Insulin Stewardship

Insulin Stewardship: Optimizing Control of Diabetes while Choosing Insulins with Cost in Mind

Introductory Comments from Robert Moore, CMO of Partnership HealthPlan of California (PHC).

In February, 2019, a friend who works at a Community Health Center complained that Kaiser was prescribing NPH insulin for her father. "At our clinic pharmacy, we dispense Lantus, which is much better."

Is this really true? Are more expensive Basal and Ultra-fast acting insulins superior to the less expensive NPH and Regular human insulins that many of us who are older prescribed happily for years? Are the different pharmacokinetic properties universally superior or are we as health care professionals being subconsciously affected by a very thoughtful and clever marketing campaign?

Before answering this question, keep this in mind: it is now proven that several pharmaceutical companies conspired to change the way the entire United States health system thought about opioid pain medications, largely causing the current opioid crisis. While use of one form of insulin versus another is not creating a public health crisis the way changed opioid prescription patterns did, there is a valuable underlying lesson we should not ignore: pharmaceutical companies market their products based on a desire to maximize revenue, not based on an unbiased evaluation of conflicting evidence.

I was one of those doctors who was misled into thinking that there is no upper limit of safety for opioids and that using opioids for pain does not lead to addiction. This caused me to be more critical of marketing on the superior pharmacokinetics of newer basal and ultra-fast acting insulins.

My suspicion was first aroused when I learned about Kaiser Permanente's practice pattern around use of insulin. More than 80% of long-acting insulin prescriptions at Kaiser are for NPH insulin. In comparison, less than 10% of long-acting insulin prescriptions at Partnership HealthPlan of California's (PHC) non-Kaiser primary care providers are for NPH or NPH-containing combinations.

Control of hemoglobin A1c in Kaiser is excellent on a population level. For the two California Kaiser Medicaid plans, 63% and 71% of patients had HbA1c at or below 8.0, both well above the 90th percentile (which was 59% in 2017).

If we assume that NPH is "inferior" to the newer analogues (glargine and detemir forms of insulin), then we must conclude that it is the excellent diabetes management programs at Kaiser that are overwhelming the disadvantages of using inexpensive insulins.

This conclusion was shaken in 2018, when a study in *Journal of the American Medical Association* showed that NPH insulin has equal or better outcomes compared to starting with glargine insulin.

This is not to say that NPH should always be used instead of newer basal insulins, but it does suggest the marketing campaigns of pharmaceutical companies have been successful at making

newer insulins to be prescribed preferentially in the United States when less expensive options work well for many patients.

PHC's "Insulin Stewardship" Initiative was inspired by Antibiotic Stewardship campaigns of the last decade, which successfully helped reduce the use of expensive newer generation antibiotics. The goal was to prevent the development of multidrug resistant bacteria and side effects such as clostridium difficile enterocolitis. For

Insulin Stewardship, the goal is excellent diabetes control done cost effectively.

One physician asked me, "Yes, the basal and ultra-fast acting insulins are expensive, but they cost much less than specialty drugs such as new treatments for Hepatitis C and cancer. Why focus on insulin cost?"

Currently, Partnership Health Plan spends more money on Insulin than on all Hepatitis C drugs put together. The reason: the combination of a large and growing population of people with diabetes, and the chronic nature of this illness, which multiplies the effect of higher prices.

Many newly trained physicians have little experience with NPH and regular insulin, so an Insulin Stewardship campaign starts first and foremost with education. In preparing this educational material, we found that many clinician-patient dyads are not specific with defining blood sugar control goals. It seems likely that the newer insulins with their "superior" pharmacokinetics has made us complacent in the basics of education of patients and empowering them with the self-education to achieve excellent control. This realization expanded the scope of education on insulin to include a "back to basics" approach informed by newer knowledge.

One final note on the importance of conscious goal setting with regard to blood sugar control, and the trap of mental shortcuts.

If a prescriber thinks to themselves, "I want all my patients to have excellent blood sugar control," then the mental shortcut: "The newer basal insulins can even be used with the most labile blood sugars," leads them to start everyone on insulin glargine.

If instead we think, "let's start out with NPH and Regular (or 70/30 combinations of NPH and Regular), with sufficient education to use these well," we will find some patients who we decide are more appropriate to have moderate blood sugar control (for a variety of possible reasons), who do very well on this regimen.

Physicians and other prescribers often bristle when managed care plans and government try to re-direct their prescribing. Can education on cost-effective insulin prescribing overcome well-funded marketing to make a difference in prescribing patterns? Only if we keep an open mind to new information, with an understanding of how our beliefs were formed in the first place.

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Insulin Prescription Data for Partnership Health Plan based on dispensing claims data.

PHC Hemoglobin A1c Data from measurement year 2017 HEDIS data collection.

Back to Basics—best practices in insulin use for type 2 diabetes: Insulin Educational Module/Primer

Jay Shubrook DO BC-ADM, Clipper Young PharmD, MPH BC-ADM, Sumera Ahmed MD, BC-ADMPre-Test:

Question 1: When is insulin needed?

Which of the following scenarios should insulin be considered first line therapy for the patient?

a. Type 2 diabetes with an A1c > 10%
b. Type 2 diabetes being admitted to the hospital for a critical illness
c. Gestational diabetes
d. Type 1 diabetes
e. All of the above

Question 2: How do I start a basal insulin?

Which of the following is a best practice when starting a basal insulin?

a. Start basal insulin at 10 units and titrate at each patient visit
b. Start basal insulin at 10 units twice daily
c. Start basal insulin at 0.2-0.3 units/kg daily and let patient titrate dose
d. Start basal insulin at 50 units and reduce if the patient drops low

Question 3: Which of the following indicates the patient may be on too much basal insulin?

a. Hypoglycemia when missing a meal
b. Hypoglycemia in the morning
c. Unexplained glucose variability in the am glucose readings
d. Basal insulin dose more than 1 unit/kg/day
e. All of the above

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Question 4: Insulin is insulin- cost is the same

Which of the following is true regarding the cost of insulin?

a. Insulin costs are the same across name brand
b. All human insulins (NPH, R) are the same price
c. Vials and pens cost about the same
d. Analog insulins are two to 20 times more expensive than human insulin

Introduction

As I am sure you can appreciate, the healthcare system is being consumed by a diabetes epidemic. Currently more than 10% of our adult population has diabetes. (1) Most of these people, especially in primary care, have type 2 diabetes. This usually means that their diabetes is not the only problem they have. They often have hypertension, abnormal lipids, obesity and complications of obesity including obstructive sleep apnea, fatty-liver disease and musculoskeletal problems consequently, it is easy to become overwhelmed when caring for these patients. However, this is just the beginning. It is projected that by 2050 1 in 3 Americans will have diabetes. (2) What is even more concerning is that we are seeing a rapid increase in children with type 2 diabetes. There is good evidence that the younger one develops type 2 diabetes the more virulent the disease becomes. (3)

While most people with type 2 diabetes initially start on therapeutic lifestyle change and oral antidiabetic medications, they often will need insulin therapy to maintain glycemic control due to the progressive beta-cell function decline in the pancreas. The American Diabetes Association (4) and the American Association of Clinical Endocrinologists (5) recommend that patients with type 2 diabetes have diabetes therapy intensified every three months if they have not achieved the glucose treatment goal. (4,5) The guidelines continue to say that patients should be started on insulin therapy at the latest nine-twelve months after being treated with oral medications if blood glucose levels have not been at goal. (4,5)

Insulin is an important and potent treatment for type 1 and type 2 diabetes. While many people with type 1 diabetes are treated at specialty centers, the overwhelming majority of people with type 2 diabetes are treated by primary care providers. Therefore, a working knowledge of insulin and administration, dosing, and best practices is critical for primary care physicians. Starting people on insulin can be easy, and there are some key best practices to maximize adherence and safety.

In this monograph we will explore the best practices of choosing an insulin, starting insulin on your patients, helping them get to goal with an appropriate dose of insulin, and finally identifying when we should be looking to other options to treat our patients. While insulin is appropriate for all types of diabetes, most of our attention in this monograph will be on the use of insulin for type 2 diabetes.

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When should I consider insulin for my patients?

Insulin is used for all types of diabetes and even in people who experience hyperglycemia in the absence of diabetes. Type 1 diabetes is an autoimmune disease that attacks the beta cell with the result that the person makes little to no insulin. They need insulin to live, so for these patients, insulin is the primary treatment. Insulin is also the preferred treatment for most people when they are admitted to the hospital and for many women when diabetes complicates pregnancy. (4) Finally, insulin is indicated for people who have type 2 diabetes and they are severely hyperglycemic (A1c> 10%), fasting glucose above 250mg/dl indicating glucose toxicity, at the time or surgery to regular glucose or during an admission to the hospital in which guidelines recommend that oral medications are stopped and insulin is the preferred treatment. (4)

Table 1: Indications for insulin use

Indications for when insulin should be considered First line
Type 1 diabetes
Pregnancy, when oral metformin insufficient
Hospitalization
Decompensated type 2 diabetes Fasting glucose > 200 mg/dl A1c > 10% Patient has polyuria, polydipsia and weight loss
Children with type 2 who failed metformin and lifestyle

Why not use insulin for everyone with type 2 diabetes?

While insulin can be used in any person with diabetes it is not the best therapy for everyone. In type 2 diabetes a core pathophysiologic mechanism is insulin resistance. If someone has insulin resistance and we indiscrimately add insulin, we will contribute further to insulin resistance. Therefore, insulin is best used if it is used at key times in diabetes, started and titrated in a timely manner and each dose

of insulin is targeted to address a specific problem. For example, using insulin when someone is admitted to the hospital can help provide glucose control in a medically supervised setting and can reduce potential adverse events. Insulin is indicated for use in type 2 diabetes when a patient needs to have surgery but is above the goal A1c for the surgical team. Use of insulin can safely and effectively get the person to goal to allow for the needed procedure and often can be withdrawn or substituted after surgery.

When is insulin a less optimal treatment for type 2 diabetes?

Let's look at a case: Juanita is a 48 year/old female with type 2 diabetes for 2 years. She was diagnosed upon screening. She has not had diabetes education. She also has hypertension, coronary artery disease s/p MI, dyslipidemia, and fatty liver disease. She does not smoke, drink or use any recreational drugs, multivitamins or supplements. She tried metformin in the past but got diarrhea, so she stopped it. She has a BMI of 42 (5'5", 252 lbs) and BP 142/80. Her A1c today is 8.2%.

Many clinicians would start a basal insulin at 10 units per day and titrate the dose slowly, but this is not the best plan for several reasons. For a person and at this weight, that small of a dose of insulin will not likely make much of a difference. She was nervous about taking insulin, so she would only increase the dose at your direction. After three months she is up 40 units and her glucose readings are only slightly lower. She also has gained weight. She is frustrated as she is injecting every day and not seeing much of an effect.

Best practices for this patient: She is severely obese. She has a history of coronary artery disease. Weight loss is critical for her. We should select treatments that lower glucose, contribute to weight loss, and reduce her risk of future cardiovascular events. I would try to give metformin another try in this patient- use a slow titration, or extended release formula. You could also consider a GLP-1RA or SGLT-2 inhibitor that has been shown to reduce CV risk. Both of these agents would lower glucose and weight. While not for everyone—another option is weight reduction or metabolic surgery. This aggressive treatment-when applied early has been shown to be highly cost effective.(6)

I would consider using insulin in this patient if the A1c was > 10%, if the fasting glucose was > 200mg/dl (if she had catabolic symptoms (polyuria, polydipsia and weight loss), or if she had contraindications to other classes of medication. If you were going to start insulin I would suggest a weight based dose of NPH, Glargine or Detemir. Teach the patient to self-titrate the dose to quickly get to goal and then have an exit strategy once she is in control. (7)

Insulin: new understanding of an "old" hormone

Once a decision to start insulin is made, there are many theoretical factors that can impact the decision of which insulin regimen to choose initially, as shown in this example: (Figure 1)

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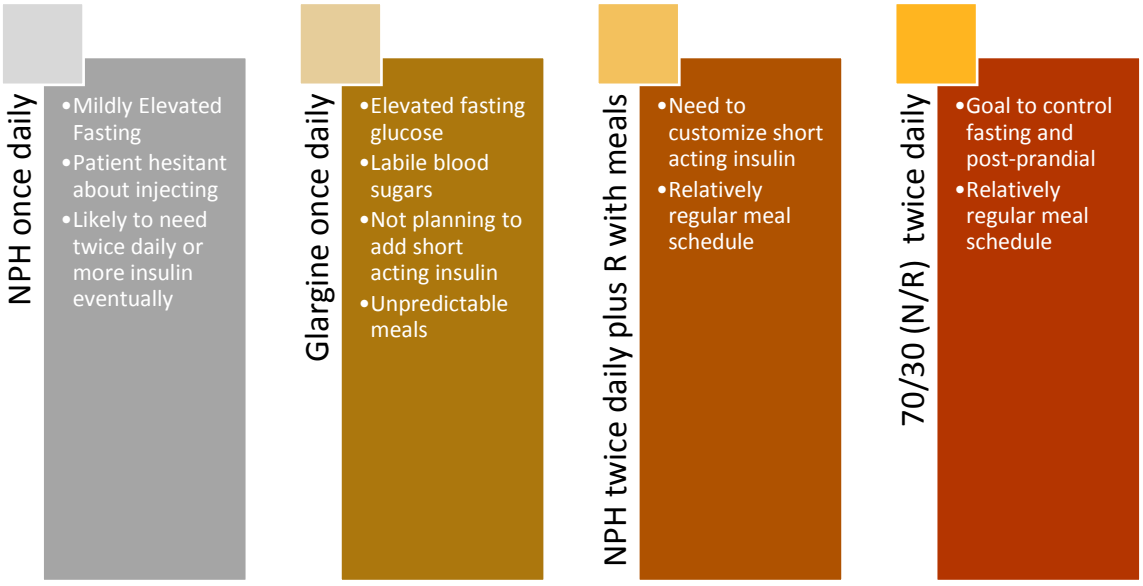

There are so many factors to be considered in selecting an initial regimen that most clinicians to use mental short-cuts, such as choosing one regimen as their default. Before glargine was available and marketed, a common starting regimen was 70/30 NPH/Regular combination, twice daily. To move beyond mental shortcuts clinicians must have a deeper understanding of the many drugs available for treating diabetes. We begin with a brief but essential review of the latest understanding of insulin physiology.

What is normal insulin physiology?

Glucose is normally very tightly controlled in people without diabetes. Insulin and glucagon are secreted as opposing factors to prevent glucose from going too high or too low.

Biosynthesis of insulin:

Insulin is produced and released by the β cells of the pancreatic islet cells. Insulin is a polypeptide hormone that consists of two chains (chain A with 21 amino acid residues and B with 30 amino acid residues). They are linked by two disulfide bridges. The first form is preproinsulin. Soon after production, it is released from the rough endoplasmic reticulum when proteolytic enzymes cleave into pro-insulin. Then it is transplanted to the Golgi apparatus in microvesicles. Pro-insulin converts to insulin when other proteolytic action cleaves the C chain (c-peptide) and leaves the active insulin molecule in the vesicle for secretion. This physiologic feature is convenient in that one molecule of c-

peptide is produced for each insulin molecule. This makes c-peptide a good measure of endogenous insulin production, as it is not affected by exogenous insulin. (8)

Normal Insulin Secretion (8):

Insulin secretion from the β cell vesicles is stimulated by a number of triggers. Glucose is taken up in the β cell via a GLUT-2 receptor. When the glucose is not elevated, potassium ATP channels on the cell membrane allow potassium to leave the cell and keep the membrane at a negative action potential. When glucose levels rise above 90 mg/dl glucose enters the cell and is oxidized by glucokinase, which also acts as a glucose sensor. When glucose exceeds these levels, the potassium ATP channel closes (so potassium cannot leave the cell) leading to membrane depolarization of the β cell, and thus causing voltage – gated calcium channels to open. Increasing intracellular calcium stimulates the release of insulin via exocytosis from the β cell. (8)

Human endogenous insulin secretion is continuous at baseline within the above parameters (basal insulin secretion). The pancreatic β-cell secretes insulin from vesicles in a pulsatile manner. The first pattern is a pulse every 6 minutes. The second pulse is every 30-40 minutes. The amplitude of these pulsatile secretions is based on the ambient glucose level presenting to the pancreas. There is a diurnal pattern as well whereby insulin secretion is lowest in the middle of the night and greatest first thing in the early morning. In a fasting state, insulin secretion suppresses glycogenolysis and stimulates gluconeogenesis and lipogenesis.

Insulin secretion is also modulated by the intake of nutrients (bolus secretion with food). In response to meal ingestion, insulin secretion is biphasic. There is a large and rapid first phase insulin secretion followed by a slower and more sustained second phase secretion. The incretin system significantly contributes to bolus insulin secretion via the gastrointestinal peptides (GLP-1 and GIP). These incretin hormones stimulate insulin release and suppress glucagon release from the pancreas. The incretin effect provides a much larger increase in insulin secretion than ambient glucose levels.

Insulin released from the pancreatic β cell is then released into the portal venous system. The liver removes at least fifty percent of insulin released. The remainder passes on into systemic circulation where it interacts with target site receptors. At the target sites, insulin binds to receptor sites on plasma membranes. This binding begins a cascade of intracellular reactions that trigger significant cellular responses such as glucose uptake, glycogen synthesis, and lipogenesis. (8)

Exogenous insulin does not replicate the kinetics of endogenous insulin released by the pancreatic β-cells. Exogenous insulin which is given subcutaneously is distributed equally throughout the body (no first pass liver uptake), so the ratio of insulin to the periphery compared to the liver is much higher. This administration is the basis for exogenous insulin pharmacokinetics and additional side effects that differ from endogenous insulin.

Table 2: Side effects of exogenous insulin

Common Side Effects from Exogenous Insulin
Hypoglycemia
Weight gain
Fluid Retention/edema

What is the landscape of commercially available insulins?

The insulin market has expanded in the last 20 years with more insulin products made available for prescription. There are two types of human insulin (regular and NPH), four U-100 basal insulin analogs (Lantus, Basaglar, Levemir, and Tresiba), five mealtime insulin analogs (Novolog, Humalog, Apidra, Fiasp, and Admelog), and one inhaled insulin (Afrezza). In addition, there are four concentrated insulins (U-500 regular insulin, U-200 Tresiba, U-300 Toujeo, and U-200 Humalog). There are three types of pre-mixed insulin product (e.g., 70/30, 75/25, 50/50). Each of these insulin products has different pharmacokinetics, onset of action, and duration of action. Thus, optimizing effectiveness and ensuring safety of insulin therapy involves many factors for clinicians to consider.

Table 3: Landscape of Human and Analog insulins (9)

(BOLD are PHC preferred, italic are NOT on PHC formulary)

Insulin	Analog	Analog Brand name	Human	Human insulin Brand name
Ultra Rapid	*Insulin Aspart*	*Fiasp*	Inhaled human insulin	*Afrezza*
Rapid	Aspart Biosimilar Lispro Glulisine Lispro	NovoLOG Admelog Apidra HumaLOG		
Fast			**Regular**	HumuLIN R

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				NovoLIN R ReliOn* R
Intermediate			**NPH**	HumuLIN NPH NovoLIN R ReliOn* R
Long Acting	Detemir Glargine	Levemir Lantus **Basaglar**		
Ultra Long acting	Degludec	Tresiba		
Pre-mixed insulin combinations	Aspart/Pegylated Apart Lispro/Peglyated Lispro	NovoLOG 70/30 HumaLOG 75/25 Humalog 50/50	**Regular/NPH**	HumuLIN 70/30 NovoLIN 70/30 ReliOn* 70/30
Concentrated Insulin			Regular U500	HumuLIN U500
	Degludec U200 Glargine U300 Lispro U200	Tresiba Toujeo HumaLOG		

*ReliOn is only available at Walmart for cash paying patients

How are these insulins different?

Endogenous insulin is active when it is in its monomeric form. This is important as keeping insulin in the monomeric form or delaying breakdown into monomers can be used pharmacologically to change the time action profiles of insulin. The body can buffer insulin with zinc which allows it to form dimers and hexamers which in turn acts as stabilizers to insulin, particularly in β cell vesicles. When insulin is injected into the subcutaneous tissue, it is usually in hexameric form and then dissociates into monomers. This rate of dissociation from hexamers and dimers is responsible for the onset and duration of action.

The same is true when developing commercially available insulins. The use of a zinc buffer can help increase the stability and duration of action of Regular insulin (R), and Neutral Protamine Hagedorn

(NPH). To further the duration of NPH, a phosphate buffer is used and the molecule is protaminated. The time action profiles of the analog insulins start with an amino acid substitution to change the kinetics- either to keep insulin as a monomer, or to extend time action by keeping insulin molecules in dimers and hexamers. Further, glargine uses an acidic pH to help provide longer stability. Detemir and Degludec are also bound to a free fatty acid which then binds to albumin which prolong duration of action. Degludec has the longest duration of action-this is made possible by its ability to form chains of hexamers which slow the dissociation into monomers and allow for a longer duration of action.

There are a number of ways that insulin can be modified to affect its pharmacokinetics and clinical effects.

Insulin Pharmacokinetics:

To have a useful clinical understanding of insulin pharmacokinetics, there are three key elements to know about each insulin. These are: 1. onset of action; 2. time to peak levels; and 3. duration of action.

Historically, human insulins have included Regular (R) and Neutral Protamine Hagedorn (NPH), Lente (L), and Ultralente (U). Only R and NPH are still available today. Regular insulin is used most commonly as mealtime insulin. Its kinetics are such that it should be dosed 30-45 minutes before a meal. This is a challenge for some people as they cannot always predict the content and timing of food intake to that level of specificity. Regular insulin is ideal if cost is the most important factor in choosing an insulin and if the person maintains a regular schedule of meals spaced four to eight hours apart.

NPH insulin has a longer duration of action, can be dosed four to six hours before a meal, and is used one meal in advance (taken before breakfast to cover lunch), or as a basal insulin two to three times per day. NPH has a prolonged use due to the addition of a positively charged protamine. It is buffered with phosphate which provides greater stability of the hexamers and slows the release to the active monomeric form. NPH is ideal for people where cost is a major issue and they either only need insulin overnight (gestational diabetes as an example) or if they can take this twice daily with regular insulin and can maintain a regimented schedule of meal schedule and carb content.

The development of genetically engineered insulin analogs in the 1990s led to new formulations that made treatment even more convenient for people with diabetes. Today there are five rapid-acting

analog insulins (Aspart, Lispro, Glulisine, biosimilar Lispro, FIASP) and four long acting analogs (Glargine, Detemir, biosimilar glargine, Degludec).

Table 4: Pharmacokinetic profiles of currently available human insulins and insulin analogs (9)

Insulin	Brand name	Manu.	Species Source	Conc.	Time of Action (hrs.)		
					Onset	Peak effect	Duration
Glulisine	Apidra®	Sanofi-Aventis	human analog	U100	0.2 – 0.5	1.6 – 2.8	3 – 4
Lispro	HumaLOG®	Lilly	human analog	U100	0.25 – 0.5	0.5 – 2.5	≤ 5
Aspart	NovoLOG®	Novo Nordisk	human analog	U100	0.2 – 0.3	1 – 3	3 – 5
Insulin Aspart	FIASP ®	Novo Nordisk	Human analog	U100	0.12	1-3	3-5
Biosimilar Lispro	Admelog®	Sanofi	Human biosimilar	U100	0.25-0.5	0.5-2.5	≤ 5
Regular	HumuLIN R NovoLIN R	Lilly Novo Nordisk	human	U100	0.5	2.5 – 5	4 – 12
NPH	HumuLIN N NovoLIN N	Lilly Novo Nordisk	human	U100	1 – 2	4 – 12	14 – 24
70 NPH 30 regular	HumuLIN 70/30 NovoLIN 70/30	Lilly Novo Nordisk	human	U100	0.5	regular 0.8 – 2 NPH 6 – 10	18 – 24
50 lispro protamine 50 lispro	HumaLOG ® Mix 50/50	Lilly	human analog	U100	0.25 – 0.5	0.8 – 4.8	14 – 24
75 lispro protamined 25 lispro	HumaLOG ® Mix 75/25	Lilly	human analog	U100	0.25 – 0.5	1 – 6.5	14 – 24
70 aspart protamined 30 aspart	NovoLOG ® Mix 70/30	Novo Nordisk	human analog	U100	0.15-0.3	1 – 4	18 – 24

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70 degludec 30 aspart	Ryzodec®	Novo Nordisk	Human analog	U100	0.12-0.25	1-2	>25
Detemir	Levemir®	Novo Nordisk	human analog	U100	3 – 4	3 – 9	6 – 23
Glargine	Lantus ®	Sanofi - Aventis	human analog	U100	3 – 4	none	mean 24
Biosimliar Glargine	Basaglar ®	Lilly	human biosimliar	U100	3-4	none	Mean 24
Degludec	Tresiba	Novo Nordisk	Human analog	U100	1	none	42
Regular	HumuLIN R U500 (CONCENTRATED)	Lilly	human	U500	0.5	2.5 – 5	up to 24
Lispro	Humalog U200	Lilly	Human analog	U200	0.25-0.5	0.5-2.5	≤ 5
Glargine	Tuojeo	Sanofi	Human analog	U300	6	none	24
Degludec	Tresiba	Novo Nordisk	Human analog	U200	1	none	42

RAPID	SHORT	INTERMEDIATE	INTERMEDIATE/ SHORT ACTING MIXED	INTERMEDIATE/ RAPID ACTING MIXED	LONG	Concentrated (variable duration)

Rapid Acting Insulins

There are six FDA-approved rapid-acting insulin analogs available in the United States today: glulisine, lispro, biosimilar lispro, aspart, fast acting aspart, and inhaled insulin technospheres. Most are provided by subcutaneous injection, but Afrezza is administered by oral inhalation. All of the injectables of these are clear, colorless solutions. Timing of meals and monitoring for hypoglycemia are important with rapid acting insulins.

All of the above insulins are intended to be taken with a meal. They should be dosed 15-30 minutes before a meal to allow the time action profile of the insulin to match the absorption of food. When these two parts are well timed, the risk of post meal hypoglycemia and hyperglycemia are reduced. (12)

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Short-Acting Insulin

Regular insulin (Humulin R®, Novulin R ®, ReliOn brand R) is a short-acting human insulin. It is produced using recombinant DNA techniques. Its form is a clear, soluble crystalline zinc solution. This insulin molecule will aggregate in dimers and hexamers when administered in high concentrations. This slows absorption. Regular insulin is normally administered 30 to 45 minutes prior to a meal and tends to last longer than rapid acting insulins, anywhere from four to twelve hours. The duration of action is dose dependent. Regular insulin can be given subcutaneously or intravenously. Regular insulin is particularly useful as an intravenous infusion and is frequently used in hyperglycemic crises such as diabetic ketoacidosis and hyperglycemic hyperosmolar non-ketosis syndrome.

Intermediate Acting Insulin

NPH (neutral protamine hagedorn, or isophane) is a cloudy suspension that contains insulin and protamine. The addition of protamine creates a longer duration of action. When administered, enzymes slowly break down the protamine to allow for the slow absorption of insulin. NPH absorption is often variable, having an onset from one to five hours and duration of action from 4 to 12 hours. Insulin NPH is available as HumuLIN N® (Lilly) or NovoLIN N® (Novo Nordisk). In the clinical setting NPH is typically given one meal in advance (for example before breakfast to cover lunch) or before dinner to cover a bedtime snack) or as 2-3 doses per day to serve as a basal insulin. NPH insulin has been available since 1982.

Pre-Mixed Insulins

Premixed insulins were developed to improve convenience for patients. There are human insulin mixes and rapid analog insulin mixes. The human premixed insulin uses R insulin mixed with NPH. The pre-mixed analog insulins use rapid acting insulin analog and a protaminated version of the rapid acting analog. The time to onset, peak and duration are dictated by the short acting component. Patients should be instructed on the differences between these insulin mixes (R versus analog based). Pre-mixed insulins are named by the percentage of each component insulin/analog, with the longer acting insulin being named first. To improve safety and clarity the premixed insulins are capitalizing the last three letters to better identify human from analog insulins and prevent accidental switches.

Human insulin NPH/Regular insulin mix is commercially available in two brands. HumuLIN® 70/30 or NovoLIN N® 70/30 (70% NPH and 30% regular). The 70/30 mix is a cloudy suspension (NPH is cloudy). You will notice that the last three letters are capitalized. This is to prevent confusion between

the human insulin mixes and the analog insulin mixes. For the human insulin mix the onset is around 30 to 45 minutes with a peak effect in 4 to 12 hours. This insulin is typically dosed 2-3 times per day with pre-breakfast and pre-dinner dosing. This is convenient for patients who want to limit the number of injections. Responses to this insulin, though, can be less reliable dose to dose. Regular insulin can precipitate out in the NPH insulin which can make the day to day time action profiles vary with this insulin.

Other mixed insulins available include rapid acting analog insulin and protaminated rapid acting analog insulin. The protaminated rapid acting analog will delay absorption and give a prolonged effect. The HumaLOG® 75/25 and NovoLOG ® 70/30 mixes have a more rapid onset of action and a shorter peak effect. This allows them to be dosed immediately before mealtime, which may result in more reliable clinical effects and reduced post meal hypoglycemia. These rapid acting mixed insulins came to market in the mid to late 1990s. Pre-mixed insulins are ideal for people who need both basal and meal time insulin coverage but want to limit the number of injections per day. People taking premixed insulin will want to maintain a regular schedule of meals times and carbohydrate content to maximize benefit and minimize risk.

Table 5: Distinguishing between the Human and Analog insulin mixes (9)

Insulin mix	Onset	Peak	Duration	Available as vial?	Available as a pen?
HumuLIN 70/30	30-45 mins	R ---0.8 – 2 NPH --6 – 10	18 – 24	yes	yes
NovoLIN 70/30	30-45 mins	R---0.8 – 2 NPH--6 – 10	18 – 24	yes	yes
NovoLOG 70/30	10 – 20 mins	1 – 4	18 – 24	yes	yes
HumaLOG 75/25	15-30 mins	1 – 6.5	14 – 24	yes	yes
HumaLOG 50/50	15-30 mins	0.8 – 4.8	14 – 24	yes	yes
Ryzodec 70/30	1-15 mins	1-2	>25	no	yes

Long-Acting Analog Insulin.

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Insulin glargine (Lantus®) came on the market in 2000 followed by the release of insulin detemir (Levemir®) in 2005. The introduction of a steady, long acting insulin closely mimics the basal rate of endogenous insulin. These agents alone have a lower risk of hypoglycemia (compared to NPH) due to the lack of a peak response and the continuous release of low levels of insulin. More recently a biosimilar glargine was released (Basaglar ®, concentrated glargine U300 (Toujeo ® and insulin degludec (Tresiba U100, U200). Both glargine U300 and degludec have an even longer duration of action.

Insulin glargine is a long acting analog of human insulin. The insulin structure is modified by attaching two arginine amino acids to the terminal end of the B chain and changing asparagine to glycine at the terminal end of the A chain. These modifications produce a clear, colorless solution that is soluble in acid and forms a precipitate upon subcutaneous injection. This precipitate dissolves slowly creating a continuous, steady release of insulin. Because of this mechanism, insulin glargine has no defined peak. Glargine is injected subcutaneously once daily and should not be administered intravenously or intramuscularly (16-old pcr). Given that glargine has an acidic pH, it should not be mixed with other insulins. Some patients report a burning sensation at the injection site as a result of the acidic pH, but this is not an indicator of any adverse effect.

Insulin detemir is a clear, colorless, long acting human analog insulin. The threonine on the terminal end of the B chain is dropped and C-14 fatty acid chain is attached to the B29 lysine. When injected, the fatty acid chain reversibly binds detemir to albumin. This slows each step of absorption from the subcutaneous tissue to the cell. The onset of action is generally one to two hours. It can be given once daily. Insulin detemir is administered subcutaneously.

Insulin degludec (Tresiba ®) that has a duration of 42 hours. It has the ability to not only form hexamers but chains of hexamers that lead to its protacted duration of action. It is available in both U100 and U200 concentrations.

All basal insulins have essentially the same efficacy. The ideal person to take a basal insulin analog is someone who is completely insulin deficient (type 1 diabetes), someone at high risk for hypoglycemia (day or nighttime), someone with a highly variable schedule making a consistent dosing difficult.

Concentrated insulins:

With the global pandemic of obesity we are seeing much higher rates of diabetes. Those who are obese and have type 2 diabetes typically need more insulin for a therapeutic effect. This often means very large doses of daily insulin (200-300 units per day). Once a person needs more than 300 units of insulin per day, the number of injections increases and the pharmacokinetics of the insulin can be less consistent due to potential depot effects at the injection site. Concentrated insulins are a

potential solution to this challenge. Another potential solution is to use other complimentary therapies (including lifestyle and other medications) that limit the insulin burden in those with type 2 diabetes and substantial insulin resistance.

Most insulin products in the United States are U100 insulin (100 units/mL) which means that there are 100 units in each mL of insulin. This standardization is important in terms of safety and reliable clinical effect. Each “unit” is standardized for a similar clinical response — one unit of lispro, aspart, and glulisine should all have similar glucose lowering effect — which allows for accurate prescribing and dosing even when switching between insulins. A vial of U100 insulin holds 10 mL or 1000 units. An insulin pen holds 3 mL or 300 units.

Which insulins come in a concentrated form?

Regular insulin (Humulin ®U500), Lispro (Humalog® -U200), Glargine (Tuojeo® -U300), and Degludec (Tresiba® U200) are the concentrated insulins available in the United States. (12)

Regular human insulin is available in a concentrated form, HumuLIN® R U500 with the same mechanism of action as U100 regular insulin. However, increased concentrations create more aggregation of insulin molecules into dimers/hexamers and this prolongs absorption. Humulin R U500 contains 500 units of insulin/ml versus the non-concentrated form, which contains 100 units/ml. A single dose of concentrated U500 regular insulin may have effects up to 24 hours. HumuLIN® R U500 is recommended for subcutaneous administration 30 minutes prior to a meal.

Understanding dosing of HumuLIN® R U500 is important in order to prevent severe hypoglycemia or death. Concentrated U500 insulin can be an excellent tool when used appropriately. HumuLIN® R U500 manufacturer, Eli Lilly, has online information for assistance in prescribing concentrated insulin. This insulin, while highly effective, is very expensive and can be problematic to get the dosing correctly if used by a provider and or patient unfamiliar with this medication. It is currently recommended that dosing for this insulin be by pen or if by vial- be determined by volume, not by number of units. This is intended to reduce dosing errors and improve safety. Humulin U500 insulin is currently only approved for subcutaneous insulin injections.

The other insulins that are available in concentrated formulations act very similar to the original U100 formulation and are highlighted in the table below.

Cost of insulins: (11)

The cost of insulin has become a significant clinical and public health issue. While there are many new expensive insulin products even the cost of many of the older insulins have skyrocketed. Further, the price for the older insulins has also far outpaced similar oral medications. These costs have

contributed to substantial hardships for many patients especially those responsible for some or all of the price of their medications This also has placed a coverage burden on insurers and health care plans.

Potential responses have included: patients not taking insulin as prescribed; patients relying on samples when they are not covered or underinsured; or just not filling the insulin at all. It has been estimated that one in four Americans on insulin already ration their insulin because of the cost of the insulin (12) This has resulted in professional organizations and health care systems to take action to limit the cost of insulin in the US. (ADA) Health care systems have limited access to more expensive insulin or limited the quantity allowed for a given patient per month.

The cash price for patients is approximately $24-$26 per vial (10 ml or 1000 units) for Relion brand Human insulin (R and NPH) which is only currently available at Walmart. Name brand human insulins are 3-5 times more expensive -for the same product. Vials are cheaper than syringes in terms of patient cost. Analog insulins are 10-20 times more expensive. For example, A box of pens (generally 5 pens of 3 ml or 1500 units) of analog insulins can cost up to $600. When prescribing insulin take the time to see what insulins are covered and which are preferred to limit the cost. For the great majority of people therapeutic substitution within a group can be completed easily.

So, if you have a patient for whom cost is the primary concern you may be better to prescribe Human insulin or a human insulin mix depending upon what the needs are for insulin. A patient who is paying cash for their prescription can get a ReliOn brand human insulin 70/30 mix by vial for about $25. The prices listed do not include the cost of needles, syringes, or other supplies, the added cost of which can play a significant role in patient adherence. This approach will not work for everyone.

It may be much harder to get consistent control when switching between insulins in patients with type 1 diabetes, a patient who is prone to hypoglycemia, takes large doses of insulin or when their day to day schedule varies greatly (for example shift workers). Only some of the insulins are FDA approved in pregnancy so this may limit switches in women who are pregnant or planning to become pregnant.

Table 6: Costs of insulin products

Here is what the major insulin classes cost Partnership HealthPlan (per 1000 units) with a comparison to the Walmart ReliOn brand insulin for comparison:

Insulin Type	Approximate Price per 1000 units, Feb 2019	
	Cash	**Managed Care**
Humalog	$180	$270
Novolog	$300	
Admelog	$240	$230

Humulin R		$145
Novolin R		$135
ReliOn R	$26.55	N/A
Lantus	$200	$280
Basaglar	$150	$220
HumuLIN N	$100	$145
NovoLIN N		$145
ReliOn N	$26.55	N/A

A population health-based approach:

Treating patient with diabetes can be both challenging and rewarding. We must be focused on shared decision making with our patients and make sure we individualize treatment goals for each patient. We also need to be cognizant to the benefits, risks and cost associated with each treatment.

Type 2 diabetes represents 90% of diabetes in the United States. Despite having many new treatments for type 2 diabetes, we have made little progress in gaining control of this disease. It is estimated that half of all people with diabetes do not achieve recommended A1c levels. (13,14)

What is even worse is that the goals are achieved more seldom when basal insulin is started. In two studies less than 33% of people started on basal insulin achieved a goal A1c of < 7.0%. (15,16,17).

This was further reinforced by a recently published study that showed real world experience with starting patients on insulin. The Diabetes Unmet Need with basal insulin Evaluation (DUNE) study in type 2 diabetes was published in (18) This study evaluated the efficacy of basal insulin initiation in a real world setting for those patients with type 2 diabetes. This global study enrolled more than 3000 patients with type 2 diabetes who had recently started basal insulin. In this study the health care provider declared the desired A1c goal to be achieved with this insulin. The primary outcome was ability to achieve the individualized goal and rates of hypoglycemia. After 3 months, only 27% of patients placed on insulin actually achieved the desired A1c goal. This was largely attributed to under-dosing of insulin and minimal titration to an effective dose.

There is a growing body of evidence that the benefits of analog insulin, in terms of A1c reduction and prevention of severe hypoglycemia, are small. Two recent large studies found that use of human insulins were as effective and as safe as analog insulins. A Kaiser Foundation study found that starting a basal insulin analog did not reduce hypoglycemic related emergency room visits or hospitalizations nor did it improve control compared to NPH insulin. (19) A recent retrospective trial of more than 14,000 Medicare beneficiaries found that patients (mean age 72.5 years, 93% type 2 diabetes) could safely be switched from analog basal insulin to NPH. HbA1c was similar 0.14%

difference between those who switched and those who did not. There were no significant differences in the rates of severe hypoglycemia between the groups.

Further, there was a 50% reduction in the number of patients who hit the Medicare gap in the switch group (11.1%) compared to baseline (20.6%). Total insulin expenditures reduced by more than 50% due to the switch ($3,214,437, to $1,432,701). (20,21) CMS reported that 1.6 million beneficiaries used glargine (basal insulin analog) at an annual cost of $4.6 billion dollars. (22) These studies challenge current common practices for insulin use in type 2 diabetes. To further evaluate trends, we need a prospective RCT with real-life (as opposed to idealized) conditions.

Can we use the older insulins in people with type 2 diabetes?

There is good evidence that the potency and efficacy of the older insulins is the same as the newer insulins. (23,24) The main differences have been patient-centered. These include the ability to take basal insulin injection once daily and concerns about insulin peaks that can lead to mid-day or overnight hypoglycemia. This fear or experience can lead to defensive eating, poorer adherence to the insulin regimen, and potentially increased risk of adverse events from hypoglycemia. This is most pronounced with nocturnal hypoglycemia. (25)

Noting the above studies that show that under-treatment/hyperglycemia is so prevalent, the risk of hypoglycemia is much less in those with poor or fair control. The actual benefit of the analog insulins was less in pragmatic or real-world studies especially when target A1c is not achieved. (26,27)

Meal time analog insulins can be easier for many patients as the can take their injection at the time of the meal. People may have a better sense of how much they are going to eat once they are going to start eating. Regular insulin should be dose 30-45 minutes before the meal. This gap of time can be problematic if the time or content of the meal was not properly anticipated. This can lead to post-meal hyperglycemia or hypoglycemia. While these concerns are significant, recent studies show that Regular insulin can be safely used in managed care programs and for Medicare patients. (26,27)

Because of a combination of training practices and marketing, many younger clinicians have never been trained on the use of Regular and NPH insulins and feel anxious about how to dose these options. In the following pages we will give several scenarios and clinical pearls to help gain confidence in the use of R and NPH options.

Insulin is an important part of treating diabetes mellitus. As mentioned earlier it is the only treatment of choice for certain settings (type 1, inpatient and surgical setting). For type 2 diabetes insulin has traditionally been used when non-insulin treatments have failed. Insulin has no ceiling effect and is the most potent medication for diabetes. However, for insulin to be the workhorse for diabetes it needs to be dosed in a rational and calculated manner. We can get quick results with insulin but only if dosed with best practices.

Insulin Stewardship

Practical clinical pointers for insulin use:

When to start insulin?

Insulin is the primary treatment for type 1 diabetes and will, eventually, be required by most people with type 2 diabetes. Current guidelines by the ADA and ACCE support the use of insulin as early as 1 year after diagnosis if glucose remains uncontrolled after use of combination oral therapy and therapeutic lifestyle changes (4, 5). In addition, insulin may also be the preferred initial treatment for patients who present with severe hyperglycemia. This includes those with a fasting glucose >250 mg/dl, HgA1c >10% or acute symptoms of insulin deficiency including polyuria, polydipsia, and weight loss.

How to start insulin?

Primary care providers treat the majority of patients with type 2 diabetes. Increasingly insulin is part of the treatment plan for people with type 2 diabetes. For these patients, starting insulin usually means starting a basal insulin -for example NPH, glargine, detemir, degludec. Basal insulins allow for suppression of hepatic glucose production overnight and can help normalize morning blood glucose. Therefore, controlling fasting glucose is a logical first step. By removing glucose toxicity, the remaining functioning β cells are better able to address prandial hyperglycemia.

We recommend a weight-based dose for starting insulin:

If the A1c is below 8.5% start at 0.2 units/kg/day—if the A1c is higher start at 0.3 unit/kg/day.

If you are starting NPH you will need to split that into 2 doses. This is best given 8-12 hours apart and preferably knowing that some food will be eaten 4-6 hours after the dose. If you are starting an analog basal insulin the dose is given once daily-anytime of the day and irrespective of meals. These starting doses are rarely have enough insulin to normalize morning glucose at the first dose, so patients should be instructed to titrate the dose once to twice weekly until morning glucose reaches target range.

What medications should have the dose lowered or discontinued when I start my patient on insulin?

Any medication that also increases secretion of insulin should be examined. These include the sulfonylureas and the metglinides. If the A1c is greater than 8.5% you can add the insulin and lower the dose of these medications once the glucose is starting to improve. If the A1c is between 7.5% -

8.5% you may want to cut the dose of the meds in half to reduce the risk of hypoglycemia. If the A1c is below 7.5% when you add insulin it is safer to stop these meds.

Sulfonylureas and metglinides should be stopped if the patient is starting on meal time insulin as this combination substantially increases the risk of hypoglycemia.

The TZD (pioglitazone) should have the dose lowered if the patient is already having problems with weight gain or edema. If the patient has risk of or current heart failure pioglitazone should be stopped.

What medications can patients take safely with insulin?

Most medications can be safely used with insulin. Metformin should be continued in most patients as long as possible (until renal function declines to eGFR 50 ml/min—dose reduction, and if eGFR < 30 ml/min-metformin should be stopped).

The DPP-4 inhibitors (Alogliptin- Nesina (*PHC preferred*), sitagliptin- Januvia, saxagliptin-Onglyza, linagliptin -Tradjenta) can be safely taken with insulin and often is complimentary to basal insulin. No dose adjustment is needed when starting insulin. Remember, this is the class of medication that should always be started at the maximum dose until there is renal disease)

The GLP-1 receptor agonists can be safely used with insulin. In fact, this is a potent combination and many people who start a GLP-1 RA after insulin can reduce the insulin dose and maintain improved control. The GLP-1RA include liraglutide-Victoza (*PHC preferred*), exenatide-Byetta, Bydureon, dulaglutide- Trulicity, semaglutide- Ozempic. In fact recent studies have shown that it may be better to start a GLP-1RA rather than meal time insulin in type 2 diabetes and can be comparable to basal insulin.

The SGLT-2 inhibitors can also be used safely with basal insulin. Often these meds will also help to reduce the need for insulin. The SGLT-2 inhibitors include: Ertugliflozin- Staglatro (*PHC preferred*), empagliflozin- Jardiance, canagliflozin—Invokana, dapaglifozin-Farxiga.

While the alpha-glucosidase inhibitors as used less frequently—they can be ideal medications to combine with basal insulin. In very high carbohydrate diets (India, Asia) these medications reduce glucose rise by delaying glucose absorption. No dose adjustment is needed with basal insulin. These medications include: acarbose-Precose, and miglitol- Glyset.

Switching between insulins:

Most insulins can be switched with no changes to the prescription. This is particularly true for changes between R insulin and meal time analog insulins. The main difference to know between R

insulin and meal time analog insulins is when each insulin is given relative to meal time. See Tables above.

Changing between basal insulin requires a little more effort.

Table 7: Changing between insulins:

Going From (below) to (right)	R	NPH	Basal insulin analog	Meal time Analog insulin
R	----	-------	------	1 unit/1 units
NPH	------	------	Consolidate dose and give as a single injection once daily	
Basal insulin analog	------	Give half dose before B and half before D	-------	_____
Meal time analog insulin	1 unit to 1 unit	_____	____	--------

Case Study:

Jeffrey has type 2 diabetes and has been taking metformin 1000 mg bid and Glipizide 10 mg bid for the last 3 years. He has seen his A1c climb to 9.4%. He is having knee trouble and is hoping to be able to have knee surgery in the next 3 months His surgeon will not allow him to have surgery until his A1c is at least below 8.0%. He is willing to take insulin and he is motivated to get his readings down. He weighs 100 kg. He will also work on his eating schedule and non-weight bearing physical activity in addition to medication changes.

Sample ways to start insulin in this patient:

NPH—total dose 0.3 units/kg/day. When NPH is used as a basal insulin, it is most commonly dosed 2-3 times per day. Twice daily dosing is best, before breakfast and before dinner. We will ask him how he distributes his calories. While this insulin is intended to cover his basal insulin needs we do

need to make sure he is eating around the time of the peak of his insulin action. Let's say he eats 3 meals per day—all about the same calorie and carb amount and he eats breakfast at 7:30 am, lunch at noon and dinner at 5:30 pm. We will give him a total of 30 units/day and we will divide it equally between the am and pm dose. He can take his am dose just before breakfast (although it is not really covering his breakfast) and then he can try the second dose at dinner. The gap between breakfast and dinner should be covered but the time from dinner to breakfast is a bit longer and we will need to see if the dose and timing of his second injection gets him to goal. If not, we can increase the dose of the second injection or move it a bit later in the evening.

Analog basal insulin- if we choose an analog basal insulin we will also start with 30 units per day. The timing of the dose is less critical since it is very slow acting. I would typically ask the patient what time of the day is best for them and what time can they get access to insulin reliably.

I recommend that the very **first injection be given in the office**. If you have access to samples of insulin you can use the sample to teach how and where to give the insulin. This practice can also help to diffuse patient stress and diminish hesitancy before the first injection. This also helps you to know that your patient is able to take an injection and you can provide feedback on the technique. If you do not have access to samples you can write a prescription, ask the patient to pick it up and then bring them back into the office to take the first shot. Further, by having the patient take the first injection of basal insulin in the office the provider is communicating that this medication can be taken without food, and does not impair any ability to drive, as most patients drive home upon leaving the doctor's office.

Once they have conquered the first injection you will want to lay out the plan for dosing and make sure the patient knows how to monitor their response to the insulin dose. If they are on a basal insulin analog, please instruct the patient to check the glucose fasting in the morning as this is the best predictor of adequate response. If the patient is on NPH then they will need to check at least twice daily just before an injection to determine if the dose prior was adequate. I usually let the patient stay one week on this initial dose in order to allow them to see how they respond to the insulin and gain trust and familiarity with how they will respond to insulin. Since you are doing weight based doing you should see an improvement in the glucose readings.

How to titrate basal insulin doses:

Once they have the first week insulin regimen down, we teach the patient how to titrate their insulin dose. This is important as most patients will need more insulin to get to goal glucose levels. There are many evidence-based titration approaches that work. Patient driven titrations have proven to be more effective that provider-driven titrations (4).

Table 8: Sample insulin titration schedule

1 unit per day

2 units q 2-3 days

Measure	**ADA/EASD (4)**
Algorithm	
Titration	2 Units Q 3 days
Target FBG, mg/dL	70-130
Target HbA_{1c}, %	<7.0

When patients titrate their own insulin, it is recommended that physicians provide some parameters for titration. This actually will help many patients know that it is ok to keep titrating within the parameters that you specified. It is very important to emphasize to patients should monitor the am glucose and to titrate slowly and consistently. I recommend that you also provide a ceiling dose for which the titration would stop if goal glucose is not achieved. This provides a safety net to prevent "overbasalization" and lets the patient know the range of insulin dosing you are comfortable with them managing. We usually ask the patient to stop when one of the following occurs: the patient reaches 0.5 units/kg, the morning blood glucose at the target range you desire (example 100-130 mg/dl) when the patient experiences a hypoglycemic episode (then we ask them to reduce 2 titrations and call us)

When is it appropriate to use premixed insulin?

Premixed insulin combines a short-acting human insulin or a rapid-acting analog with an intermediate-acting insulin (NPH, or protaminated rapid acting analog). The premixed insulin is named by the percent long acting insulin and then the percent short acting insulin. For example, if a person was taking 40 units of HumuLIN ® 70/30 (this would be 70% or 28 units of NPH and 12 units of Regular insulin. If the person was taking NovoLOG ® 70/30 they would be taking 28 units of protaminated NovoLOG® and 12 units of NovoLOG®.

Premixed insulin allows a person to take fewer injections compared to injecting both basal bolus and short acting insulin separately. Many patients are happy with fewer injections. However, premixed insulin can be associated with hypoglycemia if meal time or carb amount is changed. This often

results in an inflexible daily and meal schedule in order to prevent hypoglycemic episodes. If a patient has a regular, spaced meal schedule this regimen can be very effective and easy for the patient.

Premixed insulin can be successfully used in people who have stable and reliable daily schedules with fixed meal times and fixed carbohydrate content. Premixed insulin can also be used for someone who has poor control but who is not motivated to engage in 3 or more shots per day. Premixed insulins are best used in patients who have a more relaxed glucose goal and HgA1c target ($\geq$ 8%). For patients who have very high A1c levels (>12%) and who want to limit the number of injections this may be a good first step for insulin use. There are a couple of schedules for premixed insulin. If a person distributes calories throughout the day equally- many providers would start with 2/3 of the total daily dose in the morning and 1/3 in the evening. Typically, these are given before breakfast and dinner. However, many Americans eat half of their calories after 6 pm—in this case we will provide ½ of the total daily dose before breakfast and ½ before dinner.

Maria is a 54 year old female with 12 years of type 2 diabetes mellitus. She was on metformin for and glipizide initially. She had good control for about 8 years and then basal insulin was added 3 years ago. She had taken a total of 52 units of glargine per day. She had some gaps in her medical insurance for the past 15 months. She returns today to get established for care. Her A1c is now 12.6% and her random in office glucose is 324 mg/dl. She felt better when her glucose was in control and would like to return to treatment.

How would you approach your treatment for Maria?

Maria is motivated to get better control. Her A1c is very high so insulin is definitely needed as part of her treatment—at minimum to reduce glucose toxicity. If you were going to start premixed insulin you could choose a human premix insulin. She spreads her calories throughout the day and does not eat a lot at night. She weighs 100 kgs. If you chose a weight-based approach to you start with a total of 0.5 units/kg day. This would be 50 units—she can take 30 units in the am and 20 units in the pm. Both doses should be given before the respective meal and she will need to check her glucose at least 2 times daily before each injection. Since this is a new treatment for her this would be an ideal time to offer diabetes education again to review therapeutic lifestyle change and to assist with the initiation and titration of her insulin. While it is not the most pressing issue now restarting metformin is a good idea if her renal function is ok.

When to use meal time insulin?

If a patient achieves fasting glucose goals but the A1c is still elevated, or if the patient is still experiencing post-meal hyperglycemia, then attention should be shifted to address meal time glucose excursions. There are a number of options to treat postprandial hyperglycemia, including oral agents

(DPP-4 inhibitors, SGLT-2 inhibitors, glinides or alpha-glucosidase inhibitors), and injectable agents (GLP-1 receptor analogs, human regular insulin or rapid acting insulin analogs).

Before starting mealtime insulin, it is important to make sure the patient is not getting too much basal insulin (overbasalization). If the basal insulin is covering some of the rise associated with mealtime ingestion, then the patient will be prone to more hypoglycemia once mealtime insulin is added.

Table 9: Factors suggestion that the patient is getting too much basal insulin

Factors suggesting "overbasalization"
More than 1 unit/kg daily of basal insulin
Fasting glucose variability (wide range of first am glucose readings without explanation
Hypoglycemia that occurs overnight or between meals
Hypoglycemia that occurs if a meal is missed

Daniel has had type 2 diabetes for 8 years. He never had much luck getting control. He works swing shifts at Amazon and he eats many meals out. He occasional checks his glucose but feel that he knows what his glucose is based on "how he feels". He was on metformin 1000 mg bid, glyburide 20 mg daily, alogliptin 25 mg daily, insulin glargine 120 units per day at night. Despite all of these meds his Ac is 8.4%.

What do we do next for Daniel?

For Daniel, I would be careful about continuing to add medications until we have a better handle on what he is current actually taking and what his glucose profile looks like. We asked him to provide some glucose readings so we can help decide what modifications are needed. We agreed that he would provide 2 days of food logs and one week of glucose testing twice a day and anytime he felt bad. He returns the following week with these readings:

Friday	Saturday	Sunday	Monday	Tuesday	Wednesday	Thursday
56	248	80	62	194	112	64

180						
96	212		240		170	

What do you notice about the glucose profile?

Daniel is having lows first thing in the morning. In fact, he denies feeling bad for any of them. This means he is having more lows that he was aware of. He does endorse finding himself much hungrier in the morning than normal. You will also notice that he has wide variations in his glucose in the morning. This might mean that on the mornings he is running higher –that he might have dropped low in the middle of the night and he rebounded in response to a nocturnal low and woke up with a high reading.

His food logs were incomplete but he reported drinking alcohol on Saturday and Wednesday night (he is in a bowling league). Because he is having frequent hypoglycemia I would recommend a couple of actions. Please remind him to be moderate with alcohol use. If he is going to drink he probably needs to eat a snack before he goes to sleep. While alcohol is a carbohydrate once absorbed the liver cannot perform gluconeogenesis and process alcohol at the same time. So, while the body is processing alcohol his gluconeogenesis overnight will be suppressed. The other action is he needs insulin reduced. When a person has “hypoglycemic Unawareness” or they do not feel their lows –this is a very dangerous situation. The safest way to treat this to reduce medications so to prevent all hypoglycemic events to allow the bodies defense systems to hypoglycemia to “reboot”. For Daniel I will reduce his insulin by at least 20%. Personally, I would have reduced his glargine to 90 units. Then I would ask him to send in am readings weekly to confirm that we stopped the lows.

This is just half of the remedy. Daniel was surprised that his readings were actually a bit better and more even with less insulin. He also found out that the hungriness in the morning was indeed a sign that he was dropping as he has not been as hungry in the morning. Once we got his morning glucose stabilized to readings between 100-150 most mornings—we asked him to stop checking in the morning and start checking about 90 minutes after dinner. He was surprised to see that many of his post dinner readings were well above 200. This reflects that he is not getting adequate meal time coverage. When we review his meds—he is taking both Glyburide and Alogliptin that are intended to help cover his meals. I would recommend that you stop the Alogliptin- it is the weakest of his meds, then you can probably reduce or stop his Glyburide. While this is clearly not working well enough you will see some glucose rise if nothing is used in its place. For Daniel I would prefer to start a GLP-1RA. It is long acting, focuses on the post meal readings and it much less likely to drop him low. Further, a common side effect of the GLP-1RA is appetite suppression and it may help with his snacking and will help him to lose weight.

So, for him I would stop Alogliptin, reduce Glyburide to 10 mg and start Liraglutide (Victoza) 0.6 mg daily—we would titrate liraglutide every 2 weeks to try to get to max dose of 1.8 mg daily. Often this will allow the Glyburide to be stopped completely and maybe even a further reduction of basal insulin.

After 12 weeks he is taking metformin 1000 mg bid, Glargine 60 units daily and Liraglutide 1.8 mg daily. He is not having any lows and his A1c has improved to 7.4%. He is feeling better and wants to work on making dietary changes to get below 7.0%. He never thought this was possible and now he can see the goal within his reach.

How do I start meal-time insulin?

There are two important questions to ask when starting mealtime insulin.

How many meals do you plan to cover, and how do you plan to choose a dose?

The goal of using mealtime insulin is to replicate physiologic insulin release at meals. In some cases, the patient takes an injection of mealtime insulin with each meal. The typical starting dose is 0.1 unit/kg per meal. If the patient has an elevated A1c > 8% or morning hyperglycemia > 160 mg/dl then the dose of basal insulin can stay constant in addition to the mealtime dose. If the patient is well controlled in the am, the provider may need to subtract 10% of the basal dose to prevent hypoglycemia. This will prevent or reduce the hypoglycemia risk when the second insulin is added.

How many meals to cover:

Recent studies support the principle of a **basal plus 1 insulin** schedule. In this scenario the patient continues basal insulin but only takes mealtime insulin with the largest meal of the day. For most people in the United States this corresponds to the evening meal, or dinner. When using a basal plus 1 regimen the mealtime dose may be bigger at 0.1-0.2 units per kg. (10). The ADA Standards of Care 2018 recommends, when mealtime insulin is warranted in addition to basal insulin, starting with one dose before the biggest meal of the day, then re-evaluating in 3 months and intensifying therapy if A1c is still not optimally controlled. (4)

How do I pick a starting dose of meal time insulin?

There are a few ways to pick the starting dose. The provider can: 1. use the guidelines above, 2. make the dose of insulin match the food content—this is through carb counting, 3. You can estimate insulin dose based upon size of the meal.

Insulin Stewardship

In type 1 diabetes many patients are instructed to carbohydrate count in order to match the current dose of insulin to the food about to be ingested. This works well for people who are able to master this skill. However, a more generalized dosing regimen may be more practical for the majority of people with type 2 diabetes.

The meal-by-meal adjusting of insulin dose is beyond the scope of this monograph. It only makes sense if a person is striving for very tight control and has a high degree of training and experience based on observation of how they respond to different variables at different times. Certified diabetes educators can be helpful in this circumstance.

When should I use a correction scale?

“Sliding scale” insulin has historically been used in the hospital to limit times of prolonged hyperglycemia. When sliding scale insulin is used, as the only treatment of hyperglycemia or it is used for prolonged periods of time, it has proven to be an ineffective treatment. (30) The term “sliding scale” has been replaced by “correction scale” to identify a different way to use insulin when current insulin needs are unknown.

Correction scale insulin may be used alone for initial treatment if the person’s insulin needs are unknown. However, it is intended that after 24 hours that the “correction insulin” needed in previous day would be converted to scheduled insulin in next day that will prevent the need for ongoing “sliding scale insulin”. Correction scale insulin is used in addition to scheduled mealtime insulin to supplement the current meal dose and correct a hyperglycemic reading in specific situations. Correction scales are more effective if the physician routinely reviews the need for correction. And, if needed regularly, this dose is then folded into the scheduled insulin dose.

Most correction scales can be individualized in people who are already on chronic insulin. To make a specific correction scale the physician can use the rule of 1500 for type 2 diabetes. Take the total daily dose of all insulin injections and then divide this into the constant of 1500. This will estimate the amount of glucose reduction for 1 unit of insulin. (29)

Correction scale example:

Jonathan is on NPH insulin 20 units twice a day (7 am and 6 pm). He also takes Regular insulin 10 units before breakfast and 10 units before dinner. He finds that he wants to be able to adjust his insulin dose based upon his glucose before dinner. To be able to calculate a correction scale we will do the following steps:

1. Add up all scheduled insulin to get total daily dose: (18 units NPH x 2)+ (7 units R x 2)= 50 units total daily dose

2. Take the total daily dose and divide into 1500 (1500/50) =30
3. The result is 30. This means that each unit of insulin given will lower the glucose by 30 mg/dl.
4. Next you want to develop the interval. This could easily be 30 or many centers use a fixed ratio of 50 mg/dl. I will show you both below.

Sample Correction scale based on correction factor of 30 and intervals of 30.

Glucose level	Insulin correction dose	
Below 150 mg/dl	No additional correction	
150-180	+1	
181-210	+2	
211-240	+3	
241-270	+4	
➢ 270	+5	

Sample Correction scale based on correction factor of 30 and intervals of 50. (we rounded up as there are nearly two 30s in 50)

Glucose level	Insulin correction dose	
Below 150 mg/dl	No additional correction	
150-199	+2	
200-249	+4	
250-299	+6	
>300	+8	

As you can see the scales vary based upon what intervals you decide. For type 2 diabetes we will typically round up if there is needed improvement in glucose control. Conversely, we will typically round down if the person has type 1 or if the person with type 2 diabetes is already well controlled.

Examples:

Two examples are listed below:

A person presents to the hospital with community acquired pneumonia. He has no history of diabetes but he is hyperglycemic at the time of admission with a glucose of 212 mg/dl and no history of diabetes. Because this patient is acutely ill, sliding scale insulin is started using 2 units for every 50 mg/dl above 150 mg/dl. After the first 24 hours he needs 20 units of insulin from the scale. Using the correction scale correctly the physician, on day 2, takes the total of the previous correction scale

insulin from day 1 and converts it to scheduled insulin. Typically, half the insulin would be once daily basal insulin (10 units) or twice daily NPH (5 units BID) and the remaining scale insulin would be used to cover the meal content, divided equally among the meals (about 3 units per meal). This is repeated daily until the correction insulin need is negligible.

A person with type 2 diabetes is on 40 units of Glargine each evening and 6 units of lispro with each meal. She has been checking her glucose regularly and her fasting glucose is at goal. However, she is routinely high at lunch and dinner. She corrects for the high readings with an additional 4 units at these meals. To use correction properly, the 8 additional units of insulin should be added to the scheduled mealtime dose. Adding 3 units with each meal to a total of 7 units would allow for better coverage of the meals.

Dangerous Combinations:

While insulin can be very safe to use there are some combinations that should be avoided or approached with caution. The following combinations substantially increase the risk for hypoglycemia (be sure you understand ***why*** each is risky)

1. Pre-mixed insulin with meal time insulin
2. Pre-mixed insulin with basal analog insulin
3. Combining LIN insulins (human short acting) with LOG insulins (rapid acting analogs)
4. Any insulin product with sulfonylureas
5. Dosing Regular insulin closer than 4 hours apart
6. Dosing NPH insulin closer than 8 hours apart
7. Dosing Regular insulin at bedtime or without a meal

When to de-intensify?

We have also learned that we strive to get better control early in the disease as we have many years to protect. Conversely, we can loosen our targets in older adults, those with limited life expectancy and those with high risk of hypoglycemia or those with substantial diabetes related complications. The ADA recommends that you take these factors into account when setting glucose and A1c targets. For example, a young person newly diagnosed with type 2 diabetes who has no complications and is motivated to get better control could have an A1c goal of less than 6.5%. An older patient with a long standing history of diabetes, and who now has advanced renal disease we may set a goal of 8%-8.5%. Most people will fall in between these two scenarios.

Insulin Stewardship

Writing insulin prescriptions:

The examples below are intended to show best practices in writing prescriptions of insulin and supplies. Estimating the volume to be used each month will help you to write an accurate prescription. To make this calculation it is best to base this on the daily dose:

Each vial of U100 insulin will hold 1000 units. Divided by a typical month that has 30 days, that leaves 33 units per day. To allow for different numbers of days per month, estimate 1 vial per month.

If a person typically takes 40 units per day of insulin by vial, write for 2 vials. (Pharmacies will fill 1 vial or 2 vials depending on the daily dose and the days supply allowed by the plan). When prescribing vials insulin syringes will also be needed. The current sizes for insulin syringes include 0.3 ml, 0.5 ml and 1 ml which will allow for an injection of 30 units, 50 units and 100 units respectively.

Insulin pens hold 300 units of insulin and typically come in a box of 5 pens for a total of 1500 units. This means that a person who uses 45 units per day of insulin will use one box of 5 pens per month. (Please remind patients that most pens are good for use 28 days after first use before they should be replaced) When writing for insulin pens the prescriber will also need to write for pen needles. Pen needles come in regular (8 mm), short (5 mm), Mini (4mm) and nano (3 mm). Recent evidence has shown that all needle lengths are equally effective across the spectrum of people with diabetes (30).

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Appendix : Supplemental Materials

Clinical: How Do I Use Insulin Safely and Effectively?

Best practices in insulin use, titration, and injection techniques

Summary of best practices from above:

1. Start basal insulin at no less than 0.2 units/kg/day
2. Have the patient take the first shot in the office.
3. Let the patient titrate insulin dose between visits.
4. Provide a projected ceiling dose for the patient to stop titrating insulin until next appointment.

Troubleshooting Insulin Regimens

Table 11. Out of Range Blood Glucose Levels and Actions for Insulin Dose Adjustment. (10)

Out of Range	**What to Adjust**
Fasting	Evening basal or NPH
Before Lunch	Morning Bolus
Before Dinner	Always make sure adequate basal dose. If on NPH, then look at morning dose; otherwise lunch bolus.
After meals	Bolus, Exercise/physical activity, and carbohydrate consumption
Before Bed	Dinner bolus and previous day's basal dose or Dinner NPH or 70/30
During Night	Bedtime insulin (may need to check at 2 AM) or Dinner NPH or 70/30

Injection technique instructions

Supplies:

- Insulin Vial/ Pen

Insulin Stewardship

- Appropriate Insulin Syringe for vials/ Appropriate Needle for Pens
- Alcohol swab
- Gauze
- Sharps Container

Preparation

- Wash your hands with soap and water
- Check insulin vial or pen to make sure the right type of insulin are selected if you are using more than one type of insulin
- Do not use your insulin if it has past the expiration date printed on the package or for more than certain amount of days after insulin has been opened or left at room temperature (check above of the exact date and recommended storage conditions for each specific insulin)

Vials:

1. For new vials, remove the plastic protective cap
2. Wipe the rubber stopper with an alcohol swab
3. Hold the insulin syringe with the needle pointing up and pull down the syringe plunger until the black tip reaches the mark for the number of units you will need to inject
4. Push the needle through the rubber stopper of the vial
5. Push the plunger all the way in to put air into the vial
6. Turn the vial and syringe upside down and slowly pull the plunger down until the black tip pasts couple units of the dose you need
7. Tap the syringe for all the air bubbles to rise to the top
8. Slowly push the plunger up to remove the excess air bubble and the tip reaches your correct dose
9. Pull the syringe out of the vial's rubber stopper
10. Choose your injection site (Stomach area, buttocks, upper legs or upper arms) and rotate injection site for each injection
11. Wipe the injection site with an alcohol swab and allow it to dry before you administer your dose
12. Gently pinch up skin to make a fold with your hand and inject the needle into your skin
13. Push down on the plunger until all the insulin are administered and slowly count to 5 to 6 seconds (depending on insulin, ask your diabetic education or pharmacist for more information) with the needle in your skin for complete absorption
14. Pull the needle out of your skin
15. Discard the syringe into a sharps container right away

Pen Preparation

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1. Remove pen cap and wipe the rubber seal with an alcohol swab
2. Check the color of the insulin and ensure it's the appropriate color
3. With a new needle, remove the paper tab from the pen needle
4. Screw the needle onto the pen until it is tight
5. Depending on the type of pen needle, pull or screw off the outer needle cover (ask your diabetic educator or pharmacist for more details); DO NOT throw it away
6. Remove the inner needle cover to expose the needle and discard the inner needle cover

Pen Priming

7. Each injection require priming to ensure you receive the accurate dose
8. Turn the dose knob to select 2 units
9. Hold the pen with the needle pointing up and gently tap the cartridge holder for air bubbles to rise to the top
10. Press and hold the dose knob and count slowly to 5, you should see insulin at the tip of the needle
    a. If you do not see insulin, repeat all the priming step, no more than 4 times
    b. Iif you still do not see insulin, then change the needle and repeat the priming sets

Administer Insulin

11. Turn the dose knob to select your insulin dose and double check the number in the dose window to ensure the correct dose has been dialed
12. Choose your injection site (Stomach area, buttocks, upper legs or upper arms) and rotate injection site for each injection
13. Wipe the injection site with an alcohol swab and allow it dry before you administer your dose
14. Gently pinch up skin to make a fold with your hand and inject the needle into your skin
15. Push and hold the dose knob until the dose counter shows "0" and continue to keep the needle in your skin and slowly count to 5 to 6 seconds (depending on insulin, ask your diabetic education or pharmacist for more information) to ensure accurate dose has been administered
16. Pull the needle out of your skin
17. Carefully cap the outer needle cover to the needle and unscrew the capped needle and discard into sharps container
18. Replace the insulin pen cap by pushing straight onto the insulin pen

Insulin Stewardship

Supplemental Patient handout

Step by step: Insulin Injection with Insulin Vial	
Supplies	· Insulin Vial · Insulin Syringe · 2 Alcohol Swabs or use rubbing alcohol (isopropyl alcohol) with cotton ball · Sharps Container · Gauze (Optional)
Prepare	1. Remove plastic protective cap (New vials) 2. Wipe the vial rubber stopper with alcohol swab 3. Hold the insulin syringe with the needle pointing up and pull down the syringe plunger until the black tip reaches the mark for the number of units you will need to inject 4. Push the needle through the rubber stopper of the vial 5. Push the plunger all the way in to put air into the vial 6. Turn the vial and syringe upside down and slowly pull the plunger down until the black tip pasts couple units of the dose you need 7. Tap the syringe for all the air bubbles to rise to the top 8. Slowly push the plunger up to remove the excess air bubble and the tip reaches your correct dose 9. Pull the syringe out of the vial's rubber stopper

Insulin Stewardship

Inject	1. Choose your injection site (Stomach area, buttocks, upper legs or upper arms); to prevent scar tissue, remember to rotate injection site for each injection 2. Wipe the injection site with an alcohol swab and allow it dry before you administer your dose 3. Gently pinch up skin to make a fold with your hand and inject the needle into your skin 4. Push down on the plunger until all the insulin are administered and slowly count to 5 or 6 seconds (depending on insulin, ask your diabetic education or pharmacist for more information) with the needle in your skin for complete absorption 5. Pull the syringe out of your skin
Discard	1. Discard the syringe into sharps container right away

Step by step: Insulin Injection with Insulin Pen	
Supplies	· Insulin Pens · Insulin Needles · 2 Alcohol Swabs or use rubbing alcohol (isopropyl alcohol) with cotton ball · Sharps Container · Gauze (Optional)
Prepare	1. Remove pen cap and wipe the rubber seal with an alcohol swab 2. Check the color of the insulin and ensure it is the appropriate color 3. With a new needle, remove the paper tab from the pen needle 4. Screw the needle onto the pen until it is tight 5. Depending on the type of pen needle, pull or screw off the outer needle cover (ask your diabetic educator or pharmacist for more details); KEEP the outer needle cover 6. Remove the inner needle cover to expose the needle and discard the inner needle cover

Insulin Stewardship

Prime	1. Each injection requires priming to ensure you receive the accurate dose
	2. Turn the dose knob to select 2 units
	3. Hold the pen with the needle pointing up and gently tap the cartridge holder for air bubbles to rise to the top
	4. Press and hold the dose knob and count slowly to 5, you should see insulin at the tip of the needle
	    1. If you do not see insulin, repeat all the priming step, no more than 4 times
	        1. If you still do not see insulin after repeating step a for more than 4 times, then change the needle and repeat the priming steps

Inject	1. Turn the dose knob to select your insulin dose and double check the number in the dose window to ensure the correct dose has been dialed 2. Choose your injection site (Stomach area, buttocks, upper legs or upper arms) and rotate injection site for each injection to prevent scar tissues 3. Wipe the injection site with an alcohol swab and allow it dry before you inject your dose 4. Gently pinch up skin to make a fold with your hand and inject the needle into your skin 5. Push and hold the dose knob until the dose counter shows “0” and continue to keep the needle in your skin and slowly count to 5 or 6 seconds (depending on insulin, ask your diabetic education or pharmacist for more information) to ensure accurate dose has been administered 6. Pull the needle out of your skin
Dispose	1. Carefully cap the outer needle cover to the needle, unscrew the capped needle, and discard into sharps container 2. Replace the insulin pen cap by pushing straight onto the insulin pen