



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

EDUCATIONAL OBJECTIVES

After completing the continuing education activity, pharmacists will be able to

- Describe different types of insulin along with their appropriate use
- Recall newer non-insulin medications for diabetes, along with risks vs. benefits
- Analyze clinical information pertaining to insulin + GLP-1 or GLP-1/GIP agonist medication adjustments
- Demonstrate medication adjustment recommendations while incorporating patient-specific data

After completing the continuing education activity, pharmacy technicians will be able to

- Describe different types of insulin along with their appropriate use
- Recognize over the counter treatment options for hypoglycemia
- Recall newer non-insulin medications for diabetes, along with risks and benefits
- Identify when to refer patients with questions about their diabetes medications to the pharmacist



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

Pharmacists are eligible to participate in this application-based activity and will receive 0.2 CEU (2 contact hours) for completing the activity, passing the post-test 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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PATIENT SAFETY: The Art of Insulin Dose Adjustments in the Setting of GLP-1 RAs and GIP/GLP-1 RAs

TARGET AUDIENCE: Pharmacists and pharmacy technicians who work with patients on complex medication regimens for diabetes.

ABSTRACT: Insulin remains a cornerstone of treatment for diabetes mellitus (DM). Access to newer DM medications, which have cardiorenal benefits and a lower risk of hypoglycemia, is increasing with improved insurance coverage and lower cost options. With these newer medications having greater accessibility, the need to adjust the patient's current medication regimen to incorporate the new medicines safely is increased. The adjustments should account for the patient's current glycemic control, glycemic targets, planned lifestyle changes, risk of hypoglycemia or hyperglycemia, and risk of adverse drug reactions.

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FACULTY DISCLOSURE: The authors have no financial relationships with an ineligible company.

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INTRODUCTION

This continuing education (CE) activity aims to guide safe insulin dose adjustments when adding glucagon-like peptide 1 (GLP-1) receptor agonists (GLP-1-RAs), and dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 RAs (GIP/GLP-1 RAs) in those with type 2 diabetes (T2D). Clinical utilization of GLP-1 RAs and GIP/GLP-1 RAs in combination with insulin has been lagging despite their benefits.¹ This is due to a lack of clinician comfort with insulin adjustment despite Food and Drug Administration (FDA) approval and improved insurance coverage. Pharmacists can optimize a patient's regimen by reducing the risk of hyperglycemia or hypoglycemia, adverse drug reactions (ADRs), and medication/injection burden.

Diabetes Basics

Diabetes is an endocrinological disorder characterized by metabolic imbalance (glucose utilization and insulin effect).² In patients who have diabetes, hyperglycemia occurs and could lead to long-term complications such as myocardial infarction, cerebrovascular accident, peripheral artery disease, retinopathy, nephropathy, and neuropathy.²

A glycated hemoglobin level (A1c) greater than or equal to 6.5% indicates a person has diabetes.³ When discussing how an A1c correlates to a patient's self-monitored blood glucose (SMBG; home blood glucose testing using a glucometer or a continuous glucose monitor [CGM]), it can be helpful to consider an estimated average glucose (eAG).³ The complete equation and calculator can be found at https://professional.diabetes.org/glucose_calc. A simplification is remembering that an A1c of 7% equals an eAG of 154 mg/dL and that each A1c percentage represents about 30 mg/dL. Generally, for an A1c goal of less than 7%, fasting blood sugars (FBGs) should be between 80 and 130 mg/dL, and 2-hour post-prandial glucose (PPGs) values should be less than 180 mg/dL.³

Previously, mainstay treatment options for glycemic control included metformin, sulfonylureas (glimepiride, glipizide, and glyburide), thiazolidinediones (pioglitazone), and dipeptidyl peptidase-4 inhibitors (alogliptin [Nesina], linagliptin [Tradjenta], saxagliptin [Onglyza], and sitagliptin [Januvia]). Newer treatment options that are focused on cardiorenal benefits, weight management, and glycemic control include⁴

- Sodium-glucose cotransporter 2 (SGLT-2) inhibitors: canagliflozin (Invokana), bexagliflozin (Brenzavvy), dapagliflozin (Farxiga), empagliflozin (Jardiance), and ertugliflozin (Steglatro)
- GLP-1-RAs: dulaglutide [Trulicity], exenatide ER (Bydureon), exenatide IR (Byetta), liraglutide (Victoza), lixisenatide (Adlyxin), and semaglutide (Ozempic)
- GIP/GLP-1 RA (tirzepatide [Mounjaro]).⁴

The diabetes management landscape is changing. Even if patients have appropriate glycemic control, their medication regimen may not be optimal based on co-morbidities. Please see the following link to the American Diabetes Association's recommendations on medication selection: <https://diabetesjournals.org/view-large/figure/5311673/dc25S009f3.tif>.

Insulin

Insulin has been a cornerstone of diabetes management for decades. With the advent of newer medication classes, it can appear as though insulin's importance in current practice is diminishing. Many individuals still benefit from the use of insulin, including those with type 1 diabetes (T1D), patients with newly diagnosed T2D with an elevated A1c, and those with access/cost concerns regarding branded medications.

Although treatment options for diabetes have advanced and include SGLT-2 inhibitors, GLP-1-RAs, and GIP/GLP-1 RAs, these drugs can be cost prohibitive depending on the situation.⁴ Insulin itself can also be cost-prohibitive depending on insurance coverage (or lack thereof) and patient-specific dosing needs. In certain situations where patients pay out-of-pocket, reducing the daily insulin dose can help reduce the cost.

Insulin's onset of action, duration of action, and concentration help to categorize it.

- Patients use bolus insulins such as ultra rapid, short, or regular insulin prior to meals to manage blood glucose spikes. These insulin types generally help lower PPGs. Checking SMBGs two hours after a meal helps to understand the effect while checking prior to mealtimes ensures safety.
- Patients use basal insulins, injected once or twice daily, to provide constant insulin action throughout the day and night. Options include intermediate, long-acting, and ultra-long-acting. These insulin types generally help lower FBGs and patients who use these insulins should check their SMBGs when in a fasting state as well.
- Examples of concentrated insulins include insulin lispro U-200 (insulin lispro U200), insulin degludec (Tresiba U-200), insulin glargine U300 (Toujeo U-300), and insulin regular U-500. Testing for insulin degludec U-200 and insulin glargine U-300 would match basal insulin testing. Testing for insulin lispro U-200 and insulin regular U-500 would match bolus insulin testing.
- Mixed insulins contain a mix of a bolus/regular insulin and an intermediate insulin in pre-fixed percentages to reduce the injection burden. Examples include insulin aspart protamine/insulin aspart (Novolog 70/30), insulin lispro protamine/insulin lispro (Humalog 75/25 or Humalog 50/50), and insulin isophane (NPH)/insulin regular (Humulin 70/30 or Novolin 70/30). For safety, these require fixed meal timings and portions and thus testing is recommended two hours before and after breakfast and dinner.

Insulin Dosing

In practice, clinicians usually start patients on a basal insulin rather than a bolus insulin as it involves fewer injections and



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SIDEBAR: Overbasalization^{6,7}

Overbasalization describes the situation in which the patient's bedtime glucose readings are significantly higher (greater than 50 points) than their fasting values. Ideally, bedtime and fasting readings should be in equilibrium. Overbasalization is common in patients whose basal insulins are titrated to a fasting goal without considering the patient's end-of-day blood sugars. It also occurs if prescribers think adding a medication would increase the patient's injection/medication burden. This generally occurs when the patient's basal insulin dosing exceeds 0.5 units/kg/day. Ideally, the provider should consider a medication that helps lower PPGs.

Using GLP-1 RAs and GIP/GLP-1 RAs has increased the ability to minimize the need for bolus insulin, reduce the risk of hypoglycemia, and lower PPG. Using a collaborative practice agreement within an interprofessional collaborative team has significantly reduced overbasalization and A1c.

provides steadier coverage throughout the day. Generally, a starting basal insulin dose is calculated using 0.1 to 0.2 units/kg/day or 10 units daily.⁵ When insulin needs increase beyond 0.5 units/kg/day of basal insulin, providers (such as clinical pharmacists) can consider the addition of bolus insulin.⁶ Using greater than 0.5 units/kg/day of basal insulin is referred to as overbasalization (see **SIDEBAR** above).

The total amount of insulin a patient takes in a day is their total daily dose (TDD). This TDD is a helpful starting point when making insulin adjustments. For example, if a patient is taking 100 units of insulin per day (this could be basal or basal + bolus) then generally 10% to 15% is a reasonable adjustment.⁵ This equates to an increase or decrease of 10 to 15 units. For a smaller TDD of 20 units the adjustment would be 2 to 3 units. Alternately, patients can self-adjust the dosing within specified parameters such as increasing a basal insulin by 2 units (up to a pre-specified maximum) every three days that the FBGs are above goal.⁵

Patient/situation specific parameters that additionally need to be considered are the patient specific glycemic goal, glycemic trends (variability vs. stability), planned lifestyle changes, hypo/hyperglycemia, and ADRs. The prior recommendations only account for medication changes while everything else remains constant. Realistically, dosing changes will likely need to be made at larger percentages to accommodate multiple changing factors.

If PPGs indicate a need for improvement of glycemic control, clinicians can consider either a GLP-1 RA (for T2D) or bolus insulin (T1D or T2D). Adding a GLP-1 RA can be more complex for those on a multiple daily injection (MDI) insulin regimen (basal + bolus). Guidance regarding basal + bolus insulin dose deprescribing varies.

Insulin Dose Adjustment with GLP-1 RAs and GIP/GLP-1 RAs

Three studies have reviewed the efficacy of adding liraglutide to an MDI insulin regimen in patients with T2D.⁸⁻¹⁰ They documented a significant reduction in A1c from baseline in the GLP-1 RA group compared to the MDI control groups. Two studies—one conducted by researchers at the Mountain Diabetes and Endocrine Center, Asheville, NC and a second conducted in Europe and Saudi Arabia called the MDI Liraglutide Trial—showed significantly reduced insulin dosing in the liraglutide groups.^{8,9} In contrast, the third study (N = 71), conducted at the University of Texas Southwestern Medical Center (UTSMC), Dallas, did not show a significant reduction in insulin dosing.¹⁰

The Mountain Diabetes and Endocrine Center study made insulin dose adjustments based on A1c but included only 37 participants. The study protocol indicated that researchers should reduce the basal dose by 20% for those with an A1c less than or equal to 8%.⁸

In the MDI Liraglutide Trial (N = 124), the insulin adjustments were based on FPGs and PPGs. When fasting values were less than 90 mg/dL or participants had nocturnal hypoglycemia, the researchers reduced the basal dose by 20% to 40%. If the fasting values were 90 to 126 mg/dL, the researchers reduced the basal doses by 20% to 30%. The researchers did not adjust the basal insulin dose if fasting glucose levels were above 126 mg/dL. If they found the patient's pre-meal glucose value to be less than 126 mg/dL, they reduced the bolus dose of the prior meal by 10% to 20%. If participants experienced daytime hypoglycemia, the researchers reduced the bolus dose of the preceding meal by more than 20%.⁹

The UTSMC study protocol reduced insulin doses by 20% if the A1c was less than or equal to 8%. The investigators did not adjust the insulin dose if the A1c was greater than 8%. They did not define the specific bolus and basal insulin dose adjustments.¹⁰

The TRANSITION2D study (N = 60) reviewed insulin deintensification with once weekly semaglutide.¹¹ These researchers transitioned patients who were reasonably well controlled (A1c 7.5% or less) from bolus insulin to a GLP-1 RA (semaglutide) in a one-step approach. They discontinued bolus insulin upon initiating semaglutide, then titrated the semaglutide dose.¹¹ A limitation to real-world applicability was that less than 25% of the participants were on 80 to 120 units of insulin per day.¹¹ Concerns in the real world would be a lack of tolerance to semaglutide or lack of follow-up on the patients' behalf, as this would lead to hyperglycemia. Also, shared decision making between the patient/provider would first need to optimize glycemic control using insulin dose adjustments to reduce the risk of hyperglycemia/diabetic ketoacidosis (DKA)/hyperosmolar hyperglycemic state (HHS).

Traditional insulin dosing guidance and these studies show that insulin dose adjustments can vary widely from 10% to 40%. One

Table 1. Action Steps to Address Hypoglycemia¹³

Appropriate step	Assessment questions
Patients must check initial and subsequent glucose values to have objective data	What values did you see when you checked your blood sugar?
Initial treatment should consist of 15 grams of simple carbohydrates for the quickest improvement of hypoglycemia symptoms. Of note, treatment with complex carbohydrates or carbohydrates + protein/fat* will delay the improvement of hypoglycemia symptoms.	What food/drink/treatment option did you initially use to address the low blood sugar?
Overtreatment with more than 15 grams of carbohydrates leads to overcorrection (hyperglycemia)	How much of the food/drink/treatment option did you initially use to address the low blood sugar?
After consuming a simple carbohydrate, the patient should consume a complex carbohydrate + protein pairing, to prevent hypoglycemia from recurring within two hours	Once the blood sugar returned to a safe range, what did you eat to keep the blood sugar steady?
* Examples of complex carbohydrates (wheat/corn/peas/potatoes/fruit) and carbohydrates + protein/fat (apple + peanut butter/pizza/candy bar)	

path isn't necessarily correct as adjusting insulin doses is an art of sorts.

HYPOGLYCEMIA TREATMENT

Accounting for and incorporating historical patient-specific parameters helps minimize the risk of hypoglycemia. Patient education regarding appropriate identification, treatment, and prevention of recurrence is paramount for safety. Common hypoglycemia symptoms are hunger, difficulty concentrating, headache, shakiness, sweating, and irritability. The 15-15 Rule advises patients with low blood sugar, defined as less than 70 mg/dL, to consume 15 g of carbohydrates and then wait 15 minutes to recheck the SMBG. Options to increase the blood sugar are 4 ounces of regular juice or non-diet soda, 1 tablespoon of sugar, honey, or syrup, 3 to 4 glucose tablets, or 1 dose glucose gel.¹² It is important to know that glucose tablets and gel are available without a prescription. Most patients know that if they experience hypoglycemia, they should eat something sweet. However, without following the treatment/prevention steps, patients may experience additional concerns. **Table 1** (above) describes appropriate action steps.

NEWER THERAPIES

As this activity discusses newer therapies, new information is consistently being learned. To provide comprehensive and current or guideline-directed care, these must be a part of the patient assistance process. Some patients have strong feelings for or against newer therapies, so it is helpful to be able to provide the information in a non-biased manner.

SGLT-2 Inhibitors

SGLT-2 inhibitors increase urinary excretion of excess glucose and thus can increase the risk of genitourinary infections such as yeast infections and urinary tract infections. This class of medications also has significant long-term cardiorenal benefits.¹⁴

Optimization of these medications would also be ideal, especially when affordable, to reduce the need for insulin.

Although this CE activity's focus is to review insulin dosing adjustments when introducing concurrent GLP-1 RA and GIP/GLP-1 RA dose adjustments, clinicians can apply some of the same practices when adjusting other medications, such as SGLT-2 inhibitors.

GLP-1 RAs

The FDA approved the first GLP-1 RA, exenatide, in 2005, and patients needed to inject it twice daily.¹⁵ Now, patients can inject GLP-1 RAs daily or weekly. In 2019, the FDA approved the first non-injectable GLP-1 RA, oral semaglutide (Rybelsus).¹⁵ Additionally, this group of medications provides cardiorenal protective effects and weight loss.¹⁶ Common ADRs are gastrointestinal intolerances such as nausea, upset stomach, constipation, and vomiting.¹⁶

Semaglutide is the most effective medication in this class from a glycemic management perspective.¹⁶ Dulaglutide, liraglutide, and exenatide are the most tolerated in this class; however, of these options dulaglutide is the most effective.¹⁶ Before these newer DM medications were available, the commonly utilized PPG-lowering options were metformin, sulfonylureas, bolus insulin, and mixed insulin. Of those, metformin is the only one that does not increase risk of hypoglycemia.

GIP/GLP-1 RAs

GIP/GLP-1 RAs have a dual hormonal activation that promotes satiety, slows digestion, and reduces hunger. Common ADRs are similar to that of GLP1-RAs but even though tirzepatide is more potent at improving glycemic control than semaglutide, it is also better tolerated.¹⁶ Currently, the FDA has approved tirzepatide as the only medication in this class. Additionally, despite the dual

activation, patients tend to tolerate tirzepatide better than some GLP-1 RAs based on anecdotal experience. Tirzepatide also provides cardiorenal protective effects.¹⁷

Combination basal insulin + GLP-1 RA medications

Currently, the FDA has approved two fixed-ratio combinations (FRC) of basal insulin/GLP-1 RA: insulin degludec/liraglutide, also known as iDeglira (Xultophy), and insulin glargine/lixisenatide, also known as iGlarlixi (Suliqua).¹⁸ These medications have a fixed level of a basal insulin and a once daily GLP-1 RA combined into a single pre-filled pen. Insulin has no maximum daily limit but the GLP-1 RAs do. Thus (because these products are fixed ratios combinations) the maximum daily GLP-1 RA dose limits the daily insulin dose in FRCs.¹⁹ The dosing is based on units of the insulin component.

For example, each unit of iDeglira contains 1 unit of insulin and 0.036 units of liraglutide.²⁰ The maximum dose is 50 units, which contains 50 units of insulin degludec and 1.8 mg of liraglutide (liraglutide's maximum daily dose). The manufacturer advises patients who are insulin and GLP-1 RA naïve to start at 10 units daily, whereas those that are currently on basal insulin can start at 16 units daily.¹²

iGlarlixi is available in the United States as Soliqua 100/33, indicating that there is 0.33 mg of lixisenatide for every unit of insulin glargine. The maximum dosage of iGlarlixi is 60 units; however, this is based on the lixisenatide daily maximum of 20 mcg. Those transitioning from less than 30 units of basal insulin would be started on 15 units of iGlarlixi. For those between 30 to 60 units of basal insulin, the starting dose would be 30 units of iGlarlixi.²¹

A study completed at the Diabetes Center of the Békés County Central Hospital in Hungary (N = 62) sought to review the safety and efficacy of switching well-managed patients with T2DM (A1c less than 7.5%) from basal/bolus insulin (low TDD) to insulin degludec/liraglutide combination.²⁰ The study defined low TDD as less than or equal to 70 units of insulin per day. The transition method was to stop the prior basal/bolus insulin regimen and to start 16 units of iDeglira. Then the FBGs were titrated to 90 to 108 mg/dL by increasing the iDeglira dose by 2 units every 3 days. The study continued or initiated metformin and titrated it up to 3000 mg (the maximum daily dose of metformin is higher in Hungary than in the United States.). The intervention reduced the TDD from 43.3 units to 22.55 units, which was significant.²⁰

Theoretically, this is a wonderful way to reduce injection burden and optimize adherence.⁶ These medications' clinical utility depends on the patient's lifestyle patterns, insurance coverage, medication availability, and out-of-pocket cost. Depending on the patient, the fixed ratio dosing and once-daily dosing could be a

benefit or a drawback. Patients who would like to minimize injection burden and can safely delay insulin may prefer a once weekly GLP-1 RA or GIP/GLP-1 RA injection. Having the ability to titrate basal insulin and a GLP-1 RA separately allows more dosing individualization, which leads to more patients achieving goal FBGs.²²

INTRODUCTION TO THE CASES

The rest of this activity focuses on case-based learning. For these cases, learners should assume that any information not provided is within normal limits, there is no change from baseline, or any change has been addressed. These cases derive from patients in a primary care setting, but this information can help in various settings. Also, due to the focus on insulin dose adjustments, the healthcare provider does not discuss the use of GLP-1 RAs or GIP/GLP-1 RAs for an indication of obesity. As obesity can co-exist with T2D, healthcare providers should monitor weight during initiation and titration of GLP-1 RAs or GIP/GLP-1 RAs.

CGMs have been more accessible in recent years, and they provide excellent graphic review of glycemic control. This learning experience uses glycemic charts. The charts depicted here would be gathered from a patient's glucometer or SMBG log and commonly depict the last 14 days of glycemic control. Clinicians should crosscheck values from a SMBG log with the patient's glucometer if they have concerns about inaccuracy. Each column that lists a glucose value specifies the timing with regard to meals; AcB is before breakfast, aCL is before lunch, aCD is before dinner, and HS is at bedtime. During the initial pharmacist visit, pharmacists need to manage patients expectations and urge frequent testing because it allows for the safest insulin dose adjustments. It also ideally decreases the testing needs moving forward by limiting the patient's insulin doses and frequency.

PAUSE AND PONDER: Thought Questions

Safety:

- Is the patient tolerating the current regimen?
- Is the patient experiencing any hypoglycemia?

Efficacy:

- Is the current regimen helping the patient achieve glycemic goals?
- What medication adjustments would help move the current glycemic patterns towards the goal?



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CASE 1: Arya Brown—pronouns: he, him, his

Arya is a patient who presents for his first pharmacist visit. First, the pharmacist reviews the electronic medical record for Arya's recent history.

Visit 1

Arya reported that he was doing well with dulaglutide 0.75 mg weekly and his current insulin glargine dose of 18 units daily. He reported that his appetite was more controlled, and he felt more energetic since starting dulaglutide. The patient was excited to increase the dose of dulaglutide.

The patient's current SMBG log shows he checks his FBGs only sporadically, and they fall between 128 and 154 (average = 143), no hypoglycemia, and consistent values above goal. Based on the anticipated improvement of glycemic control throughout the day by increasing the dulaglutide dose to 1.5 mg weekly, the pharmacist started shared decision making to continue the current insulin glargine for now. The pharmacist asked the patient to check his blood sugars in the evening, either before dinner or at bedtime, to allow for further assessment of glycemic trends throughout the day. Arya verbalized understanding of this request, but reports that he will likely only check blood sugars once a day and therefore asked to alternate testing times.

Visit 2

Arya presented for his second pharmacist visit after his third dose of dulaglutide 1.5 mg. He said that his blood sugars were at goal and that he had slight but tolerable nausea with the current dulaglutide dose. He reported that the nausea improved since the first injection at this dose. The pharmacist and Arya discussed the option of maintaining the dulaglutide dose for the next prescription to allow additional time for tolerance. However, Arya prefers to increase it to dulaglutide 3 mg weekly with the next

Table 3. Arya Visit 3

Date	AcB	HS	HS dose (insulin glargine)	comment
			12 units	
	134		12 units	
		147	12 units	
	136		12 units	
			12 units	
	124	149	12 units	
			12 units	Dulaglutide 3 mg (dose 1)
			12 units	
	117	146	12 units	
			12 units	
		137	12 units	
	120		12 units	
		131	12 units	
	116		12 units	Dulaglutide 3 mg (dose 2)
		127	12 units	
Visit 3			12 units	
Average	125	140		

prescription after four doses of 1.5 mg have been taken. He indicates the symptoms have improved over time and are barely noticeable.

His current SMBGs show FBGs ranging from 128 to 141 (average = 135). Since his glycemic control is now closer to goal than previously, he will need to adjust insulin glargine dosing to minimize the risk of hypoglycemia. The risk of causing temporary hypoglycemia is higher than that of causing temporary hyperglycemia. Thus, the pharmacist decided to reduce the insulin dose by 6 units. This is a 33% insulin reduction.

Visit 3

At Arya's third visit, he reports feeling nauseous and vomiting after injecting the second dose of dulaglutide 3 mg weekly. He says he vomited after the first dose and thought it may have been related to a food choice at that time. The vomiting improved after a couple of days, but it recurred after the second dose of dulaglutide 3 mg. The patient shows his glucometer for SMBGs as noted in Table 3 below.

The SMBGs indicate improved glycemic control. The pharmacist suggested that Arya's ADRs seem intolerable. Arya agrees. He was amenable to stopping the dulaglutide 3 mg weekly and resuming the lower 1.5 mg weekly dose when his symptoms abate (at least a week after the last dose). Now the discussion turned to what insulin dose the patient should take with the lower dose of dulaglutide.

The patient's prior glycemic control is a blueprint for patient specific response to insulin dose adjustments. Since Arya is returning to the 1.5 mg of dulaglutide weekly, and he has taken that dose before, the glycemic control information presented

during visit 2 is helpful. The general takeaway is that his glycemic control was close to goal while on dulaglutide 1.5 mg weekly and insulin glargine 18 units daily. The pharmacist and the patient make a shared decision to adjust the insulin glargine to 20 units daily to move the patient's glycemic control closer to goal.

They agree to re-try dulaglutide 3 mg weekly in the future if he tolerates the 1.5 mg weekly dose better over time. They also discuss the possibility of using a different GLP-1 RA or a GIP/GLP-1 RA, as tolerance between medications can vary.

CASE 2: Alex Devi – pronouns: They/them/theirs

Visit 1

Alex presented to their first pharmacist visit and reports that their insurance now covers tirzepatide for diabetes at a reasonable cost, so they would like to minimize MDI insulin regimen. The patient denies any contraindications to GIP/GLP-1 RA. The pharmacist tells Alex that they can adjust their insulin doses based on tolerance to tirzepatide, but there is no guarantee that insulin can be stopped.

Based on the current optimized glycemic control (Table 4 below), starting and titrating tirzepatide will necessitate insulin dose adjustments. They are currently injecting insulin degludec 36 units daily and insulin lispro 8 units with breakfast, 10 units with lunch, and 14 units with dinner. To limit the risk of hypoglycemia, the pharmacist and Alex planned to decrease doses and assess this specific patient's response. As tirzepatide will primarily

impact post-prandial glycemic control, and the patient is on a medication (insulin lispro) that can cause post-prandial hypoglycemia, the goal was to focus on bolus insulin reduction. In this case, glycemic control appears steady throughout the day. The pharmacist planned to reduce all prandial doses equally to allow blood sugars to rise throughout the day and let the full effect of tirzepatide occur while limiting hypoglycemia due to insulin. Due to tirzepatide's potency as a dual GIP/GLP-1 RA and Alex's current glycemic control, they will reduce the insulin lispro dose by 4 units per meal. Thus, the patient's total daily insulin dose was reduced by 12 units per day, an 18% reduction in TDD of insulin.

Visit 2

Table 5 (on the next page) summarizes Alex's glycemic control when they returned for their second appointment. The pharmacist looks for trends and sees that the blood sugar averages appear to be lowest pre-dinner and then highest at bedtime. A potential concern is that Alex may overeat at dinnertime as a response to rapidly decreasing blood sugars between lunch and dinner. Alex denies any hypoglycemia symptoms or adverse effects from tirzepatide. They just finished the fourth dose of tirzepatide 2.5 mg and are interested in increasing the dose. To increase tirzepatide, the pharmacist used the information gathered to minimize the patient's insulin intake. Based on the response and current SMBGs, roughly 4 units is an appropriate dose reduction per meal. Logistically, this would eliminate the breakfast insulin, reduce the lunchtime dose to 2 units, and reduce the dinnertime insulin dose to 6 units. The pharmacist needs to evaluate the lunchtime dose of 2 units

Table 4. Alex Visit 1

Date	acB	acB dose (insulin lispro)	acL	acL dose (insulin lispro)	acD	acD dose (insulin lispro)	HS	HS dose (insulin degludec U100)	Notes
	117	8	109	10	137	14	171	36 units	
	93	8	129	10	128	14	161	36 units	
	107	8	91	10	145	14	127	36 units	
	126	8	79	10	141	14	152	36 units	
	93	8	133	10	147	14	131	36 units	
	82	8	121	10	124	14	170	36 units	
	107	8	132	10	128	14	160	36 units	
	112	8	125	10	111	14	165	36 units	
	105	8	89	10	147	14	170	36 units	
	77	8	96	10	133	14	130	36 units	
	108	8	111	10	91	14	146	36 units	
	92	8	103	10	113	14	164	36 units	
	97	8	110	10	118	14	151	36 units	
	101	8	89	10	97	14	132	36 units	
	122	8	131	10	121	14	130	36 units	
Visit 1	104	8	125	10				36 units	Start tirzepatide 2.5 mg
Average	103		111		125		151		

further. For someone with T2D, 2 units is a minimal dose of insulin. The actual effect is questionable, especially in this individual, where another medication is being titrated up.

Reviewing the pre-dinner glycemic values (the lowest throughout the day) and eliminating the lunchtime insulin dose would help reduce the risk of hypoglycemia. Thus, the consensus was to eliminate the breakfast and lunchtime insulin doses while reducing the dinner time dose to 6 units. Therefore, they decided to reduce the patient's total daily insulin dose by 14 units, a 25% reduction in TDD of insulin. The pharmacist advised the patient that he can skip testing his SMBG before lunch as he is not injecting a bolus insulin at that time.

Visit 3

Alex presented for their third appointment and denies any adverse effects with tirzepatide 5 mg weekly. Alex was happy with reducing injection burden from four times a day to twice a day! They reported they have lost some weight. They have also increased activity slightly and are planning to make that a priority in the upcoming month. They would like to continue titrating tirzepatide when able. Looking at current glycemic values (Table 6 on the following page), the adjustments made at the last visit stabilized control again.

Based on this patient's previous responses, it seems that the insulin dose should be reduced by about 12 to 14 units of insulin to accommodate the tirzepatide dose increase. Additionally, due to Alex's anticipated activity change, they may need to reduce

the total daily insulin dose further. The pharmacist can help reduce the injection burden by eliminating the dinnertime dose of insulin lispro. Next, the basal dose needs to be adjusted. There is room for discussion, based on the factors noted (current glycemic control, planned activity changes, and dose increase of tirzepatide). To limit the risk of hypoglycemia, they decide to reduce insulin degludec from 36 units to 26 units. This is a reduction of 16 units of insulin. They could have reduced the patient's basal dose to accommodate everything except the activity change if it was unclear that they were planning to make a change soon.

All plans must be patient-specific, and with this discussion, the patient is reliable and was waiting to change their activity once this discussion occurred. For other patients who are not as clear that they are planning a change, the pharmacist could advise reducing the basal insulin dose to approximately 30 units daily for now and then communicate with the clinic when they make the change for review of SMBGs to allow for additional adjustments.

CASE 3: Zephyr Hernandez – She/her/hers

Visit 1

Zephyr's provider referred her to the pharmacist because her A1c was above goal and she was experiencing hypoglycemic episodes. From a complete assessment of the patient's medication and lifestyle routine, it appeared that the patient's mealtimes were inconsistent. Zephyr indicated her schedule dictates whether she can eat breakfast and/or lunch, but that she tries to eat dinner consistently. She injects insulin aspart protamine/insulin aspart

Table 5. Alex Visit 2

Date	acB	acB dose (insulin lispro)	acL	acL dose (insulin lispro)	acD	acD dose (insulin lispro)	HS	HS dose (insulin degludec U-100)	Notes
	113	4	95	6	79	10	150	36 units	
	79	4	122	6	91	10	139	36 units	
	107	4	107	6	113	10	162	36 units	
	102	4	125	6	91	10	172	36 units	
	104	4	118	6	99	10	164	36 units	tirzepatide 2.5 mg (Dose 2)
	81	4	118	6	81	10	156	36 units	
	120	4	102	6	101	10	158	36 units	
	85	4	123	6	75	10	169	36 units	
	77	4	127	6	79	10	168	36 units	
	84	4	108	6	103	10	126	36 units	
	111	4	89	6	79	10	139	36 units	
	112	4	115	6	92	10	140	36 units	tirzepatide 2.5 mg (Dose 3)
	87	4	87	6	101	10	174	36 units	
	73	4	102	6	76	10	139	36 units	
	85	4	127	6	98	10	163	36 units	
Visit 1	107	4						36 units	
Average	95		111		91		155		

70/30 mix, 24 units in the morning and 30 units in the evening. Based on Zephyr's readings ([Table 7](#) on the next page), she has hypoglycemia before dinner when she skips lunch. She treats the hypoglycemia with soda or candy. The patient says she skips her breakfast mixed insulin dose when she skips breakfast but then ends up with hyperglycemia pre-dinner.

During the visit, the pharmacist and Zephyr reviewed the 15-15 Rule for identifying and treating hypoglycemia. They also discussed the fact that mixed insulin, unfortunately, does not allow mealtime flexibility due to the fixed ratio. The patient says she will try to maintain steady mealtimes and portions. She also asked to try a medication like semaglutide and has no contraindications.

The pharmacist said that the first dose of semaglutide is a tolerance dose and is not expected to have a significant clinical impact. Transitioning to an MDI insulin regimen would help stabilize blood sugars, minimize hypoglycemia, and provide insulin dosing flexibility. However, Zephyr preferred not to switch insulin to MDI insulin at this time. She said she will focus on having consistent meals instead. So, they adjusted the current insulin regimen to reduce the risk of hypoglycemia. The pharmacist told her to reduce the insulin aspart protamine/insulin aspart 70/30 morning dose to 20 units, the evening dose to 26 units, and to start semaglutide 0.25 mg weekly.

Visit 2

At the second visit, Zephyr reported that she could not maintain steady meal times despite her efforts. She initially reduced her insulin doses as requested, but once she realized she couldn't

maintain steady mealtimes, she resumed her previous dosing. Therefore, her current SMBG values closely resemble her last visits' values ([Table 7](#)). The pharmacist advised Zephyr to communicate questions, concerns, and changes to the clinic in between appointments moving forward. As Zephyr was unable to maintain steady meal choices, she couldn't safely remain on mixed insulin due to safety concerns.

Consequently, the pharmacist talked with Zephyr about two options based on her goal to increase the semaglutide dose to 0.5 mg weekly. One option would be to transition to basal/bolus insulin (administered TID or QID), but the patient previously rejected this option. An alternative option (dependent on the patient's prandial insulin dose) would be to transition the patient to basal-only insulin and eliminate prandial insulin. This option creates a risk of hyperglycemia until the semaglutide doses can be titrated. Thus, periodic clinical assessment of hyperglycemia would be critical. DKA and HHS are a concern with significantly elevated blood sugars. Still, temporary elevations in the high 100s to low 200s may be acceptable if the patient is not safe or willing to take alternate recommended options.

After this review, Zephyr stated she cannot tolerate more than two insulin injections a day. They decided to transition Zephyr to once daily basal insulin and then a bolus insulin with dinner, as that is her largest and most consistent meal of the day. Based on her current regimen, she was injecting 37.8 units of basal insulin and 16.2 units of prandial insulin per day. She could transition to a bolus insulin dose of 4 to 8 units and a basal dose of 34 to 38 units with a goal of a total insulin dose of 42 units per day (~22% reduction from the prior TDD). Eliminating the prandial insulin

Table 6. Alex Visit 3

Date	acB	acB dose (insulin lispro)	acD	acD dose (insulin lispro)	HS	HS dose (insulin degludec U100)	Notes
	110	0	111	6	115	36 units	
	119	0	106	6	132	36 units	
	133	0	129	6	96	36 units	
	126	0	100	6	99	36 units	
	126	0	99	6	151	36 units	tirzepatide 2.5 mg (Dose 4)
	118	0	111	6	97	36 units	
	130	0	110	6	124	36 units	
	112	0	131	6	149	36 units	
	134	0	106	6	144	36 units	
	99	0	105	6	103	36 units	
	97	0	117	6	154	36 units	
	98	0	111	6	153	36 units	tirzepatide 2.5 mg (Dose 5)
	115	0	121	6	141	36 units	
	119	0	96	6	129	36 units	
	122	0	98	6	154	36 units	
Visit 1	102	0				36 units	
Average	116		110		129		

would be risky. Dependent on Zephyr's motivation, ability to tolerate semaglutide, and attention to portion sizes and SMBGs, she may do well without any prandial insulin.

Semaglutide does not require set mealtimes or portions for safety. The pharmacist believed that with time, the patient would do well on basal insulin + semaglutide at higher doses, if tolerated. Sometimes, this interim period is the toughest for clinical decision-making.

CASE 4: Sahar Kim – pronouns they/them/theirs Visit 1

Sahar presented for their first visit, reporting that despite their FBGs being at goal, their A1c has been above goal. The insurance company did not cover their CGM so the pharmacist asked Sahar to test SMBGs more frequently. They sporadically checked, when possible, at the day's beginning or end (Table 8 on the next page).

They were currently prescribed insulin glargine-yfgn (Semglee), which is a biosimilar to insulin glargine (Lantus), and inject 52 units once daily. The SMBG chart indicates FBGs of 80 to 100 mg/dL, and bedtime values are in the high 100s to low 200s.

PAUSE AND PONDER: What would be the appropriate term for this situation regarding glycemic control/treatment?

Sahar declined an oral medication, as they have trouble swallowing them. They were amenable to an alternate once daily injection, as they would prefer not to have more than one

injection daily. Sahar and the pharmacist deemed that an FRC would be the preferred option due to overbasalization and the patient's preference to minimize injections. After some investigation into insurance coverage and discussion, they determined that iGlarlixi would be reasonable.

The pharmacist started Sahar on 30 units of iGlarlixi daily, which equates to 30 units of insulin glargine and 10 mcg of lixisenatide. Additionally, they were previously injecting at bedtime, but the FDA-approved labeling recommends morning dosing of iGlarlixi.²¹ Sahar reported that they will not be able to attend the next appointment (intended to be in approximately 2 weeks) or speak on the phone for the next 6 weeks. As they have been reliable and this was a transitional period in their treatment, the pharmacist developed a self-adjustment dosing plan. The pharmacist advised Sahar to increase iGlarlixi by 2 units once a week (up to 42 units daily) for each week that all their FBGs are greater than 130 mg/dL.

Visit 2

Sahar returned 6 weeks later and indicates that they increased iGlarlixi to 42 units over time based on the guidance the pharmacist provided at the last visit. They denied any ADRs (including hypoglycemia) associated with the FRC. A review of SMBGs shows stabilization between morning and bedtime values, indicating that the bedtime values have come down and the FBGs have increased. Although the FBG average is above 136, the trend shows decreasing FBGs over the last week or so. Through shared decision-making, Sahar and the pharmacist decided to maintain the current dose. The pharmacist expects to see an

Table 7. Zephyr Visit 1

Date	acB	acB dose (insulin aspart protamine/insulin aspart 70/30 mix)	acL	acD	acD dose (insulin aspart protamine/insulin aspart 70/30 mix)	HS	Notes
	123	24	122	113	30	137	
	134	24	106	78	30	257	skipped lunch
	88	24	114	112	30	118	
	159	24	109	76	30	188	skipped lunch
	76	24	121	111	30	123	
	118	0	156	189	30	187	skipped breakfast
	123	0	164	190	30	128	skipped breakfast
	139	24	116	106	30	164	
	95	24	96	68	30	196	skipped lunch
	113	24	107	102	30	141	
	117	24	120	109	30	186	
	159	0	145	189	30	145	skipped breakfast
	149	24	132	72	30	179	skipped lunch
	117	24	127	109	30	125	
	107	24	114	79	30	212	skipped lunch
Visit 1	96	0	163				skipped breakfast
Average	120		126	113		166	

improvement in the A1c based on this improved PPG control. This is because although FBG and HS readings are being tested for ease, the improvement in HS readings indicates an improvement in PPGs.

TAKEAWAYS

We've reviewed many situations where insulin still plays a significant role in diabetes care. The advent of newer medications and greater coverage and affordability require a balance between new and old therapies to maximize the benefits and minimize the risks of both. Many medications for diabetes or coexisting obesity and diabetes (diabesity) are in the pipeline. This balance of optimal medication management will continue to change as the FDA approves new medications for diabetes.

Patient safety, especially prevention of hypoglycemia, is paramount in insulin dose adjustments, but monitoring and education regarding side effects is a close second. The pharmacist will need to adjust the dose or medication if there is a safety risk. Especially with the positive benefits associated with GLP-1 RAs, some patients may want to tolerate the adverse effects or hope they improve.

While these cases are extrapolated from the ambulatory care perspective, this knowledge can be helpful in a variety of settings. For example, pharmacists can use the principles discussed here for people obtaining their medications in the retail setting or those in the process of being titrated who are then hospitalized.

Figure 1 summarizes the key points from this CE.

Table 8. Sahar Visit 1			
Date	acB	HS	HS insulin (insulin glargine-yfqn)
	78	198	52
	89		52
		201	52
	123	188	52
	111		52
			52
	97	187	52
	79		52
		210	52
	83	218	52
	98		52
		189	52
	109		52
		186	52
	87	199	52
Visit 1	98		52
Average	96	197	

Figure 1. Remembering the Key Points when Adjusting Insulin with GLP-1 Drugs

Best

- ① **Be COMMUNITY CHAMPIONS** and whenever possible, talk about diabetes and ways to manage it, stressing tight control and the need for patients to have good support systems
- ② **Encourage discussion** with patients about essential monitoring and ways to augment medication to control blood glucose levels
- ③ **Collaborate actively with prescribers** when you see questionable patient responses or indications that medication needs to be adjusted

Better

- ① **Talk about the benefits** of new non-insulin medications when patients have new prescriptions or are ambivalent about starting a new drug
- ② **Also cover risks** so patients know what to look out for!
- ③ **Monitor tapering plans for insulin carefully** and advise patients to maintain good records of their blood sugars

Good

- ① **Brush up on the many types of insulin** and know when patients will use them
- ② **Be aware that hypoglycemia** can be life-threatening; help patients find OTC remedies to have on hand
- ③ **Ask patients about recommended dosing adjustments** when they bring new prescriptions; pharmacists can counsel and technicians can review the labels with patients

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