for many patients because of the perception that they will be less able to detect and manage the problem while asleep than when awake.³⁹

Possible disadvantages of concentrated insulins include the need for dosing conversion and risk for error if switching from or to a less concentrated product. The possibility of error in dispensing the wrong concentration also is a concern. Instructions are available from manufacturers of concentrated insulin products for the approach to converting from conventional U-100 insulins to concentrated products, but fewer data are available to guide conversion from concentrated products to U-100 insulins. Severely insulin-resistant states sometimes are temporary, requiring conversion from a concentrated insulin to U-100 insulin after the situation has resolved.⁴¹

New and Concentrated Insulin Products

Insulin degludec. Insulin degludec is a new “ultra-long-acting” basal insulin with a duration of action of at least 42 hours, half-life of approximately 25 hours, and relatively flat and stable pharmacokinetic/pharmacodynamic profile, which may reduce the risk for nocturnal hypoglycemia.³² The administration schedule is flexible; insulin degludec may be used once daily at any time of day and at a time that varies for an individual.³⁹ Two concentrations are available (100 units/mL, or U-100, and 200 units/mL, or U-200) only in pens (Table 5). Doses are dialed in increments of 1 unit for the U-100 pen and 2 units for the U-200 pen. Steady state plasma concentrations are achieved within 3-4 days of once-daily s.c. administration of U-100 or U-200 insulin degludec.³² When converting from a single daily dose of another basal insulin to insulin degludec U-100 or U-200, the same dose should be used.³²

The FDA declined to approve insulin degludec in 2013 because of concerns about cardiovascular safety. A large phase 3, randomized, double-blind clinical trial known as DEVOTE comparing the cardiovascular safety of insulin degludec with that of insulin glargine in patients with type 2 diabetes who are at high risk of cardiovascular events began in 2013. Interim results of the study were evaluated by FDA and found promising when the agency approved insulin degludec in 2015.⁴²

Concentrated insulin glargine (U-300). The basal insulin glargine is now available in a 300-units/mL (U-300) concentration as well as a 100-units/mL (U-100) concentration.^{30,31}

The U-300 form is available only in pens, although the U-100 concentration is available in pens and vials. Compared with U-100 insulin glargine, the U-300 concentration has a smaller depot surface area and slower rate of absorption after s.c. injection, resulting in a flatter (i.e., more consistent) and more prolonged pharmacokinetic/pharmacodynamic profile.^{39,43,44} Insulin glargine U-300 has a half-life of approximately 23 hours and a duration of action that extends beyond the 24 hours provided by insulin glargine U-100 for up to 36 hours.^{31,43} Insulin glargine U-300 is considered “ultra-long-acting” and may reduce the risk for nocturnal hypoglycemia. Steady state plasma concentrations are reached after 4 days of once-daily s.c. injection of insulin glargine U-300.⁴³ Doses may be administered at any time of day, but the same time of day should be used by an individual.³¹

When converting from a single daily dose of another basal insulin to insulin glargine U-300, the same dose should be used.³¹ In patients previously treated with insulin glargine U-100, a larger daily dose of U-300 probably will be required to maintain glycemic control based on observations in clinical trials. However, if twice daily administration of another basal insulin was used, the total daily dose of insulin glargine U-300 should be decreased by 20% and administered as a single daily dose when converting to U-300 insulin glargine.

Regular human insulin U-500 pen. A U-500 (500 units/mL) concentration of regular human insulin has been available in vials since 1994.²⁷ This concentration is fivefold higher than U-100 regular human insulin, and it is approved by FDA only for patients with large dosing requirements (>200 units/day). The introduction of U-500 regular human insulin pens with 5-unit dial increments provides a new delivery system for these patients. In the past, U-100 or tuberculin syringes were used with U-500 vials, requiring dosage conversion with a risk for error.⁴⁵ In July 2016, FDA approved a new U-500 syringe for use with U-500 regular human insulin vials. The scale on these syringes measures from 25 units to 250 units in 5-unit increments (with the first hash line at 5 units). The availability of U-500 regular human insulin pens and syringes circumvents the need for dosage conversion and the risk for error associated with the use of U-100 and tuberculin syringes.

Regular human insulin U-500 is considered a “mixed basal/bolus” type of insulin because it has a rapid onset of action (15 minutes) similar to U-100 regular insulin and a duration of action (21 hours) similar to NPH insulin.²⁷ In a randomized, double-blind, crossover study comparing single

50-unit and 100-unit doses of regular human insulin U-100 with U-500 in 24 healthy, obese subjects with a body mass index (BMI) of 30-40 kg/m², the overall insulin exposure was similar at equivalent doses.⁴⁶ However, the time to peak serum insulin concentration was increased and the duration of action was prolonged with U-500 compared with U-100. These findings may have implications for the use of regular human insulin U-500 pens, although the study subjects did not have type 2 diabetes or extreme obesity (BMI >40 kg/m²) and the insulin doses were lower than what might be required for severely insulin-resistant patients.

In converting from any U-100 insulin to regular human insulin U-500, empiric changes in the total daily dose have been recommended based on the A1c.⁴⁰ If the A1c is 8% or less, the total daily dose (TDD) of insulin should be decreased by 10% to 20%. Conversely, if the A1c is 10% or higher, a 10% to 20% increase in the TDD may be considered. If the A1c is between 8% and 10%, a unit-for-unit dose conversion may be used. The TDD usually is given as two to four divided doses approximately 30 minutes before meals (the use of three daily mealtime doses is common).^{27, 41} Patients receiving U-500 insulin should be monitored for hypoglycemia. Algorithms to facilitate switching from U-100 to U-500 insulin have been published.^{40, 41}

Concentrated insulin lispro (U-200). The rapid-acting insulin lispro has been available as U-100 pens, vials, and cartridges. The introduction of a 200-units/mL (U-200) concentration addresses the problem of frequent refills for patients requiring large doses. Insulin lispro U-200 is available only in pens. The pharmacokinetics and pharmacodynamics are similar for U-200 and U-100 insulin lispro, with a half-life of 1 hour and a duration of action of approximately 4–6 hours.^{18, 22}

Adverse Effects and Safety

Various strategies may be used to avoid or minimize adverse effects and overcome safety concerns associated with insulin therapy in patients with type 2 diabetes. Hypoglycemia is a common concern and barrier to insulin use for these patients. When hypoglycemia occurs during the daytime, it is primarily caused by excessive bolus insulin therapy.³⁹ Nocturnal or early morning hypoglycemia usually is attributed to excessive basal insulin therapy. The use of insulin degludec or U-300 insulin glargine may avoid or minimize nocturnal hypoglycemia because of their prolonged, consistent pharmacokinetic/pharmacodynamic profiles.^{43, 47}

What new insulin products have been or will be considered for addition to the formulary at your institution? What considerations enter into your formulary decisions about these products? Is there a mechanism to identify patients who stand to benefit from the use of these products?



To avoid hypoglycemia, a conservative approach should be used when starting and adjusting insulin therapy (Figure 3) and converting between different types and concentrations of insulin. Patient education should emphasize that insulin is a high-risk medication requiring full attention to dose preparation and administration.

Weight gain also is a concern with the use of insulin in patients with type 2 diabetes.⁴⁸ One or more diabetes medications that are weight neutral or promote weight loss (e.g., metformin, GLP-1 agonist) may be used in conjunction with insulin to attenuate weight gain.¹¹

Possible institutional strategies to promote insulin safety include developing protocol-driven, evidence-based insulin order sets so that the proper type, concentration, and delivery system for insulin is selected to meet individualized patient needs consistent with treatment guidelines. Policies, procedures, best practices, and information technology solutions should be implemented to promote safety.^{49, 50} For example, menus with the insulin types, concentrations, and delivery devices available on formulary and dosing conversion information could be incorporated into a computerized prescriber order entry system to reduce the risk of prescribing error. Insulin orders should specify a type, concentration, number of units, and volume (e.g., U-500 regular human insulin 50 units in 0.1 mL).⁴⁰

The potential advantages and disadvantages associated with new insulin products should be weighed in making formulary decisions. Although limiting the availability of products may be considered to reduce the risk of dispensing error, excluding concentrated insulins from the formulary altogether should be avoided because of the versatility these products provide in meeting the needs of certain patients with large dosing requirements.

Policies and procedures should require the storage of concentrated insulin products in designated locations (e.g., U-500 insulin vials and U-500 syringes only in the pharmacy) to reduce the risk of wrong concentration and dosing errors.⁴⁰ The use of standardized tall-man lettering throughout the medication-use process (i.e., prescribing, storing, dispensing, and administering) may be helpful in differentiating among insulin products with look-alike packaging or sound-alike names.

The new concentrated insulin products are available only as insulin pens, except for U-500 regular insulin, which also is available in vials. Potential advantages of insulin pens over conventional vials and syringes include improved dose accuracy, convenience, ease of use, and adherence.⁵¹⁻⁵³ The use of insulin pens has been associated with potential safety risks, however, such as the risk for transmission of blood-borne pathogens if insulin pens are used for multiple patients, even if the needle is changed.^{54,55} Other potential problems can occur if the insulin pen is used as a multiple-dose vial, such as underdosing because of the introduction of air into the cartridge or reservoir or overdosing if a U-100 syringe is used to draw up the incorrect volume of a concentrated insulin.⁵⁶ In addition, errors in insulin pen administration technique by patients and healthcare professionals have been reported, with the potential for underdosing and hyperglycemia or overdosing and hypoglycemia. Underdosing has been associated with improper priming of the needle, resulting in failure to remove air bubbles, and failure to wait at least 5 or 6 seconds before withdrawing the needle, resulting in a “wet spot” on the skin due to failure to deliver the entire dose.⁵⁷⁻⁵⁹ Needlestick injuries can occur with insulin pens as well as conventional syringes.⁵⁹

A recently published report of an expert panel using the Delphi consensus development process provides guidance for hospitals and health systems to ensure safe use of insulin pen devices.⁵⁰ The recommendations are relevant for hospitals that routinely use pen devices for insulin administration to inpatients and for hospitals that are considering the addition of the new concentrated insulin products on

What strategies have you found effective for improving the safety of insulin use at your institution? What barriers have deterred you from implementing other strategies in the past, and how might you overcome these barriers?



formulary. For example, among the 35 best practice recommendations are the following:

- Include a barcode on the insulin pen label that is both product- and patient-specific,
- Establish hospitalwide policies and procedures for administration of insulin using insulin pen devices,
- Prohibit the withdrawal of insulin from the pen cartridge using a syringe and needle, and
- Have a systematic and standardized process for educating all newly hired health professional staff regarding insulin pen use, appropriate insulin pen injection technique, and the need for one pen for each patient.

Policies and procedures should address switching between insulin products at transitions of care (i.e., patient admission or discharge) because of the risk of error. Education about safe insulin use should be provided to staff and patients. The resources in the reference list and Appendix may be helpful for developing policies and procedures and planning educational programs.

Conclusion

Insulin plays an important role in treating type 2 diabetes mellitus. New types, concentrations, and delivery systems for insulin may improve glycemic control, convenience, adherence, and long-term outcomes. Adverse effects from insulin and potential risks associated with insulin pens can be avoided or minimized through various strategies to promote insulin and insulin pen safety.

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Appendix. Resources

American Association of Clinical Endocrinologists

www.aace.com

- Consensus statement on comprehensive type 2 diabetes management algorithm
 - Clinical practice guidelines on topics pertinent for patients with type 2 diabetes (e.g., obesity)
-

American Diabetes Association

www.diabetes.org

- Position statement and treatment algorithm for type 2 diabetes mellitus created in collaboration with other professional organizations
 - Standards of medical care in diabetes
-

American Society of Health-System Pharmacists

www.onepenonepatient.org

- One Pen, One Patient initiative, “Strategies for Ensuring the Safe Use of Insulin Pens in the Hospital,” with tool kit, resource center, and continuing education activities
 - *AJHP* supplement, “Best Practices in Ensuring the Safe Use of Insulin Pens in the Hospital”
-

Centers for Disease Control and Prevention Safe Injection Practices Coalition

www.oneandonlycampaign.org

- One & Only campaign
 - Insulin pen posters and brochures for healthcare professionals and patients
-

Institute for Safe Medication Practices

www.ismp.org

- Insulin pen safety webpage
 - Insulin safety during a hospitalization webpage
 - ISMP Medication Safety Alert! newsletters (acute care edition)
-

International Diabetes Federation

www.idf.org

- Diabetes patient education: about diabetes
 - Guidelines for managing type 2 diabetes
 - Guidelines for managing older people with type 2 diabetes
-

Society of Hospital Medicine

www.hospitalmedicine.org

- Glycemic control implementation guide
- Best practices on glycemic control in the inpatient setting, including safe use of insulin pens and transition of care

Continuing Education Instructions

Activity Title: Use of Insulin Therapy in Managing Type 2 Diabetes Mellitus

ACPE Activity Number: 0204-0000-16-481-H01-P

Release Date: November 1, 2016

Expiration Date: March 1, 2018

Activity Type: Knowledge based

CE Credits: 1.5 hours (0.15 CEUs), no partial credit

Activity Fee: Free of charge

ACCREDITATION FOR PHARMACISTS



The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Once you have read the discussion guide, click on the link below to take the online assessment (study aid below, minimum score 70%), complete the evaluation, and claim credit. Continuing pharmacy education (CPE) credit will be reported directly to CPE Monitor. Per ACPE, CPE credit must be claimed no later than 60 days from the date of a live activity or completion of a home-study activity.

Study Aid

This assessment is provided as a study aid only. Follow the instructions above to complete the assessment and evaluation online to obtain CPE credit for this activity.

- 1. Compared with diabetes, the prevalence of prediabetes in the United States is**
 - a. Approximately half as high.
 - b. Comparable.
 - c. Nearly twofold higher.
 - d. Nearly threefold higher.
- 2. The metabolic changes that result in the macrovascular and microvascular complications of type 2 diabetes mellitus typically begin**
 - a. Shortly before the time of diagnosis.
 - b. Shortly after the time of diagnosis.
 - c. Long before the time of diagnosis.
 - d. Long after the time of diagnosis.
- 3. The amount of β -cell function remaining at the time of diagnosis of type 2 diabetes mellitus is approximately**
 - a. 15% to 20%.
 - b. 50% to 60%.
 - c. 80% to 85%.
 - d. 90% to 95%.
- 4. Which of the following is part of the pathogenesis of type 2 diabetes mellitus?**
 - a. Increased glucose uptake by muscle cells.
 - b. Increased lipolysis by fat cells.
 - c. Decreased release of glucagon by pancreatic α cells.
 - d. Decreased hepatic glucose production.

5. **Which of the following changes are associated with the progression of type 2 diabetes?**
 - a. Decreased β -cell mass, increased ratio of α cells to β cells, and hyperglucagonemia.
 - b. Increased β -cell mass, increased ratio of β cells to α cells, and hypoglucagonemia.
 - c. Decreased β - and α -cell mass and no change in ratio of α cells to β cells or glucagon levels.
 - d. Decreased β -cell mass, increased α -cell mass, increased ratio of α cells to β cells, and hyperglucagonemia.
6. **According to current evidence-based guidelines for the treatment of type 2 diabetes mellitus from the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE), the role of basal insulin in treating patients with an A1c of 7.5% to 9.0% is**
 - a. First-line monotherapy only.
 - b. Part of first-line dual therapy only.
 - c. Part of second-line dual therapy or third-line triple therapy.
 - d. Part of first-line dual therapy or second-line triple therapy.
7. **Which of the following is an advantage of insulin over other diabetes medications?**
 - a. Lack of weight gain.
 - b. Use in prediabetes.
 - c. Unlimited reduction in A1c.
 - d. Ability to target all dysfunctional organs.
8. **Which of the following insulin strategies is associated with the highest risk for hypoglycemia and weight gain?**
 - a. Basal insulin + metformin.
 - b. Basal + bolus insulin + metformin.
 - c. Basal insulin + a glucagon-like peptide-1 agonist.
 - d. Basal insulin + a glucagon-like peptide-1 agonist + metformin.
9. **Which of the following is a potential advantage of concentrated basal insulins over U-100 insulins?**
 - a. Smaller injection volume and less weight gain.
 - b. More rapid onset of action and longer duration of action.
 - c. Larger subcutaneous depot for absorption and more consistent pharmacokinetic/pharmacodynamic profile.
 - d. More consistent pharmacokinetic/pharmacodynamic profile and less nocturnal hypoglycemia.
10. **Which of the following new insulin products is associated with a low risk of nocturnal hypoglycemia and is used once daily with a flexible administration schedule (i.e., at any time of day and at a time that varies for the individual)?**
 - a. Degludec U-200.
 - b. Glargine U-300.
 - c. Lispro U-200.
 - d. Regular human U-500.
11. **Which of the following diabetes drugs may be used with insulin to attenuate weight gain?**
 - a. Metformin or a sulfonyleurea.
 - b. Metformin or a glucagon-like peptide-1 agonist.
 - c. Metformin or a thiazolidinedione.
 - d. A thiazolidinedione or a glucagon-like peptide-1 agonist.
12. **Which of the following strategies is recommended to reduce the risk of dosing errors involving concentrated insulins?**
 - a. Store only one pen containing each concentration on the nursing unit, and use it for all patients receiving that concentration.
 - b. Order insulin doses using the type, concentration, number of units, and volume.
 - c. Include only U-100 insulin products on the formulary.
 - d. Dispense concentrated insulin vials only with tuberculin syringes.
13. **Which of the following is a potential advantage of insulin pens over conventional vials and syringes?**
 - a. Versatility for safely giving injections to multiple patients using one pen.
 - b. Versatility for use as a multiple-dose vial if needed.
 - c. Improved dose accuracy.
 - d. Lack of risk for transmission of blood-borne pathogens.