

---

## 8. Insulins and New Injectables

---

---

### *When does a patient with type 2 diabetes need to be started on insulin?*

---

Indications for insulin in type 2 diabetes are listed below:

- Presence of severe symptoms (such as polydipsia, polyuria, or weight loss), marked hyperglycemia (fasting plasma glucose level >350 mg/dL), or ketonuria at diagnosis or during the course of the disease
- Diabetic ketoacidosis or a hyperosmolar state
- Ineffectiveness of oral agents alone to maintain glucose levels within the patient's target range
- If oral agents are contraindicated
- During pregnancy (and, ideally, prior to conception)

---

### *What do I need to teach my patients about insulin?*

---

Some essential points to share with patients about insulin follow:

- In type 1 diabetes, insulin is necessary to sustain life.
- Type 2 diabetes is a progressive disease, and insulin is part of the continuum of care for most patients. Taking insulin is not a sign of patient or provider failure or evidence that the diabetes is worse.
- Diabetes is not a “sugar problem” but a disease of absolute insulin deficiency (type 1) or relative insulin deficiency and insulin resistance (type 2). The injection or inhalation of insulin is the only way to treat type 1 diabetes and the most natural and effective method for replacing this essential hormone

in type 2 diabetes that no longer responds to other treatments.

- Provide written information about the name of the insulin, the dosage, the timing with food and exercise, peak times, and possible drug interactions.
- Hypoglycemia prevention, symptoms, and treatment; managing insulin dosing during an acute illness; and the need for diabetes identification are essential components of education for patients taking insulin.
- Discuss a plan for contacting you about hypoglycemia (e.g., any severe episodes, more than two events per week) and hyperglycemia.
- Food intake and activity may need to be adjusted to prevent weight gain.
- Discuss how to handle forgotten and missed doses.
- Inform patients that exercise increases insulin sensitivity and, hence, that adjustments to insulin are often required when exercise is undertaken.

## Types of Insulin

The goal of insulin therapy is to mimic normal physiologic insulin secretion as closely as possible. Normal insulin consists of low levels of basal insulin secreted at all times to regulate hepatic glucose production overnight and between meals. At mealtimes, nutrient ingestion stimulates an acute, first-phase secretion of insulin followed by a second secretion phase that lasts for as long as blood glucose levels are elevated. Mealtime insulin dynamics inhibit hepatic glucose production and promote glucose disposal, maintaining glucose levels within the normal range until they return to pre-meal levels. As this occurs, insulin secretion also decreases to basal concentrations.

Insulins available for clinical use can be categorized as basal insulins or prandial insulins. Insulins used for basal requirements are long-acting and intermediate-acting insulins. These include insulin glargine, insulin detemir, and neutral protamine Hagedorn (NPH) insulin. (The latter is an intermediate-acting insulin that has both basal and prandial characteristics in that it peaks about 4–8 hours after administration.) Insulins used for prandial requirements are the rapid-acting insulin analogues (insulin lispro, insulin aspart, and insulin glulisine) and short-acting regular insulin.

Premixed insulins can be used to provide both basal and prandial requirements. Premixed insulins are either human insulin mixtures (containing NPH and regular insulin) or insulin analogue mixtures. Premixed insulins include those listed below.

- 70/30 insulin (70% NPH and 30% regular)
- 50/50 insulin (50% NPH and 50% regular)
- Humalog mix 75/25—contains 75% neutral protamine lispro (NPL), which has similar pharmacokinetic properties to NPH insulin, and 25% lispro (Humalog)
- Humalog mix 50/50—contains 50% NPL and 50% lispro (Humalog)
- NovoLog mix 70/30—contains 70% neutral protamine aspart, which has similar pharmacokinetic properties to NPH insulin, and 30% aspart (NovoLog)

Insulin preparations that are currently available in the United States are shown in **Table 8-1**. Insulins are either recombinant human insulin products or insulin analogues. Pork and beef insulins are no longer sold in the United States. The rapid-acting analogues are generally preferred to regular insulin because their pharmacodynamic properties are more physiologic and are associated with less intersite and intrasite variability in absorption (between different sites and at the same site when injected on different days). Similarly, basal insulin analogues are less variable than NPH insulin.

In January 2006, the U.S. Food and Drug Administration (FDA) approved a powdered insulin formulation for administration via the pulmonary route. The pharmacokinetics of insulin administered via inhalation are similar to those of the rapid-acting insulin analogues, and thus this formulation is suitable for prandial use. Additionally, clinical trials have shown that inhaled insulin is as effective as subcutaneously administered insulin, and many patients prefer it. Inhaled insulin use is associated with a clinically insignificant increase in the titer of nonneutralizing insulin antibodies but no significant change in pulmonary function when compared with subcutaneously administered insulin. However, pulmonary function testing should be performed prior to starting a patient on inhaled insulin, 6 months after starting the insulin, and at least annually thereafter. Inhaled insulin is contraindicated in patients with chronic obstructive pulmonary disease and in those who smoke or who have smoked within 6 months. It is not contraindicated in patients with stable asthma.

## Insulin Regimens for Type 2 Diabetes

In patients with type 2 diabetes, the addition of a basal insulin is often the first step in initiating insulin treatment. In this situation, oral agents (sensitizers and/or secretagogues) are usually continued at the same dosage.

If postprandial glucose levels remain elevated despite normalization of fasting glucose levels, the addition of a prandial insulin is recommended. Once a patient with type 2 diabetes requires prandial insulin, oral insulin secretagogues can be stopped, but insulin sensitizers should be continued in obese, insulin-resistant persons.

### Basal Insulin Only

The early use of insulin when oral agents are ineffective can prevent months or years of ongoing suboptimal blood glucose control. In the

**Table 8-1. Currently Available Insulin Preparations**

Insulin Class†‡	Pharmacodynamic Characteristics*		
	Onset	Peak	Duration
Rapid-acting (insulin analogues lispro, aspart, glulisine)	≤30 minutes	0.5–3 hours	3–5 hours
Short-acting (human regular)	0.5–1 hour	2–5 hours	Up to 12 hours
Intermediate-acting (human NPH)	1.5–4 hours	4–12 hours	Up to 24 hours
Long-acting (insulin analogues glargine, detemir)	0.8–4 hours	Relatively peakless	Up to 24 hours
<i>Human insulin mixtures</i>			
70% NPH/30% regular	0.5–2 hours	2–12 hours	Up to 24 hours
50% NPH/50% regular	0.5–2 hours	2–5 hours	Up to 24 hours
<i>Analogue mixtures</i>			
75% lispro protamine/25% lispro	<15 minutes	1–2 hours	Up to 24 hours
50% lispro protamine/50% lispro	<15 minutes	1–2 hours	Up to 24 hours
70% aspart protamine/30% aspart	10–20 minutes	1–4 hours	Up to 24 hours

Note: The time course of action of each insulin may vary among persons or at different times in the same person. Because of this variation, the time periods indicated here should be considered general guidelines only.

\*Blood glucose-lowering effect.

†Preparations vary within class. Please see package inserts for specific pharmacodynamic data.

‡Inhaled insulin powder (Exubera, Pfizer) has been omitted because it has been withdrawn from the market and will no longer be available after January 2008.

Treat-to-Target study, the addition of nighttime basal insulin to oral agents lowered hemoglobin A1C values from 8.6% to 7% in approximately 10 weeks. Moreover, the addition of basal insulin is more cost effective than the addition of a third oral agent.

- Use NPH, glargine, or detemir insulin at bedtime.
- Begin with a dosage of 10 U or 0.1 U/kg.
- Titrate the basal insulin dosage every 3 to 5 days until the fasting glucose level is at goal (usually <120 mg/dL) using the algorithm in **Table 8-2**.
- Continue oral medications (insulin sensitizers and secretagogues) at the same dosage initially.

### Premixed Insulin at Supper

A single daily injection of insulin is indicated if fasting glucose and post-supper glucose levels

are elevated. Premixed analogues are the preferred type of insulin for this regimen.

- Starting dosage: 10 U or 0.1 U/kg
- Follow a general approach to adjusting insulin dosage in diabetes patients (**Table 8-3**), but ensure that the blood glucose level at bedtime does not drop below 100 mg/dL.
- If bedtime blood glucose goes below 100 mg/dL, the patient should eat a bedtime snack. If blood glucose is persistently below 100 mg/dL at bedtime, the insulin dosage should be adjusted.

### Combination Insulin Two or Three Times Daily

If a patient is taking basal insulin at night and the blood glucose level is elevated at lunch and dinner, the basal insulin alone is not sufficient. In this situation, combinations of basal and

Table 8-2. Titrating Basal Insulin\*

If Fasting Blood Glucose Level Is:	Increase Insulin Dose by:
121–140 mg/dL	2 U
141–160 mg/dL	4 U
161–180 mg/dL	6 U
>180 mg/dL	8 U

\*Starting dose: 10 U or 0.1 U/kg body weight. Titration should stop if blood glucose drops below 70 mg/dL during the night.

prandial insulin should be injected twice (or, occasionally, three times) daily. Typically, a combination of prandial and intermediate (basal) insulin—either premixed or mixed by the patient—is injected before breakfast and before dinner. In patients with nocturnal hypoglycemia, the intermediate-acting insulin should be given at bedtime rather than before dinner, necessitating a third injection and ruling out the use of a premixed insulin. The success of this insulin regimen depends on the consistent intake of carbohydrates at meals and snacks.

- Starting dosage of insulin is approximately 0.6 U/kg daily but may be higher in obese patients because of their increased insulin resistance.
- Traditionally, the dosage of the premixed insulin is divided to provide two thirds of the insulin in the morning and one third in the evening before meals. If the fixed-dosage premixed insulin is not effective, patients may need to mix the individual components of these insulins in individualized combinations (split-mix insulin regimen).
- When split-mix insulin regimens are used, the ratios of prandial and basal insulin are usually initiated as follows:
  - Two thirds of the morning dosage is given as basal insulin (NPH).
  - One third of the morning dosage is given as prandial insulin (rapid-acting analogue or regular insulin).
  - The evening dosage of insulin is split evenly between prandial (rapid-acting or

regular) and basal insulin (NPH). The basal insulin may be given either before supper or at bedtime.

- The insulin dosage is titrated based on blood glucose levels before meals and at bedtime as follows (with corresponding dosage decreases if glucose levels are below target):
  - If fasting glucose is elevated, increase pre-supper (or bedtime) basal insulin.
  - If bedtime glucose is elevated, increase pre-supper prandial insulin.
  - If pre-lunch glucose is elevated, increase morning prandial insulin.
  - If pre-dinner glucose is elevated, increase morning basal insulin.
- Insulin secretagogues should be stopped once regimens containing prandial insulin are instituted. Insulin sensitizers should be continued in obese, insulin-resistant patients.

### Basal-Bolus Regimens

This is the most “physiologic” of the insulin regimens and comprises prandial insulin (“bolus”) given before each meal and basal insulin given once or twice daily. Although basal-bolus regimens require several injections daily (typically, four injections), they provide more dietary flexibility and allow patients to skip meals or change mealtimes. As with mixed insulin regimens, insulin secretagogues should be stopped when this regimen is begun, but insulin sensitizers may be continued.

- The long-acting insulins (glargine or detemir) are the most commonly used basal insulins in this regimen. The basal insulin is usually taken before bedtime but is sometimes taken before breakfast. Sometimes, it is taken twice daily. NPH insulin may also be used.
- Rapid-acting insulin analogues are recommended as the bolus/prandial insulin and are taken prior to each meal.

Table 8-3. General Approach to Adjusting Insulin Dosage in Diabetes

Problem	Cause	Solution
Fasting hyperglycemia	Not enough basal insulin at bedtime <i>OR</i> Too much basal insulin at bedtime (rebound from overnight hypoglycemia)	Check 3 am blood sugar. If high, increase basal insulin at bedtime (NPH or insulin glargine). If low, decrease basal insulin at bedtime.
Pre-lunch hyperglycemia	Not enough rapid acting insulin at breakfast <i>OR</i> Not enough morning NPH	Increase amount of rapid-acting insulin at breakfast—adjust correction dose or the insulin-to-carbohydrate ratio <i>OR</i> Increase morning NPH.
Pre-supper hyperglycemia	Not enough rapid-acting insulin at lunch <i>OR</i> Not enough morning NPH	Increase amount of rapid-acting insulin at lunch—adjust correction dose or the insulin-to-carbohydrate ratio <i>OR</i> Increase morning NPH.
Bedtime hyperglycemia	Not enough rapid-acting insulin at supper	Increase amount of rapid-acting insulin at supper—adjust correction dose or insulin-to-carbohydrate ratio.
Fasting or nocturnal hypoglycemia	Too much basal insulin at bedtime	Decrease bedtime NPH or insulin glargine.
Pre-lunch hypoglycemia	Too much rapid-acting insulin at breakfast <i>OR</i> Too much morning NPH	Decrease amount of rapid-acting insulin at breakfast <i>OR</i> Decrease morning NPH.
Pre-supper or bedtime hypoglycemia	Too much rapid-acting insulin at lunch or supper	Decrease amount of rapid-acting insulin at lunch or supper.

- Starting basal-bolus insulin dose allocation (**Table 8-4**): If glargine or detemir is used as the basal insulin, the starting dosage allocation is 50% of the total daily dose given as basal insulin and the other 50% as prandial insulin divided equally before meals. If NPH is used, 30% of the total daily dose should be given as NPH at bedtime and the other 70% divided equally before meals.
- Dosage adjustments based on blood glucose levels:
  - If post-breakfast or pre-lunch glucose is elevated, increase pre-breakfast prandial insulin.
  - If post-lunch or pre-supper glucose is elevated, increase pre-lunch prandial insulin.
  - If post-supper glucose is elevated, increase pre-supper prandial insulin.
  - If fasting glucose is elevated, increase basal insulin.
- When making dose adjustments based on blood glucose levels, it is important to remember that factors other than the amount of insulin given can affect these levels:
  - Variability in insulin absorption based on the anatomical site: Insulin is usually absorbed faster from abdominal sites than from the arms and legs. This faster absorption will result in an earlier peak and, possibly, a shorter duration of action.
  - Variability of insulin absorption from day to day and from person to person.
  - The carbohydrate content of a meal: The number of grams of carbohydrate consumed at a particular meal should be consistent from day to day unless the patient has learned how to adjust insulin doses based on carbohydrate counting.
  - The fat content of a meal: Fat content can affect the rate of digestion (i.e., high-fat meals take longer to digest), which can lead to a mismatch between the anticipated insulin action and the actual prandial blood glucose excursions.
  - The type of carbohydrates consumed: Simple carbohydrates (e.g., juice) will increase blood glucose levels faster than complex carbohydrates (e.g., whole grains and fruits) will.

Table 8-4. Basal-Bolus Insulin Dose Allocation\*

**If a long-acting insulin (glargine or detemir) is used as the basal insulin:**

- 50% rapid-acting or regular insulin (divided equally) before meals
- 50% long-acting insulin at bedtime

**If NPH is used as the basal insulin:**

Rapid-acting or regular insulin

- 30% before breakfast
- 20% before lunch
- 20% before dinner

30% NPH at bedtime

\*Percentages of doses are based on a percentage of the estimated total daily dose of insulin.

---

*What do I need to teach patients taking multiple daily insulin injections?*

---

Some information to share with patients who take multiple daily injections of insulin follows:

- Because of financial or other concerns, many patients choose to take one of their medications but not others. Stress the action and synergistic nature of insulins with oral medications or the need for both basal and bolus insulins.
- Basal and bolus insulin coverage is needed in order to mimic physiologic insulin secretion by the pancreas as closely as possible. Explain to patients which insulin provides which type of coverage.
- Although more intensive and requiring greater commitment and effort, multiple-injection insulin regimens provide greater flexibility and may result in improved glucose control. Multiple daily insulin regimens require more time to get insulin dosages balanced. Often, a process of trial and error is involved.
- Patients can use pattern management to adjust insulin dosages based on blood glucose levels.

## Pattern Management— Fine-Tuning Insulin Regimens

### Insulin Correction Dose Adjustments—Basic Carbohydrate Counting

Insulin correction doses are based on the pre-meal blood glucose level and assume consistent carbohydrate intake (basic carbohydrate counting) at each meal. The correction doses do not adjust for the amount of carbohydrates ingested at the meal. The optimal way to employ an insulin correction dose is to add or subtract insulin from the calculated dosage based on the pre-meal glucose level. (Table 8-5 presents an algorithm for adjusting prandial insulin.) You will need to provide individualized insulin dosage changes based on patients' activity levels and blood glucose readings.

### Advanced Carbohydrate Counting

In advanced carbohydrate counting, the prandial insulin dosage is adjusted based on the amount of carbohydrates eaten at the meal and the pre-meal glucose level. The degree of adjustment is determined by the patient's insulin-to-carbohydrate ratio, pre-meal blood glucose level, and pre-meal glucose target. Advanced carbohydrate counting is most commonly used when patients are taking a basal-bolus regimen or are using continuous subcutaneous insulin infusion pumps.

- The *insulin-to-carbohydrate ratio* is the amount of insulin required to “cover” the carbohydrates in a meal; for example, an insulin-to-carbohydrate ratio of 1:15 means that 1 U of insulin should be given for every 15 g of carbohydrates eaten.
- The *sensitivity factor* reflects the decrease in blood glucose caused by 1 U of insulin. A sensitivity factor of 1:50 means that 1 U of insulin given in the fasting or basal state would decrease the blood glucose level by 50 mg/dL.

Table 8-5. Example of an Algorithm for Adjustment of Prandial Insulin

Blood Glucose (mg/dL)	Prandial Insulin Adjustment
<60	Orange juice -33%
60-80	-25%
81-120	Usual dose
121-160	+10%
161-200	+25%
201-240	+33%
>240	+50%

For example, imagine that a patient's pre-meal glucose target is 100 mg/dL, his insulin-to-carbohydrate ratio is 1:15, and his sensitivity factor is 1:50. If the pre-meal glucose level is 150 mg/dL and the patient is going to eat 60 g of carbohydrates, he would inject 5 U of prandial insulin (4 U to cover the amount of carbohydrates eaten and 1 U because the pre-meal glucose is 50 mg/dL above target).

## Insulin Pump Therapy

Continuous subcutaneous insulin infusion (CSII) using an insulin pump is a form of intensive insulin therapy that is most commonly used in type 1 diabetes. However, it is becoming a viable treatment option for patients with type 2 diabetes who require insulin and want both greater lifestyle flexibility and improved glycemic control without taking multiple daily insulin injections.

CSII provides physiologic insulin replacement by delivering a continuous, preprogrammed basal rate along with bolus dosages for meals and to correct hyperglycemia. The amount of prandial insulin is usually determined by using insulin-to-carbohydrate ratios and prescribed algorithms for management of prandial glucose levels that are outside the target range.

CSII therapy enables more accurate titration of insulin delivery to match insulin needs, thereby minimizing blood glucose excursions

and reducing the likelihood of hypoglycemia. Because only rapid-acting insulins are used in insulin pumps, this approach features less day-to-day variation in insulin absorption and more predictable pharmacokinetics.

CSII therapy should be an option for any insulin-requiring patient who desires improved metabolic control and increased lifestyle flexibility. The pump does not, however, automatically make adjustments to the amount of insulin infused on the basis of sensor readings. Therefore, to successfully use CSII therapy, patients must meet the following requirements:

- Be capable and willing to monitor their blood glucose at least 4 to 6 times daily
- Know how to accurately count carbohydrates
- Be motivated to make frequent insulin dosage adjustments (e.g., before each meal) based on self-monitoring of blood glucose and carbohydrate intake
- Have the manual dexterity to operate the pump
- Have adequate insurance coverage or be able to afford the pump, associated supplies, and monitoring supplies

Patients who may benefit from CSII therapy include those who:

- Have not been able to achieve glycemic goals on an intensified insulin regimen of multiple daily injections
- Have unacceptable rates of hypoglycemia when following insulin injection regimens that combine intermediate or long-acting insulin (NPH, glargine) with prandial insulin
- Have a marked dawn phenomenon
- Have erratic lifestyles (travel, shift work)

Any patient considering the use of an insulin pump should be referred to a diabetologist or an endocrinologist who is experienced in this mode of therapy and who has the requisite staff to provide training and support.

## Helping Patients Make the Transition to Insulin

Initiation of insulin treatment in patients with type 2 diabetes is often delayed. Reasons for this are numerous but include reluctance on the part of both the physician and the patient to start insulin. Insulin is regarded by many patients as ineffective or used to treat only “severe diabetes.” Patients often feel that they are failures or feel angry, betrayed, anxious, or frightened when told they need insulin. Overcoming such barriers to insulin use—on the part of the physician as well as the patient—leads to more timely initiation of insulin and potentially improved glycemic control.

In patients taking two or more oral agents, the addition of basal insulin when fasting glucose levels are elevated can safely and easily be achieved in the primary care physician’s office. In other cases, a one-time referral to an endocrinologist or referral to a diabetes educator can facilitate the move to insulin.

---

### *How can I help my patients with type 2 diabetes make the decision to move to insulin?*

---

Prepare the patient from the time of diagnosis by discussing the progressive nature of type 2 diabetes and mentioning that insulin will likely be needed at some point. Never suggest that a patient may be able to avoid insulin as a “reward” for improving blood glucose levels or for being successful with a weight loss or exercise plan.

Assess the patient’s concerns regarding insulin so that appropriate information can be provided. Questions to ask may include:

- How satisfied are you with your current blood glucose levels?
- What do you need to know to consider insulin therapy?
- What is your biggest fear about insulin? What problems do you think you will encounter?

- What do you see as the biggest negative to starting insulin? Biggest positive?
- What support do you have for overcoming barriers?
- How faithful do you think you will be in taking your insulin?
- Are you willing to try insulin? If not, what would make you more willing to try it?

---

### *How can I help my patients overcome their fears about starting insulin?*

---

The first step is to determine the real cause of the fear. Although patients often say that they are afraid of the pain of injecting the insulin, this is rarely the real reason. Rather than responding to the issue that is first raised, ask “why is that?” until you get to the heart of the problem. Common concerns and tips for addressing relevant issues are outlined in **Table 8-6**.

Although it is tempting to respond to fears with just facts, a facts-only approach is rarely effective. In addition, such responses may cause patients to feel devalued and embarrassed. Instead, statements such as “Would it help to know that I have started many patients on insulin and none have had to have an amputation?” acknowledge the patient’s belief without supporting misinformation.

---

### *What do patients need to know to initiate insulin therapy?*

---

Education is a critical component of successful insulin initiation and use. Even if the patient has been to a diabetes education program in the past, initiation of insulin therapy often means that additional education can be reimbursed. Key areas to address are listed below.


- How to monitor blood glucose levels and use the information for making decisions

Table 8-6. Assessing and Addressing Common Concerns about Starting Insulin

Common Concerns	Strategies
Fear of needles or pain from injections	Describe/show very fine needles. Encourage patients to insert needle or give a 'dry' shot well before insulin is needed. Offer insulin pens or other devices that hide the needle from view or may be less painful. Point out that injections are less painful than blood glucose self-monitoring fingersticks. Psychological counseling may be indicated.
Fear of hypoglycemia	Describe new insulins, insulin action times. Explain how to limit and/or prevent episodes. Describe differences in risks for hypoglycemia between multiple and less frequent daily injections. Help the patient identify strategies to maintain independence.
Weight gain	Educate the patient about strategies to minimize weight gain (e.g., decrease caloric intake, increase exercise).
Adverse impact on lifestyle (inconvenience, loss of personal freedom)	Discuss multiple injections as a way to increase flexibility. Demonstrate insulin pens or other devices. Assist patient to identify strategies to maintain independence. Offer available resources and support.
Belief that insulin does not work	Discuss insulin as the most natural and effective way to treat diabetes. Review diabetes as a disease of insulin deficiency and not a "sugar problem."
Belief that insulin means diabetes is worse or a more serious disease	Starting with the initial encounter, discuss all options for treatment as a logical progression. Explain that insulin replacement is a logical step in the progression of the disease in terms of insulin resistance and beta cell failure.
Seeing initiation of insulin as a personal failure	Teach initially and review periodically the concept that beta cell failure is progressive. Avoid statements such as "you've failed oral agents." Reframe the statement as "oral agents/your body has failed you." Avoid using insulin as a threat to encourage weight loss and physical activity.
Belief that insulin causes complications	Provide information about your experience with other people with diabetes. Explain that in the largest study of diabetes to date (UKPDS), tight blood glucose control, with oral agents or insulin, reduced heart disease and stroke as well as diabetic eye disease and kidney damage for people with type 2 diabetes.
Will be treated differently by family and friends	Discuss support patient desires and how to ask for what is needed. Include family in education if requested by patient.

Adapted with permission from Funnell MM, Kruger DF, Spencer M. Self-management support for insulin therapy in type 2 diabetes. *Diabetes Educ.* 2004;30:274-80.

- The basal-bolus concept of diabetes management and which specific medicines the patient uses for each
- How to use a pen or draw up and inject the correct dosage
- How to use pattern management and make anticipatory and compensatory adjustments in medication dosages
- How to prevent, recognize, and treat hypoglycemia
- How to use glucagon
- The importance of wearing and carrying diabetes identification at all times

See *Getting Started with Insulin* in Chapter 8 of  the *Diabetes Care Guide Toolkit* for practical tips your patients can use to successfully begin insulin therapy.

## Insulin Regimens for Type 1 Diabetes

The ideal regimen for someone with type 1 diabetes is either basal-bolus treatment or an insulin pump with advanced carbohydrate counting. If neither of these regimens is used, the patient should take at least three injections

per day: a mixture of prandial and basal (NPH) insulin prior to breakfast, prandial insulin prior to supper, and basal (NPH) insulin at bedtime.

For patients unable to understand or implement advanced carbohydrate counting, then basic carbohydrate counting with a consistent amount of carbohydrates ingested at each meal is recommended.

- The usual starting dosage of insulin for someone with type 1 diabetes is 0.3 to 0.6 U/kg daily. (Note that the starting dosage in patients with type 2 diabetes is generally higher than this because of insulin resistance.)
- Increased dosage requirements occur in adolescence, during pregnancy, and during times of stress or infection.
- Decreased dosage requirements occur during the honeymoon phase of the disease, during periods of increased physical activity, and during the immediate postpartum period.

Although fine-tuning an insulin regimen is highly individualized for every patient, some glycemic patterns are commonly seen. Refer back to Table 8-3 for a general approach to adjusting insulin in patients with type 1 or type 2 diabetes.

## Insulin for Gestational Diabetes

Insulin is indicated in women with gestational diabetes if medical nutrition therapy and exercise alone are insufficient to control fasting and postprandial glucose levels within the target range. The insulin regimen used varies from person to person and depends on which glucose concentrations are elevated. Sometimes, using basal insulin (usually NPH) alone is sufficient; in other situations, both basal and prandial insulins are required.

## Helping Patients Succeed With Insulin Therapy

---

*What facts about each insulin do my patients need to know?*

---

Rapid-acting insulin analogues (lispro, aspart, glulisine):

- Take no more than 15 minutes prior to meals to prevent hypoglycemia
- Greatest effect is on postprandial glucose levels

Short-acting (regular) insulin:

- Most effective if taken 30 minutes prior to meals
- Greatest effect is on postprandial glucose levels

Intermediate-acting (NPH) insulin:

- NPH given at night lowers the fasting glucose level; when taken in the morning, its greatest effect is controlling the post-lunch and pre-dinner glucose levels

Long-acting insulin (glargine, detemir):

- Take at about the same time each day
- Do not mix in the same syringe with other insulins

Premixed insulins:

- Not all premixed insulins are the same; do not purchase brands and types other than those that were prescribed

---

*What should I ask my patients about their insulin regimens at each visit?*

---

The following questions are helpful for monitoring patients' success and comfort level with their insulin therapy:

- Are you having any problems with high or low blood glucose levels?
- About how often do you miss taking your insulin?
- Do you have difficulty paying for your insulin or any other medications?
- Would you like to learn to adjust your insulin dosage based on your glucose levels or carbohydrate intake?
- Are you having any problems with your insulin? What specific problems have you encountered? What have you tried to solve this problem? What other options do you think may be effective?
- How well do you think your treatment plan is working to manage your diabetes?
- Do you have any questions about your insulin?
- How can I help most?

---

*Can I provide tips to help patients get the most from their insulin?*

---

The following information should be shared with patients to optimize their insulin therapy:

- Take your insulin at the same time each day (unless the patient is on basal-bolus insulin, in which case the insulin is given before meals, whatever time they are eaten).
- Take your insulin when you do other routine activities (e.g., eat meals, get ready for bed).
- Putting off an injection does not make it easier.
- Unopened insulin can be safely stored in the refrigerator until the expiration date.
- Opened vials of insulin can be safely stored at room temperature (less than 30 °C [86 °F]) for 28 to 30 days. If insulin freezes or is exposed to temperatures above 30 °C [86 °F]),

it becomes completely ineffective and must be discarded.

- Insulin pen cartridges have different expiration dates depending on the brand and type of insulin. Follow the manufacturer's instructions.
- Syringes can be safely re-used if handled appropriately: avoid touching the needle and replace the cap over the needle; move the plunger up and down to help prevent clogs; and do not wipe the needle with alcohol, as this removes the silicone coating. Smaller-gauge needles have fewer re-uses than larger-gauge needles before becoming painful.
- Provide information regarding appropriate needle disposal for the patient's community based on local regulations.

## New Injectables

In 2005, the FDA approved two new injected drugs for the treatment of diabetes—exenatide (Byetta) and pramlintide (Symlin). Both drugs lower postprandial glucose levels, but they have different clinical applications. **Table 8-7** compares the key considerations of using insulin, exenatide, and pramlintide.

### Exenatide

Exenatide is a synthetic form of exendin 4, a naturally occurring hormone that has actions similar to those of glucagon-like peptide type 1 (GLP-1). GLP-1 is an incretin hormone with several actions, including the stimulation of glucose-dependent insulin secretion, the inhibition of glucagon secretion and hepatic glucose production, the delay of gastric emptying, and the suppression of appetite through central pathways that have yet to be elucidated. Endogenous GLP-1 has a half-life of a few minutes and, hence, is not suitable for pharmacologic use, but exenatide, which acts through the GLP-1 receptor, has a longer half-life and can be detected in the circulation 10 hours after administration. The availability of other GLP-1

Table 8-7. Comparison of Insulin, Exenatide, and Pramlintide

Key Considerations	Insulin	Exenatide (Byetta)	Pramlintide (Symlin)
Associated with hypoglycemia	Yes	Yes*	Yes†
Associated with weight loss	No	Yes	Yes
Adjust dose for meals or exercise	Yes	No	No
Use with insulin	—	No	Yes
Use with oral agents	Yes	Yes	Yes

\*Hypoglycemia can occur when exenatide is used in combination with a sulfonylurea.

†Pramlintide potentiates the effects of insulin and therefore can cause potentially severe hypoglycemia. The prandial insulin dose should be reduced by approximately 50% when pramlintide is started.

analogues with different pharmacokinetic properties is expected shortly.

### Indications

- FDA approved for use in combination with metformin, sulfonylureas, or both
- Currently not FDA approved for use as monotherapy or with insulin
- Currently not approved for use with thiazolidinediones (although approval is expected shortly)

### Administration

- Twice-daily subcutaneous injection using pen device with a fixed dosage is preferred.
- Starting dosage is 5 µg before meals (breakfast and supper), increasing to 10 µg twice daily after 1 month if glucose targets are not achieved and the medication is well tolerated.
- Patients should measure blood sugar frequently, including postprandially, before starting this medication.

### Side Effects

- Nausea and vomiting—usually self limited and less common on lower dosages; patients on this drug who stop eating may need to stop the medication.
- Hypoglycemia if the drug is used in combination with a sulfonylurea. The dosage of the

sulfonylurea should be decreased when exenatide is started. Hypoglycemia does not occur when exenatide is used in combination with metformin alone.

- Weight loss (up to 5.5 kg [12 lb] after 2 years of treatment)

### Therapeutic Benefit

- Addition of exenatide to a sulfonylurea, metformin, or both results in an absolute reduction of hemoglobin A1C value of 1 percentage point compared with placebo.
- The major effect of exenatide is the lowering of the postprandial glucose level, but a modest reduction in the fasting glucose level occurs as well.

### Contraindicated in:

- Patients with gastroparesis
- Patients who are pregnant or lactating
- Children

### Pramlintide (Symlin)

Pramlintide is a synthetic form of amylin, a naturally occurring peptide that is co-secreted with insulin by the beta cell. Amylin potentiates the effects of insulin. Persons with type 1 diabetes lack amylin (just as they lack insulin), and those with type 2 diabetes have reduced levels of the hormone. Like exenatide, pramlintide suppresses

glucagon secretion, slows gastric emptying, and promotes satiety.

### Indications

- Adjunct to insulin therapy (multiple daily injection regimens or insulin pump) in patients with type 1 or type 2 diabetes who have primarily postprandial hyperglycemia
- Can be used in patients with type 2 diabetes who use insulin, metformin, and/or a sulfonylurea

### Administration

- Subcutaneous pre-meal injection is generally 60 or 120 µg in type 2 diabetes and 15, 30, 45, or 60 µg in type 1 diabetes.
- It cannot be mixed with insulin.
- Frequent blood-sugar monitoring is required, including postprandially, prior to starting pramlintide.
- Referral to an endocrinologist is usually necessary in patients considering pramlintide.

### Side Effects

- Nausea and vomiting can be minimized by starting with a low dosage and increasing the dosage every 3 to 7 days, if tolerated.
- Hypoglycemia—insulin dosage should be reduced by up to 50% when starting pramlintide to minimize hypoglycemia. Patients who count carbohydrates and use rapid-acting insulin can often further decrease their risk for hypoglycemia by taking their prandial insulin after the meal, basing dosage on the actual carbohydrates consumed.
- Weight loss is usually less than 4.5 kg (10 lb).

### Therapeutic Effect

- Lowers postprandial glucose level by up to 60 mg/dL when used with insulin prior to meals.

- Decreases hemoglobin A1C value by approximately 0.6%.

### Contraindicated in:

- Patients with delayed gastric emptying or who are taking other drugs that delay gastric emptying
- Patients who are pregnant or lactating
- Children with diabetes

---

### *What do I need to teach my patients about other injectables?*

---

The following information is helpful for patients taking or considering other injectables:

- *Similarities:* Both exenatide and pramlintide mimic hormones secreted along with insulin, and both help to lower postprandial glucose levels. Both must be taken by injection and have weight loss as a side effect.
- *Exenatide:* This drug mimics a hormone (GLP-1) secreted from the intestine when food enters the stomach. GLP-1 stimulates insulin secretion from the pancreas, slows down the production of glucose from the liver, and slows down the movement of food through the stomach. It is effective only for patients with type 2 diabetes whose bodies still make insulin naturally (endogenous insulin production).
- *Pramlintide:* This drug is a synthetic form of amylin, a hormone that is co-secreted with insulin from the pancreas and that lowers the postprandial glucose level. This, too, slows gastric emptying and suppresses glucagon secretion, thereby decreasing hepatic glucose production. Hence, this hormone increases the effectiveness of mealtime insulin. It is effective for patients with type 1 or type 2 diabetes who take preprandial insulin injections.
- Because of the risk for hypoglycemia, frequent blood glucose monitoring is critical when these medications are initiated.

- Essential components of education for patients taking these medications include a discussion of hypoglycemia prevention, symptoms, and treatment; how to manage insulin during an acute illness; and the need for diabetes identification.
- Regarding pramlintide, discuss a plan for dosage adjustments and when to contact you or another provider about hypoglycemia, hyperglycemia, and side effects. Point out that it may take some time for the drug to work properly and that adjustments can be made to regulate the dosage of pramlintide.

Because these medications are relatively new, not all payers currently provide coverage, and many require prior authorization. Patients need to check with their insurer prior to filling the prescription.

---

*What should I ask patients about their injected medication at each visit?*

---

- Are you having any problems with high or low blood glucose levels?
- About how often do you miss taking this medication?
- Do you have difficulty paying for this medication?
- Are you having any problems with this medication? What specific problems have you encountered? Have you had any nausea? What have you tried to solve this problem? Did it work?
- How well do you think your treatment plan is working to manage your diabetes?
- Do you have any questions about this medication?
- How can I help most?

---

*What facts about exenatide do patients need to know?*

---

Some key facts to share with patients about exenatide include:

- Take exenatide twice daily, 60 minutes or less before the morning and evening meals (with meals at least 6 hours apart).
- If you miss a dose, do not take it after your meal or take a larger dosage at your next meal.
- Store both opened and unopened pens in the refrigerator. Discard the pen if it freezes or looks cloudy. Unopened vials are good until the expiration date.
- Once opened, each pen is good for 30 days. Discard after 30 days even if some medication remains.
- Opened pens can be removed from refrigeration for short periods of time. The total time pens can be unrefrigerated is a cumulative total of 6 days.
- Pen needles need to be purchased separately.
- Exenatide can be injected subcutaneously in the arm, abdomen, or thigh.
- Do not adjust the dosage based on meal size or activity level.
- Because this medication can affect the absorption of some oral medications, tell all of your health care providers that you are taking this medication.

---

*What facts about pramlintide do patients need to know?*

---

The following information about pramlintide should likewise be shared with patients:

- Take pramlintide right before any meal that contains at least 250 calories or 30 g of carbohydrates.

- If you miss a dose, do not take it after your meal or take a larger dosage at your next meal.
- Do not mix pramlintide in the same syringe as insulin.
- Pramlintide can be injected subcutaneously in the arm, abdomen, or thigh. It should be injected at least 2 inches from the site of your most recent insulin injection.
- Each opened vial of pramlintide is good for 28 days when stored at room temperature. Discard after 28 days even if some medication remains. Discard if the vial has been frozen or heated above room temperature (25 °C [77 °F]).

## Injectable Drug Supplies

This section briefly describes some of the supplies patients on insulin or other injectable drugs need for managing their diabetes. A certified diabetes educator or other diabetes health care provider is an excellent resource for information about currently available diabetes supplies.

### Syringes

Syringes are available in 0.3-cc, 0.5-cc, and 1.0-cc sizes. When initially prescribing insulin syringes, consider the potential maximum dosage per injection to insure the patient has syringes that will be able to accommodate any dosage increases that may occur following diagnosis.

The length and gauge of the syringe needle can affect comfort and absorption. The “short” (5/16-inch) needles are commonly prescribed because healthcare providers and patients perceive these as causing less discomfort than half-inch needles. However, short needles, if prescribed improperly, can be associated with more discomfort because the insulin may be delivered intradermally, rather than subcutaneously. Increased leakage is possible, contributing to variable delivery and glucose fluctuations.

### Pen Injectors

Many of the injectable diabetes medications can be administered using injector devices (pens). Pens offer a greater degree of accuracy than syringes, particularly for patients with vision or dexterity problems, and are often considered more convenient than traditional syringes. However, this convenience does come at a price. Pens are often more expensive and associated with a higher copayment if a vial form of the medication is also available. Additionally, not all insurance providers cover pens, and some restrict the types of pen covered.

Some insulin pens are disposable, whereas others use disposable cartridges. All pens use specially designed pen needles. As with syringes, the pen needles are available in various lengths and diameters. Just as with syringe use, initial patient instruction with ongoing evaluation of technique is critical to avoid errors in medication delivery.

The American Diabetes Association’s annual Resource Guide ([www.diabetes.org/diabetes-forecast/resource-guide.jsp](http://www.diabetes.org/diabetes-forecast/resource-guide.jsp)) provides an up-to-date listing and description of the pens available.

### Glucagon

All patients with type 1 diabetes should be provided with a prescription for a glucagon emergency kit to be used for treatment of severe hypoglycemia. A family member or caregiver must be instructed in how and when to administer glucagon, which is reserved for when the patient cannot safely take anything orally to treat a severe hypoglycemic event or reaction. Patients with type 2 diabetes who are on insulin and have a history of severe hypoglycemia may also benefit from having a glucagon emergency kit available. Because such kits are expensive and not always covered by insurance, the decision to prescribe one for patients with type 2 diabetes should be based on the individual clinical situation.

Because glucagon is used infrequently, if at all, by most patients, it is likely to reach its expiration date. The need for a new prescription can be part of the routine assessment of patients with diabetes.

### Ketone Test Strips

Ketone monitoring is used to assess insulin deficiency in type 1 diabetes during hyperglycemia, acute illness, or stress. In patients with type 2 diabetes, regular ketone monitoring is not recommended, except during pregnancy. At least one blood glucose meter is also able to measure blood ketones. Ketone monitoring is an essential component of sick-day management for patients with type 1 diabetes. In addition, patients with type 1 diabetes who are using insulin pump therapy should monitor their ketones to assess insulin delivery, especially during unexplained hyperglycemia.

## Beta Cell Replacement Therapies

Beta cell replacement therapy, which offers an intuitive method to obtain normoglycemia, attracts inquiry from patients and providers alike. Currently, beta cell replacement is reserved for those who have lost significant secretory capacity, usually because of autoimmune diabetes, pancreatitis, or pancreatic surgery. Available options for beta cell replacement include whole-organ pancreas transplantation and islet transplantation.

Whole-organ pancreas transplantation is generally considered an acceptable alternative to continued exogenous insulin in patients with diabetes who have imminent or established end-stage kidney disease and have had or plan to have a kidney transplant. The procedure involves transplanting a donor pancreas into the peritoneal cavity with drainage of the digestive juices of the exocrine pancreas into the ileum (or, less commonly, the bladder) and drainage of the

insulin-containing venous return into the portal or systemic circulation. Quality of life studies show improvement after pancreas transplantation, often with normalization of A1C values and stabilization or improvement in many complications of diabetes. One-year graft survival rates are 85% for simultaneous pancreas-kidney transplants, 78% for pancreas transplants after kidney transplantation, and 77% for pancreas transplants alone; 5-year graft survival rates are 69%, 46%, and 42%, respectively. Because graft survival rates are far superior with simultaneous kidney-pancreas transplantation, such surgery is the preferred method.

Pancreas transplantation has significant morbidity and carries a small, but not negligible, risk of mortality. Potential complications include intra-abdominal infection and abscess, vascular graft thromboses, and anastomotic leakage. Cytomegalovirus infection, cytopenia, malignancy, hypertension, hyperlipidemia, insulin resistance, and other metabolic abnormalities have also all been seen secondary to the required immunosuppression after transplantation.

With islet transplantation, the endocrine portions of the pancreas—the islets of Langerhans—are transplanted, usually via an infusion of isolated islets into the portal vein of the liver. Many insurers will at least partially cover the autotransplantation of islets in persons undergoing pancreatectomy for pancreatitis. In patients with pancreatitis who have not had prior pancreatic surgery, insulin-independence rates after autotransplantation may exceed 70%. An added benefit is that immunosuppression is not required, as in allotransplantation. In contrast, islet allotransplantation, which is currently being studied for the treatment of type 1 diabetes, remains an experimental procedure and is not covered by insurance. Medicare may pay some of the costs associated with participation in a National Institutes of Health–sponsored clinical trial. In most clinical trials, islet allotransplantation candidates have been relatively thin and insulin sensitive, minimizing the number of islets required for transplantation.

Complications related to islet transplantation have included peritoneal hemorrhage, portal vein thrombosis, peri-islet hepatic steatosis, and transient transaminitis. In addition, oral ulcerations, diarrhea, weight loss, decline in glomerular filtration rate, proteinuria, cytopenia, hypertension, hyperlipidemia, pneumonitis, and small bowel ulcerations have all been associated with the requisite immunosuppression for allotransplantation. The most frequent indication for

islet allotransplantation has been severe, life-threatening hypoglycemia. Although hypoglycemia is much improved after islet transplantation, the glycemia achieved remains inferior to that seen with whole-organ transplants. Insulin independence in those with type 1 diabetes has also been fleeting. The median duration of insulin independence is only 15 months, and fewer than 10% of recipients remain insulin independent at 5 years.

© 2007 American College of Physicians, Inc. (ACP)

ACP reserves all rights not specifically granted by this license. Any modifications to license must be made by an authorized officer of ACP in writing. Requests for modifications may be sent to MKSAP® Permissions, ACP, 190 N. Independence Mall West, Philadelphia, PA 19106-1572.

Recipient of this publication is granted a nonexclusive, revocable, and transferable license to copy a particular chapter, form, patient education sheet, chart, or directory item from this publication for distribution to a medical associate, patient with diabetes, or family member of a patient with diabetes for educational purposes only. ACP may revoke or modify this license at anytime without notice to the recipient.

Recipient may not copy the entire publication, make derivative works, collective works, or compilations from this publication. Recipient may not copy or distribute any part of this publication for consideration. Recipient may not distribute any material from this publication via electronic transmission such as email, FTP, or HTTP. Recipient may not display any contents of this publication on any type of web page. This license terminates immediately if recipient fails to conform with any provision in this license agreement.

ISBN: 978-1-930513-91-4

Printed in the United States of America.

For information on this program in the United States or Canada, call 800-523-1546, extension 2600. Professionals from all other countries should call 215-351-2600 or send an email to [custserv@acponline.org](mailto:custserv@acponline.org).

### **Educational Disclaimer**

The editors and publisher of *ACP Diabetes Care Guide: A Team-Based Practice Manual and Self-Assessment Program* recognize that the development of new material offers many opportunities for error. Despite our best efforts, some errors may persist in print. Drug dosage schedules are, we believe, accurate and in accordance with current standards. Readers are advised, however, to ensure that the recommended dosages in this program concur with the information provided in the product information material. This is especially important in cases of new, infrequently used, or highly toxic drugs. Application of the information in the Guide in a professional situation remains the professional responsibility of the practitioner.

The primary purpose of the *ACP Diabetes Care Guide: A Team-Based Practice Manual and Self-Assessment Program* is educational. Information presented, as well as publications, technologies, products, and/or services discussed, is intended to inform subscribers about the knowledge, techniques, and experiences of the contributors. A diversity of professional opinion exists, and the views of the contributors are their own and not those of the ACP. Inclusion of any material in the Guide does not constitute endorsement or recommendation by the ACP. The ACP does not warrant the safety, reliability, accuracy, completeness or usefulness of and disclaims any and all liability for damages and claims that may result from the use of information, publications, technologies, products, and/or services discussed in this program.