



AN ONGOING CE PROGRAM  
of the University of Connecticut  
School of Pharmacy

### EDUCATIONAL OBJECTIVES

After participating in this activity pharmacists will be able to:

- Recognize common medication safety issues in diabetes
- Discuss traditional guidelines and emerging treatments for diabetes
- Outline ways to decrease the financial burden of diabetes medications and supplies
- Define proper injection technique for insulin and non-insulin injectables
- Describe "red flags" prompting a call to the physician or consultation with the patient

After participating in this activity, pharmacy technicians will be able to:

- Recognize new treatments and gaps in care in diabetes patients
- Indicate the most common drug interactions in diabetic patients to alert the pharmacist
- Outline ways to decrease the financial burden of diabetes
- Recognize medication nonadherence/misuse through early and delayed refills
- Describe "red flags" prompting a patient referral to the pharmacist or call to the physician



The University of Connecticut School of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Pharmacists and pharmacy technicians are eligible to participate in this knowledge-based activity and will receive up to 0.2 CEU (2 contact hours) for completing the activity, passing the quiz with a grade of 70% or better, and completing an online evaluation. Statements of credit are available via the CPE Monitor online system and your participation will be recorded with CPE Monitor within 72 hours of submission

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**18YC09-TXJ43 for pharmacists or**

**18YC09-KXP88 for pharmacy technicians**

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## You Asked for It! CE



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### Diabetes Dialogue for Patient Safety: Talking with Patients and Prescribers

**ABSTRACT:** Diabetes is a progressive and life-changing disease that is prevalent among Americans. Prescribers are overwhelmed by the ever-changing guidelines and treatment landscape, and pharmacy teams can help. Since 2010, the U.S. Food and Drug Administration has approved 20 new therapies for type 2 diabetes, including SGLT-2 inhibitors, new insulin and non-insulin injectables, and various combination formulations of existing medications. Proper injection of insulin and non-insulin injectables is important for both glycemic control and patient safety. Drug interactions and adverse drug events can put patients at risk of hypoglycemia and other complications. Pharmacy teams can identify patients' knowledge gaps and drug-related issues, and contact prescribers or counsel patients promptly. Pharmacy teams also need to know injectable medications' storage requirements and educate patients. Diabetes is a progressive condition, requiring frequent dose increases and medication therapy changes. Pharmacists and technicians should be aware of red flags prompting patient counseling or prescriber contact. Pharmacy teams also can help patients who have diabetes reduce their out of pocket expenses. Community pharmacists and technicians are well situated to facilitate active dialogue with diabetes patients and their providers to optimize therapy and keep patients safe.

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**FACULTY DISCLOSURE:** Dr. Hutchinson has no actual or potential conflicts of interest associated with this article.

**DISCLOSURE OF DISCUSSIONS of OFF-LABEL and INVESTIGATIONAL DRUG USE:** This activity may contain discussion of off label/unapproved use of drugs. The content in views presented in this educational program are those of the faculty and do not necessarily represent those of the University of Connecticut School of Pharmacy. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

### INTRODUCTION

An estimated 30.3 million people in the United States (U.S.) have diabetes, which represents about 9.4% of the overall population and 12.2% of all US adults.<sup>1</sup> Type 1 diabetes, characterized by a lack of insulin production, is less common, affecting 5% of diabetic patients. In type 2 diabetes, the more common form, the body fails to use insulin properly.<sup>2</sup> Both types stem from genetic and environmental causes. Type 1 risk factors are not well-established but may

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include cold climate, early childhood diet, and viral infection. Type 2 diabetes has strong genetic tendencies, but lifestyle factors like poor diet and lack of exercise also play important roles.<sup>3</sup> Risk factors for diabetes complications include smoking, overweight or obesity, physical inactivity, hypertension, hyperlipidemia, and sustained hyperglycemia.<sup>1</sup>

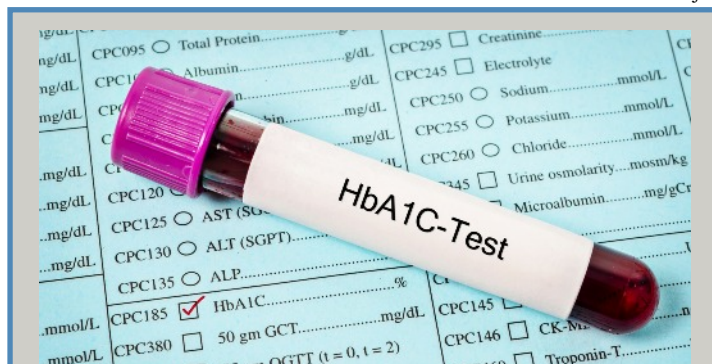
Improved control in the diabetes population is imperative. In 2014, emergency departments reported a total of 14.2 million visits that listed diabetes as a diagnosis among adults aged 18 years or older. Diabetes was also the seventh leading cause of death in the US in 2015.<sup>1</sup> Emergency department visits add to the steep cost of diabetes treatment. Statisticians estimate medical expenses attributed to diabetes care for diagnosed patients at about \$7,900 per year, and total direct and indirect costs in the U.S. at \$245 billion per year.<sup>1</sup> On average, people with diabetes spend 2.3 times more on healthcare than those without.<sup>4</sup>

Primary care providers (PCP) deliver the majority of diabetes care—more than 90%—in ambulatory settings.<sup>5</sup> Despite a plethora of treatment options, diabetes continues to be challenging to treat. Patients under a PCP's care are less likely to receive optimal care and meet glycemic goals than those who see diabetes specialists. PCPs have limited time to counsel patients adequately, and pharmacists can fill this gap.<sup>5</sup> Pharmacy technicians can greatly increase the number of diabetic patients referred to the pharmacist for necessary counseling.

## A CHANGING TREATMENT LANDSCAPE

The diabetes treatment landscape changes daily, and guideline adherence is imperative. When clinicians are aware of and follow the American Diabetes Association (ADA) Standards of Medical Care in Diabetes or American Association of Clinical Endocrinologists (AACE) algorithm, patient outcomes improve.<sup>6,7</sup> The most recent ADA guidelines outline antihyperglycemic therapy for adults with type 2 diabetes in a progressive fashion based on HbA<sub>1c</sub> (see Sidebar) and atherosclerotic cardiovascular disease (ASCVD) risk.<sup>6</sup>

While guidelines encourage lifestyle management with diet and exercise for all patients who have diabetes, medication therapy differs based on the patient's HbA<sub>1c</sub>. Clinicians should initiate metformin monotherapy for patients presenting with HbA<sub>1c</sub> lower than 9% if no contraindications exist. If the patient reaches HbA<sub>1c</sub> target after 3 months of monotherapy, patients should maintain therapy and clinicians should continue to monitor HbA<sub>1c</sub> every three to six months. If HbA<sub>1c</sub> continues to exceed 9%, clinicians should work with patients to discuss stepping up therapy. At this point, the guidelines recommend dual therapy with metformin plus an additional drug. Previously, they recommended selecting the second drug solely based on drug-specific effects and patient factors. However, the recent addition of an ASCVD component to the guidelines creates an additional consideration.<sup>6</sup>



### Sidebar: Understanding HbA<sub>1c</sub><sup>8</sup>

**What is HbA<sub>1c</sub>?** Also known as the glycohemoglobin test, HbA<sub>1c</sub> measures the attachment of glucose to hemoglobin, the protein in red blood cells that carries oxygen. Red blood cells are constantly forming and dying with a typical lifespan of three months. Therefore a HbA<sub>1c</sub> result, reported as a percentage, provides information about a person's average blood glucose levels over the past three months.

**What do the results indicate?** The higher the percentage, the higher a person's blood glucose levels have been over the past three months.

- A normal HbA<sub>1c</sub> is below 5.7%
- Results between 5.7% to 6.4% indicate prediabetes
- HbA<sub>1c</sub> at or above 6.5% indicates diabetes

**Is the test always accurate?** Patients with certain hemoglobin variants or deficiencies may experience unreliable HbA<sub>1c</sub> results. Anemia or heavy bleeding can cause a falsely low HbA<sub>1c</sub> reading while low iron or iron deficiency anemia can falsely elevate results. Kidney failure and liver disease can also interfere with the test.

For patients with ASCVD, initiation on a drug proven to reduce cardiovascular events and mortality is best. **Table 1** reviews these drugs. Clinicians should start patients who do not have ASCVD on an initial agent after consideration of drug-specific effects and patient factors. After three to six months, clinicians need to reassess HbA<sub>1c</sub>. Regardless of their ASCVD status, if patients are at goal HbA<sub>1c</sub>, they should remain on that therapy with HbA<sub>1c</sub> monitoring every three to six months. Otherwise, they should initiate a third agent based on drug-specific effects and patient factors.<sup>6</sup>

Clinicians need to consider the most aggressive treatment option, combination insulin therapy, for patients whose HbA<sub>1c</sub> is 10% or higher; blood glucose is 300 mg/dL or higher; or patients who are markedly symptomatic (increased urinary frequency,

### Pause and Ponder:

- Under what circumstances might a patient's HbA<sub>1c</sub> be falsely elevated or low?
- What should you watch for?

**Table 1. Antihyperglycemic Therapy Proven to Reduce Cardiovascular Events and Mortality<sup>6</sup>**

DRUG/CLASS	ASCVD EFFECTS
Metformin	Potential benefit
SGLT-2 inhibitors	Benefit: canagliflozin, empagliflozin
GLP-1 RAs	Neutral: lixisenatide, exenatide extended-release Benefit: liraglutide
DPP-4 inhibitors	Neutral
Thiazolidinediones	Potential benefit: pioglitazone
Sulfonylureas (2 <sup>nd</sup> generation)	Neutral
Insulin	Neutral

SGLT-2=sodium-glucose co-transporter 2, GLP-1 RAs=glucagon-like peptide receptor agonists, DPP-4=dipeptidyl peptidase

thirst, numbness in extremities, fatigue, blurred vision). Clinicians also need to initiate combination insulin therapy for patients on triple therapy who are not at HbA<sub>1c</sub> goal after three to six months.<sup>6</sup>

**Table 2** provides a comprehensive list of available type 2 diabetes treatments, demonstrating the wide array of pharmaceutical options. Since 2010, the U.S. Food and Drug Administration (FDA) has approved 20 new therapies for type 2 diabetes, highlighted in red.<sup>9</sup> This includes the addition of sodium-glucose co-transporter (SGLT) 2 inhibitors, new insulin and non-insulin injectables, and various combination formulations of existing medications. With guidelines that encourage polymedicine (the rational use of combination therapy) for the treatment of diabetes, it is important to know how existing and emerging treatments work synergistically to lower blood glucose.

A survey by the ADA shows that prescribers demonstrate wide variation in the choice and sequence of medications for diabetes management due to the large selection of drugs available.<sup>10</sup> The growing presence of electronic prescribing is also a safety concern in diabetes. When prescribers change a patient’s therapy, electronic prescribing systems have no default way to discontinue previous antihyperglycemics. This can confuse the pharmacy team as to which medications a patient needs.<sup>11</sup> Electronic prescribing is especially troublesome for insulin prescribing, as clinicians may use unclear default directions (e.g. twice daily) for meal-time insulins that should be administered shortly before food. Cases of severe hypoglycemia have been reported when patients have administered insulin long after consuming meals.<sup>11</sup> Pharmacists and technicians who enter data should be vigilant to make note of additional documentation by the prescriber on an electronic prescription and follow-up with prescribers whenever questions arise.

The growing use of injectable drugs—insulin-based products, high-dose insulins, and injectable non-insulins—is a concern. Delivery devices associated with these products are all different, and require specific training. Patients switching between products may be unaware of subtle differences, leading to

improper injection technique and loss of glycemic control.

Insulin pen injector technology is similar across the board<sup>12</sup>:

- **Check the insulin:** Remove the pen cap and check for cloudiness or particles
- **Attach needle:** Wipe the rubber seal on the pen with alcohol, remove protective seal from a new needle, and screw or push the needle straight on
- **Perform a safety test:** Select a dose of 2 units, and then:
  - Remove the outer needle cap (keep it to remove the needle later)
  - Hold with the needle pointing up and tap to remove air bubbles
  - Press the injection button and watch for insulin to come out of needle tip
  - If no insulin appears after three tests, change the needle
- **Select the dose:** Check that dose window shows “0” following safety test, then select required dose
- **Inject your dose:** Clean the injection site with alcohol. Insert the needle at a 90-degree angle, press injection button all the way in until dose window reads “0,” and slowly count to 10 before removing needle from skin
- **Remove the needle:** Place the outer needle cap back on the needle and use it to unscrew the needle from the pen; dispose of the needle in a designated biohazard container and replace the pen cap until the next injection

Approximately 31% of patients who have diabetes use insulin, creating many opportunities for pharmacy-based education.<sup>13</sup> The most common errors associated with insulin injection are site selection and site rotation, using expired insulin, and incorrect dose and timing. In one survey, about 20% of participants administered the wrong dose, which is particularly concerning due to the possibility of severe hypoglycemia with insulin overdose. Many patients also fail to perform the safety test with each new needle.<sup>13</sup> Pharmacist and technicians should identify patients starting on new insulin products or changing insulin doses and provide prompt counseling.

**Table 2. Available Type 2 Diabetes Treatments<sup>6,9</sup>**

Drug Class	Mechanism	Available Therapies
Biguanides	↓ hepatic glucose production	Metformin
Sulfonylureas (second generation)	↑ insulin secretion	Glyburide Glipizide Glimepiride
Meglitinides	↑ insulin secretion	Repaglinide Nateglinide
Thiazolidinediones	↑ insulin sensitivity	Pioglitazone Rosiglitazone
α-glucosidase inhibitors	Slows intestinal carbohydrate digestion/absorption	Acarbose Miglitol
DPP-4 inhibitors	↑ insulin secretion ↓ glucagon secretion	Sitagliptin Saxagliptin Linagliptin Alogliptin
SGLT-2 inhibitors	Blocks glucose reabsorption by the kidney, increasing glucose excretion through urine	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin
GLP-1 RAs	↑ insulin secretion ↓ glucagon secretion Slowed gastric emptying ↑ satiety	Albiglutide Dulaglutide Exenatide Exenatide extended-release Liraglutide Lixisenatide Semaglutide
Amylin mimetics	↓ glucagon secretion Slowed gastric emptying ↑ satiety	Pramlintide
Insulin (rapid acting)	Activates insulin receptors	Inhaled insulin Insulin aspart Insulin glulisine Insulin lispro
Insulin (short- and intermediate-acting)	Activates insulin receptors	Human NPH Human regular
Insulin (long-acting/basal)	Activates insulin receptors	Insulin degludec Insulin detemir Insulin glargine
Pre-mixed insulin	Activates insulin receptors	50/50 lispro mix 70/30 aspart mix 75/25 lispro mix NPH/regular 70/30
Additional combination medications approved since 2010	Variable	Dapagliflozin + metformin Dapagliflozin + saxagliptin Empagliflozin + metformin Insulin degludec + insulin aspart Insulin degludec + liraglutide Insulin glargine + lixisenatide Linagliptin + metformin Sitagliptin + simvastatin

SGLT-2=sodium-glucose co-transporter 2, GLP-1 RAs=glucagon-like peptide receptor agonists, DPP-4=dipeptidyl peptidase  
*Products approved since 2010 highlighted in red.*



Some insulins employ refillable pen and cartridge systems. These systems use digital displays and must be turned on. Patients also need to make sure the batteries are charged. To load the cartridge into the pen, the patient must push the dosage knob all the way in. Then the user should insert the cartridge straight into the pen body until it clicks. At this point, the pen is ready to use. To remove an empty cartridge, the patient should push the cartridge release button and remove the entire cartridge. With this added technology comes additional need for patient counseling; pharmacists should inform patients not to press the “start” or “cartridge release” buttons during administration as it could affect the amount of insulin delivered or cause injury to the patient.<sup>14</sup>

Non-insulin injectables offer the simplicity of fixed-dose injections with no need to dial to a required unit dose. However, injection technology for these products is far from uniform and this can confuse patients and lead to improper injection technique. Pramlintide, exenatide, and lixisenatide are incredibly user-friendly; the patient simply pulls or twists a knob to ready the product, then injects.<sup>15-17</sup> Similarly, dulaglutide is relatively easy to use. Patients use the single-dose pen to inject once weekly as follows<sup>18</sup>:

- With the pen locked, they pull the base cap straight off and throw it away
- They place clear base against the skin at injection site and unlock by turning the lock ring
- Next, they press and hold the green injection button until they hear a loud click
- They must continue holding firmly against the skin until they hear a second click (which is the needle retracting) in about five to ten seconds
- Finally, they remove the injector from skin and discard it in a designated container

Pharmacists should be aware of products that may require extensive counseling upon prescribing. For example, exenatide extended-release is available in two formulations, both requiring a lengthy mixing process. Without proper mixing before injection, these medications will not function properly. Injection technique for these products are as follows.<sup>19</sup>



#### Exenatide extended-release vial:

- Pick up the needle and twist off its blue cap
- Pick up the vial and tap several times against hard surface to loosen powder; use thumb to remove green cap
- Pick up the vial connector package and peel off its paper cover; while holding the package, in your other hand press the top of the vial firmly onto the orange connector and lift it out of package
- Pick up the syringe and firmly grasp the two gray squares on the white cap; break off the cap without pushing in the plunger
- Twist the orange connector onto the syringe until snug
- Push down on the plunger until it stops, then hold it down and shake hard until the liquid and powder are mixed well (should look cloudy)
- Hold the vial upside down while continuing to hold the plunger down and gently tap the vial with your other hand to help the medicine drip down
- Pull the plunger down beyond the black dashed line to draw medicine into the syringe; while holding the plunger still, twist the orange connector off to detach the vial
- Twist on the needle and with the cap still on, slowly push the plunger so the top of the plunger aligns with the black dashed line
- Pull the needle cover straight off and inject the entire dose subcutaneously

#### Exenatide extended-release pen:

- Remove one pen from the refrigerator and let stand at room temperature for **15 minutes**
- Check the liquid for particles or color
- Pull off the paper tap and screw the needle onto the pen (leave on cover)
- While holding the pen straight up, slowly turn the knob until you hear a click and the green label disappears
- Firmly tap the pen against the palm of your hand; rotate pen every ten taps; it may take 80 taps or more to completely mix until uniformly cloudy
- Turn knob to release injection button
- Remove needle cover and inject into a designated area; hold down the button and slowly count to ten

**Albiglutide single-dose pens** also employ a unique injection mechanism<sup>20</sup>:

- Check that [1] appears in the number window
- Twist the clear cartridge clockwise until you hear the pen “click” into place and [2] appears in the window
- Slowly, gently rock the pen side to side (like a windshield wiper) five times to mix the medicine (do not shake)
- Place the pen into a clean, empty cup to keep cartridge pointing up for **15 minutes**
- Attach the needle and twist the clear cartridge clockwise until the pen “clicks” and you see [3] in the number window; the injection button will pop out from the bottom of the pen
- Remove needle cap and inject into skin; hold for five seconds to deliver the full dose

Many of these products, insulin and non-insulin, also require priming before the patient administers the first dose to ensure that the full, correct dose is delivered upon first injection. Pharmacists should consult the package insert to counsel patients; patients mustn't overlook these initial-use requirements. Storage requirements also differ among diabetes injectables and pharmacists and pharmacy technicians should review them with patients whenever possible.

## DRUG SAFETY

Diabetes medications are infrequently associated with serious adverse events (AE) or major drug interactions. However, the most significant potential safety concern from interactions and AEs is the potential for loss of glycemic control. Hypoglycemia is a potentially serious concern in patients who have diabetes and use multiple antidiabetic agents, most commonly insulin or insulin secretagogues. In 2014, Americans made about 245,000 visits to the emergency department for hypoglycemia and about 207,000 for hyperglycemic crisis.<sup>1</sup> Pharmacists should be aware of drugs that

- increase hypoglycemia risk
- are prescribed for comorbid conditions that may lead to hyperglycemia or worsen renal function, and
- are likely to decrease the patient's ability to recognize hypoglycemia.

## Common Drug Interactions in Diabetes

Polymedicine is encouraged in diabetes treatment guidelines, but this comes with the risk of additive hypoglycemia. When new medications are added to a patient's regimen, pharmacists should ask themselves a few questions to ensure patient safety:

- Does this regimen increase the patient's risk of hypoglycemia?
- Does the patient have a clear understanding of how to use these antidiabetic agents together?
- Does the patient understand how to recognize and treat symptoms of low blood sugar?
- Does the patient have an emergency supply of glucagon on hand in the event of severe hypoglycemia, and does he or she know how to use it?

Symptoms of low blood sugar include shakiness, dizziness, lightheadedness, sweating, chills, mood changes, and skin pallor. In the event patients experience these symptoms, they should take the following actions<sup>21</sup>:

- Test blood sugar; treat if 70mg/dL or less
- Consume 15 grams of carbohydrate orally:
  - Glucose tablets/gel
  - 4 oz. juice/regular soda
  - 1 tbsp sugar or honey
  - Hard candy, jelly beans, or gumdrops
- Re-check blood sugar in 15 minutes and re-treat if needed

We've included a patient handout to the right that summarizes this process.

### HYPOGLYCEMIA Rule of 15





If you have these symptoms...

- Shakiness
- Dizziness
- Lightheadedness
- Sweating, chills
- Mood changes
- Pale skin

Check Your Blood Sugar!

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If your blood sugar is 70mg/dL or less, eat **15 grams** of carbohydrate. The following items have 15 grams of sugar:

	3 or 4 glucose tablets or 1 tube of gel
	3 to 5 pieces of hard candy (not chocolate)
	1 tablespoon of sugar or honey
	½ cup of orange juice or regular soda

- **Wait 15 minutes**
- Check your blood glucose again.

If your blood sugar is 70mg/dL or less, eat 15 more grams of carbohydrate.

Severe hypoglycemia occurs when blood glucose is lower than 54 mg/dL and causes seizures or unconsciousness. A trained individual should administer an intramuscular injection of glucagon immediately. Glucagon comes in a pre-made kit for emergency use, and pharmacy staff can increase patient safety by ensuring the patient and at least one other person close to the patient is educated on how to use it<sup>21</sup>:

- Have someone call 911
- Position the patient on his/her side
- Inject all fluid from the syringe into the vial of powder and roll vial to mix
- Draw prescribed amount of solution back into the syringe
- Inject into buttocks, thigh, or upper arm at a 90 degree angle

**Table 3 – Natural Health Products Commonly Used by Diabetic Patients<sup>23</sup>**

Health Product	Clinical Pearls
Alpha-lipoic Acid	Can increase pancreatic insulin secretion; no major drug interactions
Bitter melon	May lower blood glucose in type 1 diabetes; no identified drug interactions
Chromium	May decrease HbA <sub>1c</sub> by 0.6%; caution in renal disease and shown to interact with levothyroxine
Cinnamon (cassia)	Reported to reduce blood glucose levels; contains coumarin and may contribute to hepatotoxicity at high doses
Fenugreek	Reduces fasting blood sugars; avoid in peanut allergy; may cause some bleeding or bruising
Gymnema	Hypoglycemic and lipid-lowering if taken for three months or more; no major adverse effects
Magnesium	Generally used to correct deficiency; has a number of drug-drug interactions
Milk thistle (silymarin)	Can reduce fasting blood sugar and decrease the need for insulin by about 20%; potential CYP 450 interactions
Reishi mushrooms	Shown to reduce HbA <sub>1c</sub> but high doses reduce platelet aggregation; can cause dry mouth, pruritus, and gastrointestinal upset
White mulberry	Can prevent intestinal digestion and absorption of simple carbohydrates; conflicting evidence of appropriate use

Loss of glycemic control can also come from administration of medications to treat comorbid conditions. Fluoroquinolone antibiotics are common offenders for this type of interaction. Pharmacists should seek alternatives for diabetic patients who are prescribed this class of medications, or encourage increased blood sugar monitoring during treatment.<sup>22</sup> Pharmacists should also be cognizant of complementary and alternative medicine used by diabetic patients. Fenugreek is a medicinal plant often used by diabetic patients for its ability to reduce fasting and postprandial glucose. While this drug may provide glycemic benefit, it can theoretically interact with hypoglycemic drugs with additive effects.<sup>23</sup> Pharmacists should encourage patients who take fenugreek to monitor their glucose closely. Pharmacy technicians (who are most likely to see supplements and alternative medicines when the patient is at the register) can be on the lookout for this product and suggest the patient talk to the pharmacists for a few minutes. **Table 3** lists additional natural health products pharmacists and technicians should monitor.

Hypoglycemic unawareness is another safety concern in patients with comorbidities. A drop in blood sugar usually triggers secretion of epinephrine and generates the characteristic symptoms of hypoglycemia (palpitations, sweating, anxiety). In patients who have hypoglycemic unawareness, the patient doesn't experience the warning symptoms, and is unaware of the blood sugar drop. Beta-blockers are most often implicated medications in this phenomenon. However, they are a reasonable choice for hypertension management and for cardioprotective effects in patients with diabetes.<sup>24</sup> Pharmacists should not discourage use of cardioselective beta blockers in diabetic patients; rather they should encourage patients to monitor blood sugar levels more frequently. Beta-agonists, methylxanthines (caffeine, theophylline), and selective serotonin reuptake inhibitors may also cause hypoglycemic unawareness, and pharmacists should encourage patients to

check blood sugar levels more often if these medications are otherwise beneficial.<sup>24</sup>

Additionally, some antihyperglycemics affect the metabolism of medications used for comorbid conditions. Second-generation sulfonylureas glyburide and glipizide interact with warfarin and amiodarone respectively, increasing a patient's risk of bleeding or arrhythmias.<sup>25,26</sup> Alpha-glucosidase inhibitors and exenatide may decrease digoxin's effectiveness, while conversely, canagliflozin can increase digoxin levels in the blood.<sup>27-29</sup> Albiglutide can increase simvastatin blood levels, putting the patient at risk of rhabdomyolysis.<sup>30</sup> Lixisenatide can decrease the absorption of oral contraceptives (OCP), and pharmacists should counsel patients to take OCP one hour before or 11 hours after lixisenatide injection.<sup>31</sup>

### Pause and Ponder:

When patients pick up prescriptions and want to pay for complementary and alternative products at the pharmacy, which products may be problematic?

*Approximately 31% of patients who have diabetes use insulin, creating many opportunities for pharmacy-based education. The most common errors associated with insulin injection are site selection and site rotation, using expired insulin, and incorrect dose and timing.*

## Side Effect Management

Pharmacists and technicians should be aware of common side effects that may impede a patient's willingness to adhere to a medication regimen. The most common adverse reactions that patients experience on antihyperglycemics are gastrointestinal (GI) in nature (nausea, vomiting, diarrhea). Metformin, sulfonylureas, GLP-1 RAs, and  $\alpha$ -glucosidase inhibitors are the most common offenders.<sup>6</sup> If the AE is bothersome enough, it will affect medication adherence, so pharmacists should be cognizant of patients complaining of GI upset. Pharmacists can counsel patients experiencing adverse GI effects on metformin to take the medication on a full stomach. Pharmacists should also contact prescribers to transition patients to the extended-release formulation whenever possible, as this formulation reduces GI upset.<sup>32</sup> Alpha-glucosidase inhibitors are known to cause frequent abdominal pain, diarrhea, and flatulence due to their mechanism of action in the intestines. Pharmacists should identify patients with pre-existing GI conditions during drug regimen review and advise prescribers to avoid these medications.<sup>27</sup> Pharmacy technicians at point-of-sale are also poised to watch for over-the-counter purchases that could indicate patients are experiencing drug-induced GI upset (e.g. antacids, laxatives, anti-motility agents).

Some medications (sulfonylureas and thiazolidinediones) have a propensity to cause weight gain.<sup>6</sup> Obesity is a risk factor for diabetes and cardiovascular conditions, so suggesting alternatives for individuals already struggling with weight would be prudent. GLP-1 RAs, on the other hand, have been shown to decrease appetite and stimulate weight loss in some patients and liraglutide has been FDA-approved to treat obesity.<sup>33</sup>

More serious AEs are possible with some antihyperglycemics. Thiazolidinediones can increase the risk of edema, congestive heart failure, and bone fracture.<sup>34</sup> DPP-4 and SGLT-2 inhibitors have also been linked to an increased incidence of urinary tract infections (UTI) and subsequent infections of the genitals, more commonly in females.<sup>29,35</sup> SGLT-2 inhibitors are also implicated in a specific and dangerous type of diabetic ketoacidosis (DKA; plasma bicarbonate exceeding 10 mEq/L and blood glucose levels higher than 300 mg/dL)—euglycemic DKA, a metabolic state in which plasma bicarbonate exceeds 10 mEq/L, but with blood glucose levels lower than 300 mg/dL. In May 2015, the FDA issued a warning about this risk. Pharmacists should educate patients about the signs and symptoms of DKA and UTI and encourage them to seek treatment:<sup>36-39</sup>

- **Ketoacidosis:** nausea, vomiting, abdominal pain, tiredness, trouble breathing
- **UTI:** burning feeling upon urination, need to urinate often or urgently, pain in the lower stomach or pelvis, fever, blood in urine

In-depth review of diabetic patients' drug regimens may prompt therapy changes for co-morbid conditions complicating diabetes treatment.

*Recent prescription drug formulary trends are troublesome for the diabetes community. Formularies can change at any time throughout the plan cycle, and plan administrators may choose not to cover a medication or to bump it to higher coverage tiers.*

## Storage and Mixing of Injectables

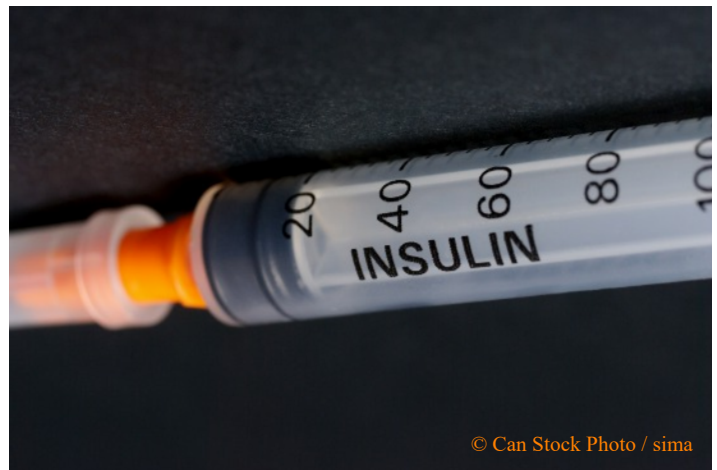
Proper storage of insulin and non-insulin injectables is imperative to their successful use, and can be a safety issue. Spoiled insulin is ineffective, and patients who use it will lose glycemic control. While all require refrigeration in the pharmacy until dispensing and before first use, patients may be unaware of special requirements following first use of these drugs. **Table 4** summarizes antihyperglycemic injectable storage requirements after opening/first use.

Some insulins can or cannot safely be mixed in the same syringe for injection. Rapid-acting insulins (lispro, aspart, glulisine) can be mixed with insulin NPH only. If these insulins are to be mixed with NPH, the patient should draw up the NPH into the syringe after the other insulin. Also, the patient must inject mixed insulin immediately after mixing to ensure effectiveness.<sup>40-42</sup> If prescribers encourage a patient to mix rapid-acting and NPH insulin before injection, pharmacists should counsel them on how to do so safely and correctly.

Patients and healthcare providers must never mix other basal insulins (glargine, detemir, degludec) with another insulin or diluent.<sup>12,48,49</sup> Additionally, they must not mix pramlintide with insulin or any other diluent before injection.<sup>55</sup> Pharmacists should recognize patients who are mixing insulins at drug regimen review and make a note on prescription bags for technicians to refer to the pharmacist for counseling at point-of sale.

### Pause and Ponder:

What symptoms suggest ketoacidosis?



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**Table 4. Storage of Insulin and Non-Insulin Injectables for Diabetes after First Use/Opening**<sup>12,30,31,33,41-57</sup>

Insulins		GLP-1 RAs		Others	
<i>aspart</i>	Room temperature for 28 days	<i>albiglutide</i>	Refrigerated until use, or room temperature for 4 weeks	<i>insulin degludec + liraglutide</i>	Refrigerated or room temperature for 21 days
<i>degludec</i>	Room temperature for 56 days	<i>dulaglutide</i>	Refrigerated until use, or room temperature for 14 days	<i>insulin glargine + lixisenatide</i>	Room temperature for 14 days
<i>degludec + aspart</i>	Room temperature for 28 days	<i>exenatide</i>	Refrigerate, discard 30 days after opening	<i>pramlintide</i>	Refrigerated or room temperature for 30 days
<i>detemir</i>	Room temperature for 42 days	<i>exenatide extended-release</i>	Refrigerated until use		
<i>glargine</i>	Room temperature for 28 days	<i>liraglutide</i>	Refrigerate, discard 30 days after opening		
<i>glulisine</i>	Room temperature for 28 days	<i>lixisenatide</i>	Room temperature for 14 days		
<i>Lispro</i>	Room temperature for 28 days	<i>semaglutide</i>	Refrigerated or room temperature for 56 days		
<i>NPH</i>	Room temperature for 31 days				
<i>regular</i>	Room temperature for 31 days				
<i>regular (inhaled)</i>	Room temperature: Sealed blister pack – 10 days Opened blister pack – 3 days				

## PHARMACY TEAM'S ROLE IN IMPROVING DIALOGUE

Pharmacists are uniquely positioned to open dialogue with patients and prescribers about diabetes management. Common “red flags” in everyday patient care should prompt education for patients or contact with prescribers for therapy changes.

### Switching between Insulin Concentrations

Progressive loss of  $\beta$ -cell function in diabetes leads to the need for increased insulin doses in patients with type 2 diabetes. Concentrated insulin formulations present a more comfortable means of delivering large doses that would otherwise require multiple doses of U-100 insulin. Basal insulins are now available in higher concentrations (degludec U-200, glargine U-300, and insulin regular U-500).<sup>44,47,49</sup> These products are two, three, and five times the concentration of U-100 insulin respectively. Rapid-acting insulin lispro is also available in a U-200 formulation.<sup>40</sup> Pharmacists should screen for patients injecting high volumes of U-100 insulin daily, and work with them and their prescribers to discuss the potential benefit of using a more concentrated insulin.

These formulations present some safety concerns. While seemingly convenient to reduce injection volume, dosing errors as-

sociated with concentrated insulin can cause significant hypoglycemia. The pharmacy team must educate patients on correct use of these products.<sup>58</sup> Pharmacists and technicians should recognize patients transitioning from U-100 to higher concentrations of insulin and provide prompt education or referral. Additionally, all concentrated insulins are available in pen formulations, reducing the need for unit to mL conversions or adjustments. Pharmacists and technicians should encourage prescribers to initiate patients on insulin pens whenever possible for safety and ease of use.

### Changes in Insurance Formularies

Recent prescription drug formulary trends are troublesome for the diabetes community. Insurance formularies can change at any time throughout the plan cycle, and plan administrators may choose not to cover a medication or to bump it to a higher coverage tier. Mid-year plan changes are particularly troubling, as patients do not have the option to change to a plan that may cover their current therapies. Prior authorizations can be time-consuming, leaving the patient to pay out-of-pocket for expensive medications until the insurance will accept the claim. Often times, this process still leaves the patient with a higher copay than normal due to off-formulary drug use.<sup>59</sup>

With the growing number of diabetes treatment options, clinicians might consider switching a patient's drug regimen to one that is covered at a lower cost to the patient. While every patient and situation are different, pharmacists should encourage prescribers to adhere to the patient's insurance formulary whenever possible to reduce out-of-pocket costs. Alternative options may be covered by the patient's plan, and asking for a medication change from the prescriber is reasonable. For example, review of one insurance formulary available online shows that of the four available insulin glargine formulations, one is in tier 1 with the lowest copay while the rest are in tier 4 with the highest copays. On this same plan, a 2-pack of liraglutide is on a lower tier than a 3-pack. Also, some SGLT-2 and DPP-4 inhibitors are tier 4 while others are tier 2.<sup>60</sup> Being aware of subtle differences that can cause astronomical price changes can help pharmacists and pharmacy technicians ensure patients use the most cost-effective option.

The diabetes drug market is competitive and ever-changing, and pharmacists should be aware of impending changes to drug availability. Albiglutide's manufacturers have announced that they will discontinue these products by July 2018. In this announcement, they attribute this decision to a steady decline in sales given the availability of multiple treatment options for type 2 diabetes.<sup>61</sup> Pharmacists and technicians should forewarn patients who are on albiglutide and discuss transition to new medication regimens with their prescribers so as not to delay treatment come July 2018.

### Pause and Ponder:

What insurances do you see most often, are you familiar with their coverage and rules for products related to diabetes?

### Patient Self-Management

Self-monitoring of blood glucose (SMBG) is an important and sometimes overlooked aspect of diabetes treatment. The ADA recommends that patients on intensive insulin regimens perform SMBG prior to meals and snacks, at bedtime, occasionally postprandially, prior to exercise, when they suspect low blood glucose, after treating hypoglycemia, and prior to critical tasks like driving. For those on basal insulin or oral agents alone, they suggest that assessing fasting glucose may be sufficient.<sup>6</sup> In an ideal world, this testing schedule is associated with lower HbA<sub>1c</sub> and fewer acute complications. However, for the average patient, it is unrealistic and results in high spending on testing supplies. Pharmacists who find that their patients are unmotivated to test or simply overwhelmed with testing frequency should reach out to prescribers to discuss a more manageable, realistic testing frequency.

## ADDITIONAL RESOURCES

Centers for Disease Control and Prevention  
Diabetes Home

<https://www.cdc.gov/diabetes/home/index.html>

DiabetesCare  
Diabetes Care Resources for Patients and Providers

<http://www.diabetescare.net/>

American Diabetes Association

Practice Resources

<http://www.diabetes.org/research-and-practice/practice-resources/>

American Heart Association

Pre-Diabetes Tools and Resources

[http://www.heart.org/HEARTORG/Conditions/More/Diabetes/AboutDiabetes/Pre-Diabetes-Tools-and-Resources\\_UCM\\_461545\\_Article.jsp#.WnhSbHxG1QI](http://www.heart.org/HEARTORG/Conditions/More/Diabetes/AboutDiabetes/Pre-Diabetes-Tools-and-Resources_UCM_461545_Article.jsp#.WnhSbHxG1QI)

Pharmacists and technicians should watch for patients whose refills indicate that they are over- or under-utilizing diabetic testing supplies. These patients may lack a clear understanding of how to test properly, how often to test, or ways to mitigate testing's costs. Over-utilization of testing supplies should prompt a referral to the pharmacist for a few reasons:

- **Training on the meter:** The patient may be wasting supplies using improper testing techniques.
- **Frequent hypoglycemia:** The patient could be experiencing frequent symptoms of low blood sugar; discussing and addressing possible reasons can identify safety issues.

Under-utilization should also prompt discussion with the pharmacist. Patients may lack the motivation to test as frequently as their prescribers suggest, or they may not know how to use the meter properly. Or, patients may be unable to afford their supplies. The aforementioned insurance formulary places testing supplies on a tiered copay system just like medications.<sup>60</sup> Pharmacists should be vigilant to determine if prescribing another brand of meter and supplies may help the patient financially.

Pharmacists and technicians should also be aware of new technology as it arrives. Continuous glucose monitoring (CGM) has recently become more convenient and affordable to patients who could benefit from it. The newest meter provides a smaller sensor that stays attached to the arm for up to ten days. The patient simply waves the meter over the sensor to retrieve a real-time blood glucose reading. The machine then prompts the patient if follow-up with a finger-stick is necessary. The web site advertises Medicare coverage and offers a free trial for current users of other CGM systems.<sup>62</sup> Pharmacists and technicians who notice over- or under-utilization of testing supplies should consider discussing CGM with patients who may benefit financially or therapeutically.

## Correct Billing of Medicare Part B

Medicare Part B covers diabetes testing supplies and insulin for use in an insulin pump for Medicare eligible patients. However, the billing for these supplies can be confusing to prescribers and pharmacists alike. Centers for Medicare and Medicaid Services (CMS) reports that denials are most frequently due to suppliers (e.g. the pharmacy) submitting claims with at least one of the following three errors<sup>63</sup>:

1. Claims without a documented diagnosis code for diabetes
2. Claims that overlapped with an inpatient hospital stay
3. Claims overlapping with a Skilled Nursing Facility (SNF) stay

To be reimbursed for a claim for any quantity of test strips and/or lancets, the supplier (the pharmacy) must maintain the following<sup>63</sup>:

- An appropriate ICD-10 diagnosis code
- Documentation that the patient requires insulin
- A physician's order (signed and dated) containing the items to be dispensed
- The specific frequency of testing (not PRN)
- Proof of delivery
- Contact with beneficiary to ensure near-exhaustion of previous supply before dispensing refills (no automated refills)

Medicare also places limits on how many strips or lancets they pay for per month without additional documentation by the prescriber:<sup>63</sup>:

- Insulin-treated diabetics: 100 test strips + 100 lancets per month
- Non-insulin-treated diabetics: 100 test strips + 100 lancets every three months

Pharmacists and technicians should also be cognizant of when a Medicare-eligible patient receives insulin for use in a pump. Pharmacy systems will not stop a claim from billing pump-use insulin to Part D because the system simply cannot distinguish insulin for a pump from other insulin. Billing pump insulin to Part D is inappropriate. Insulin for use in a pump should be billed through Part B for the best coverage. Patients must be complete a form detailing information about their pumps, and pharmacists should obtain this form by calling the Medicare Part B pharmacy help desk when an initial prescription for pump-use insulin is being processed. Pharmacists should be aware of Medicare Part B billing's specific requirements and contact prescribers whenever necessary to ensure compliance.

## Medicare Part D Pharmacy Help Desk

1 (800) 558-9363

Regular hours of operations are:

Monday - Friday 8 AM-11 PM EST

Saturday 8:30 AM -6 PM EST

After-hours coverage, 7 days a week, is available for URGENT dispensing issues.

## Clinical Inertia

Unfortunately, diabetes is a progressive disease with increasing loss of  $\beta$ -cell function. For this reason, it is unlikely that any patient can stay stable at goal HbA<sub>1c</sub> for a long period of time without dose progression. According to ADA guidelines, clinicians need to escalate pharmacotherapy if a patient does not reach goal HbA<sub>1c</sub> within three to six months.<sup>6</sup> However, this is not always the case. "Clinical inertia," or the failure to intensify treatment in the face of unacceptable glycemic control, is common. All providers do their best to provide good care, but patient hesitance can be a barrier to more aggressive treatment.

Pharmacy teams can detect patients who should be referred for follow-up. Upon drug regimen review at verification, pharmacists should be cognizant of how long it has been since the patient last changed therapy. If the answer is more than six months, discussing how long it's been since his or her last HbA<sub>1c</sub> check is wise. Ultimately, pharmacists may need to recommend follow-up with patients' providers. Pharmacists and technicians can also use refill frequency to determine possible medication non-adherence. Addressing these concerns with the patient can lead to better glycemic control and outcomes.

## CONCLUSION

The diabetes treatment landscape changes constantly and therapy options are growing. Patient safety is always a concern with the ever-present possibility of lost glycemic control, particularly hypoglycemia. Community pharmacists and technicians are well placed to facilitate active dialogue with diabetes patients and their providers to optimize therapy and keep patients safe.



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