

New and Standard Treatment Options for Patients With Type 2 Diabetes

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DIABETIC MICROVASCULAR COMPLICATIONS TODAY.

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BY NATHAN A. PAINTER, PHARM D

STATEMENT OF NEED

The epidemic of diabetes in the United States affects 7% of the population, and most of these patients have type 2 diabetes. Currently, 20.8 million Americans have diabetes, and 6.2 million more have unrecognized diabetes. Health care is an ever-changing field with drug development leading the way. The past year has seen the first new class of diabetes medications in nearly 20 years and a new method of insulin delivery.

TARGET AUDIENCE

This activity is designed for primary care physicians, endocrinologists, diabetologists, pharmacists, diabetes educators and other practitioners who treat patients with diabetes.

LEARNING OBJECTIVES

Upon successful completion of this learning program, the participant should be able to:

- identify the prevalence and pathophysiology of type 2 diabetes;
- discuss how to select oral agents as either monotherapy or in combination to achieve desired treatment goals;
- identify appropriate monitoring parameters of anti-hyperglycemic agents; and

- create a combination drug therapy regimen including new therapeutic agents to optimize patient outcomes.

METHOD OF INSTRUCTION

Participants should read the learning objectives and continuing medical education (CME) program in their entirety. After reviewing the material, they must complete the self-assessment test, which consists of a series of multiple-choice questions.

Participants have a choice of completing this activity online by visiting www.DiabeticMCToday.com or by using the print forms following this activity.

Upon completing the activity and achieving a passing score of $\geq 70\%$ on the self-assessment test, participants will receive a CME credit letter awarding AMA/PRA Category 1 Credit™ 4 weeks after the registration and evaluation materials are received. The estimated time to complete this activity is 1 hour.

ACCREDITATION

This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of The Dulaney Foundation and DIABETIC MICROVASCULAR

COMPLICATIONS TODAY.

The Dulaney Foundation designates this educational activity for a maximum of 1 AMA/PRA Category 1 Credit.[™] Physicians should only claim credit commensurate with the extent of their participation in the activity.

DISCLOSURE

In accordance with the disclosure policies of The Dulaney Foundation and to conform with ACCME and FDA guidelines, all program faculty are required to disclose to the activity participants: (1) the existence of any financial interest or other relationships with the manufacturers of any commercial products/devices or providers of commercial services that relate to the content of their presentation/material or the commercial contributors of this activity; and (2) identification of a commercial product/device that is unlabeled for use or an investigational use of a product/device not yet approved.

FACULTY DISCLOSURE DECLARATIONS

None.

FACULTY CREDENTIALS

Nathan A. Painter, PharmD, is assistant professor of pharmacy practice, Loma Linda University, School of Pharmacy. He may be reached at npainter@llu.edu.

INTRODUCTION

Given a patient case, you should be able to select appropriate oral therapy and justify that therapy, as well as explain when insulin therapy should be introduced.¹ You should also know the mechanism, indication, dosing and adverse effect profile of the medications you recommend and put forth a monitoring plan specific to the drugs that you are using.

We all know the data: 21 million people have diabetes.² The most impressive number, however, is that an estimated 41 million people have prediabetes, including those with metabolic syndrome and increased blood glucose.

With regard to the pathophysiology of type 2 diabetes, the main issue is insulin resistance. Insulin resistance leads to the increase of lipolysis and free fatty acid production, an increase in hepatic glucose production, decreased skeletal muscle uptake of glucose and increased insulin production. That increased production of insulin happens in the early diagnosis — over time, insulin production decreases resulting in a need for insulin therapy.

The other hallmark in the pathophysiology of diabetes is beta-cell dysfunction that leads to insulin deficiency and decreased insulin secretion as the primary underlying defect.

UKPDS

The United Kingdom Prospective Diabetes Study (UKPDS) showed that beta-cell function began to decline years before the actual diagnosis of diabetes. The further the disease continued, the less beta-cell function patients had.³ Patients with diabetes also have a host of other metabolic abnormalities. The longer a patient has diabetes, the larger the increases in arterial blood pressure, atherogenesis, triglycerides, fasting plasma glucose and 2-hour plasma glucose.

Before 2006, we had three classes of oral diabetes medications: (1) drugs that sensitize the body to insulin and/or control hepatic glucose production, including the thiazolidinediones and biguanides; (2) drugs that stimulate the pancreas to make more insulin, these are sulfonylureas and meglitinides; and (3) drugs that slow the absorption of starches, which are alpha-glucosidase inhibitors.

We are all familiar with the risk factors for type 2 diabetes:

- obesity >20% over desired body weight or >27 body mass index;
 - family history of diabetes;
 - race/ethnicity;
 - age >45 years;
 - a sedentary lifestyle;
 - a previous diagnosis of impaired glucose tolerance or impaired fasting glucose;
 - hypertension >140/90 mm Hg;
 - HDL cholesterol <35 mg/dL or triglycerides >250 mg/dL;
- and
- history of gestational diabetes or delivery of a baby with a birth weight >9 lbs.

Our management goals in patients with type 2 diabetes are to obtain tight glucose control; to minimize or eliminate symptoms; to prevent acute metabolic complications; to prevent, delay or minimize microvascular and neuropathic complications; and to reduce the rate of morbidity and mortality from macrovascular disease.

The glycemic goals come from the American Diabetes Association guidelines.⁴ We are looking for a HbA1c <7.0% (<6.0% is preferred), preprandial fasting glucose of 90 mg/dL to 130 mg/dL, postprandial plasma glucose <180 mg/dL and a bedtime glucose of 90 mg/dL to 150 mg.

We can break our treatment down into two plans — lifestyle changes, which are important in any treatment regimen, and drug therapy. Aspirin therapy is important for all diabetic patients unless they have contraindications, and of course tobacco cessation is essential. Our treatment algorithm includes lifestyle changes at every step, but once a patient cannot control their disease with lifestyle, step 2 is oral monotherapy, step 3 is oral combination therapy, step 4 is a combination of oral therapy and insulin, and step 5 is insulin alone.

ORAL THERAPY — INSULIN SECRETAGOGUES/SULFONYLUREAS

Insulin secretagogues or sulfonylureas include glipizide (Glucotrol, Pfizer, New York, NY), glyburide (Diabeta [Aventis, Paris], Micronase [Pfizer], Glynase [Pfizer] and Glycron [Mova Pharmaceuticals]) and glimepiride (Amaryl [Aventis]). These agents are first- and second-line drugs for patients who have failed diet and exercise, and their mechanism of action is to stimulate pancreatic insulin function.

Glipizide is started at 5 mg/daily, with a maximum dose of 40 mg/daily. There is no clinical reason to increase to the max dose; 20 mg/day provides the best HbA1c lowering you will see. It is very important to take it on an empty stomach, about 30 minutes before meals. The dosing information for glyburide is half of that of glipizide.

Glimepiride is the only sulfonylurea that is approved for once-a-day dosing, therefore it may help with compliance in some patients. The initial dose is 1 mg or 2 mg, the maximum dose is 8 mg/day.

If after 4 weeks of sulfonylurea treatment the maximum dose is met and the patient has an inadequate response, metformin (Glucophage; Merck, Readington Twp, NJ) may be added. Glyburide is contraindicated in patients with renal impairment. Begin sulfonylureas at a low dosage and increase as often as every 1 to 2 weeks. Efficacy is seen quite rapidly, and changes can be made rapidly as well. All of these agents are equally efficacious at equal doses.

Sulfonylureas reduce HbA1c by about 1.5% to 2%, equivalent to a fasting blood glucose reduction of 50 mg/dL to 70 mg/dL. The side effects are weight gain and hypoglycemia. Please note that any treatment that deals with insulin can cause weight gain.

MEGLITINIDES

Meglitinides are short-acting insulin secretagogues and are not used as much as sulfonylureas. They increase insulin production in the pancreas. Examples are repaglinide (Prandin; Novo Nordisk, Princeton, NJ) and nateglinide (Starlix; Novartis, Basel, Switzerland). These agents are indicated in monotherapy or combination therapy in patients who have difficulty regulating postprandial glucose. Because they are very short acting, they are only taken to cover meals. These agents are a good choice for patients at higher risk of hypoglycemia with sulfonylureas.

Repaglinide dosing is initiated at 0.5 mg to 2 mg with each meal, up to a maximum of 4 mg at a single meal or 16 mg/daily. The agent should be taken 15 to 30 minutes before eating and is indicated for dosing at two to four times per day. Nateglinide is dosed at 120 mg three times a day with meals, up to 30 minutes before eating. The agents

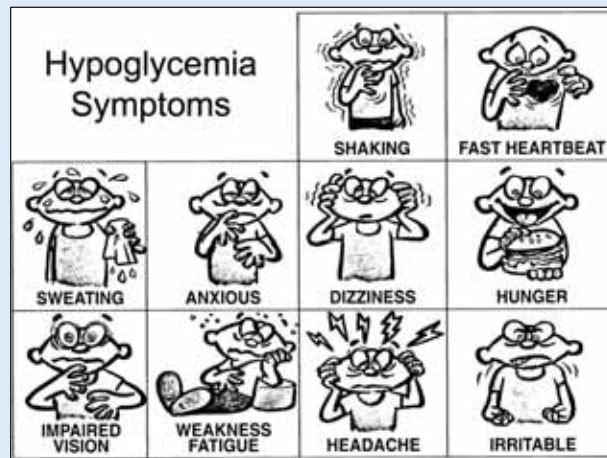


Figure 1. Be sure to review the symptoms of hypoglycemia with your patients.

decrease HbA1c by 1.5% to 2% and glucose by 60 mg/dL. The side effects include weight gain; the risk of hypoglycemia is reduced compared with other sulfonylureas.

Be sure to review the symptoms of hypoglycemia with your patients (Figure 1). Nocturnal hypoglycemia can be particularly common among patients who take sulfonylureas at bedtime. It does not always wake them up, however, and in the morning the patient may remember nightmares, experience restless sleep and often will have a headache.

Hypoglycemia is indicated by a blood glucose <50 mg/dL, and we have to worry about irregular eating patterns, increased physical exercise especially at night, gastroparesis, defective counterregulatory hormones, excessive antidiabetic medicines and drug interactions.

BIGUANIDES

In the United States, the only biguanide we have is metformin. It is indicated as first-line therapy, especially in overweight patients because it is associated with limited weight gain. It is helpful in people with metabolic syndrome. Its mechanism of action is primarily to block gluconeogenesis, and it also increases peripheral glucose uptake and decreases intestinal absorption of glucose. Biguanides have positive cardiovascular effects, including lowering triglycerides and LDL and raising HDL.

A significant side effect with metformin is lactic acidosis, which is preventable if the contraindications are followed. Metformin should not be used in patients aged >80 years, those with renal impairment, acute congestive heart failure (CHF), alcohol abuse, acute myocardial infarction, respiratory failure, CHF requiring therapy or those with chronic hepatic dysfunction.

Metformin is initiated at 500 mg with the day's largest meal, the maximum dose is 2,500 mg and it can be dosed one to three times daily. Metformin can be associated with gastrointestinal side effects that may be minimized with the extended-release formulation.

If a patient fails on 4 weeks of monotherapy with the biguanide, add a sulfonylurea. If you started the patient on a sulfonylurea and he or she fails to reach target after 4 weeks, then add a biguanide.

Biguanides decrease HbA1c about the same as the sulfonylureas, 1.5% to 2%, and decrease fasting blood glucose by 50 mg/dL to 70 mg/dL. The gastrointestinal (GI) side effects are dose-dependent and are minimized with food and slow titration. As monotherapy, biguanides do not cause hypoglycemia, as they do not affect insulin use or production. The risk of hypoglycemia does, however, increase with combination therapy. Patients should have their baseline renal function monitored annually and avoid excessive alcohol consumption. Treatment with biguanides must stop when a patient is having any procedure requiring radiocontrast dye. Monitor for lactic acidosis symptoms, which include weakness, tiredness, discomfort, unusual muscle or stomach pain, feeling cold, dizzy or lightheaded.

THIAZOLIDINEDIONES

Thiazolidinediones (ie, insulin sensitizers) include pioglitazone (Actos; Takeda, Lincolnshire, Ill) and rosiglitazone (Avandia; GlaxoSmithKline, Philadelphia). The primary mechanism of action is to reduce peripheral insulin resistance, and the secondary mechanism of action is to decrease hepatic glucose output. These are second-line agents that are often reserved for patients who cannot tolerate the sulfonylureas or metformin. We can try these before insulin.

Rosiglitazone is dosed initially at 4 mg/day with a maximum of 8 mg/day; pioglitazone is started at 15 mg/day or 30 mg/day with a maximum dose of 45 mg/day. You must wait 8 to 12 weeks to assess the response before increasing the dose.

Thiazolidinediones decrease HbA1c 1% to 1.5%; their onset is around 3 weeks, but the maximum effect may not be seen for 4 months. The drug causes changes on the cellular level in the nucleus. It has positive cardiovascular effects, including decreases in triglycerides and increases in HDL. A decrease in vascular inflammation and smooth muscle proliferation, C-reactive protein, blood pressure and microalbumin are also seen, which are useful in patients with metabolic syndrome.

Side effects include weight gain, as much as 6 lbs to 13 lbs, and we have to consider if this is due to fluid or fat. Edema also increases, and in its presence CHF can be exacerbated. Liver function tests should be monitored at

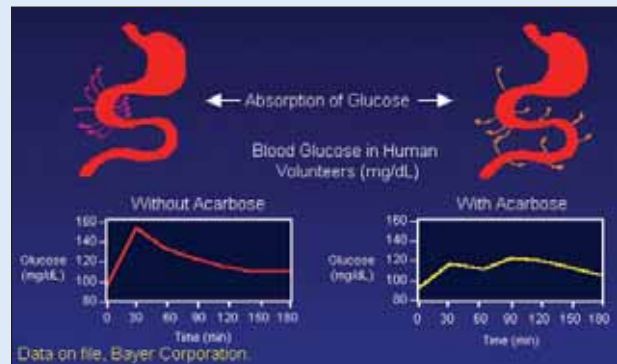


Figure 2. Alpha glucosidase inhibitors work by delaying carbohydrate absorption from the small intestine.

baseline, then periodically thereafter, as well as signs and symptoms of CHF or edema.

ALPHA-GLUCOSIDASE INHIBITORS

Alpha-glucosidase inhibitors such as acarbose (Precose; Bayer, West Haven, Conn) and miglitol (Glyset; Pharmacia) are not used regularly in the United States, but they are good drugs if the patient can tolerate them. They are third-line agents or used in monotherapy or combination therapy in mild uncontrolled diabetes. Their mechanism of action is to delay carbohydrate absorption from the small intestine.

The enzymes that transport glucose into the bloodstream are located fairly close to the stomach (Figure 2). There is a strong peak after mealtime that fades. By getting rid of the first-phase peak with acarbose administration, patients do not need the first-phase insulin as much because the absorption of carbohydrates is delayed.

The initial dose of acarbose is 25 mg with the first bite of each meal; the maximum dose is 50 mg for patients weighing <60 kg and 100 mg for patients >60 kg. Reassess dosage after 4 to 8 weeks. The maximum clinical effects are observed at 6 months; we see only about a 0.5% reduction of HbA1c. Clinically, compared with the rest of the agents, this is disappointing for glycemic control. These agents do not cause weight gain or hypoglycemia by themselves, and there is a study that shows a reduction in the incidence of heart disease with acarbose. Side effects are GI-related, including flatulence, diarrhea and abdominal pain. These should minimize once the patient is on a consistent dose.

It is very important when patients are on this medication to tell them how to treat episodes of hypoglycemia. Carbohydrates are not going to be effective, because their absorption is delayed. Patients must use glucose tablets or solution that does not rely on enzymes.

COMPARING COMBINATIONS

We can use several combination therapies, the only ones

Drug	FPG Reduction (mg/dL)	HbA1c (%) Reduction
Thiazolidinedione	35 to 40	0.5 to 1.0
Sulfonylurea	60 to 70	1.0 to 2.0
Biguanide	60 to 70	1.0 to 2.0
Meglitinide	60 to 70	1.0 to 2.0
Alpha-glucosidase inhibitor	20 to 30	0.5 to 1.0
Diet and Exercise	20 to 70	0.5 to 2.0

Figure 3. A comparison of the blood glucose and HbA1c reductions seen with various therapies.

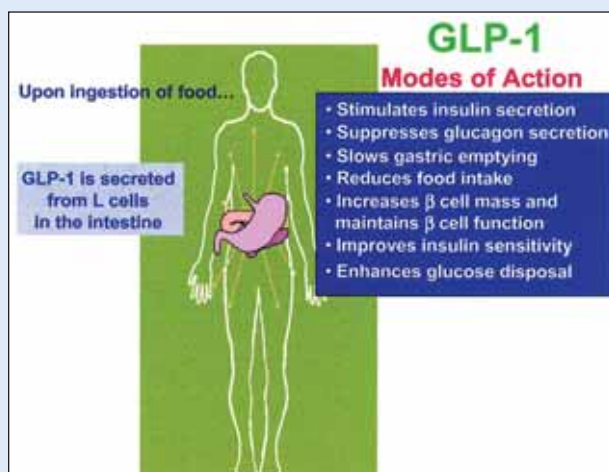


Figure 4. The mechanism of action of GLP-1.

we cannot use together are sulfonylureas and meglitinides because they do the same thing and have the same mechanism of action. Figure 3 compares the blood glucose and HbA1c reductions seen with various therapies. We can come up with any combination — including insulin — we desire to treat our patients.

There are also combination products available (eg, rosiglitazone plus metformin, metformin plus glipizide, pioglitazone plus metformin and metformin plus glyburide), that may enhance patient compliance.

CASE EXAMPLE

A 55-year-old white male with type 2 diabetes comes in with a chief complaint of increased fatigue. His glycemic control has been worsening over the past several years, while his previous self-monitoring ranges of blood glucose were 80 mg/dL to 120 mg/dL. He is on glipizide 10 mg twice/daily, which he has been taking for 10 years, metformin 1,000 mg twice/daily for 5 years, and he started rosiglitazone 4 mg/day last year. His current blood sugars are

185 mg/dL to 225 mg/dL in the morning, 200 mg/dL to 230 mg/dL at noon, 210 mg/dL to 240 mg/dL at 5 p.m. and 250 mg/dL to 268 mg/dL at bedtime.

In this case, we would start insulin therapy. You could add an alpha-glucosidase inhibitor, but with blood sugars >200 mg/dL to almost 300 mg/dL, acarbose is not going to get us there and neither is switching glipizide for another meglitinide. There is really no other option than to start bedtime insulin with daytime sulfonylurea (BIDS) therapy. It is going to help ease the patient into insulin therapy, while giving him better glucose control.

Calculate the number of basal units at bedtime of an intermediate or long-acting insulin. In obese patients, we need a higher dose because they have more insulin resistance; you can titrate every 1 to 2 weeks based on blood sugar levels. Typically, the calculation we use is 0.25 units per kg at bedtime; in obese patients or anyone suspected of insulin resistance, we can start anywhere from 0.25 to 0.5 units per kg at bedtime.

COMBINATION BIDS

Insulin at bedtime helps the pancreas rest during the night and build up insulin so when sulfonylurea is administered first thing in the morning, there is some insulin in the pancreas to be released. It also helps to decrease hepatic glucose production overnight. The sulfonylurea is intended to take care of the caloric intake during the day, again easing the patients into insulin administration and hopefully giving them a good base understanding of how they are supposed to self-titrate. They are looking at one time of day for their blood sugars and one time of day for insulin administration, so it is easy for them to connect what their blood sugar is in the morning based on the insulin they gave themselves the night before.

Insulin as initial therapy in type 2 diabetes is indicated when glucose is >300 mg/dL and there is ketonuria, as well as suspected glucose toxicity, pregnancy (oral agents are contraindicated), and if the patient wants to start insulin therapy.

ASSESSMENT OF GLYCEMIC CONTROL

Self-monitored glucose is the hallmark when assessing glycemic control. It aids in patient understanding of their diet, exercise and medication, and it also reduces the frequency of hypoglycemic episodes. Patients are able to see trends and test their blood sugar beforehand and see if they are headed in that direction. The frequency of monitoring is variable, depending on how long the patient has had diabetes and what treatment they are on, anywhere from once a week to two to three times a day.

With HbA1c, we are looking for trends. It is very important for patients to know what their treatment goals are and

for them to ask what their HbA1c is. When stable, this can be monitored every 6 months; every 3 to 4 months for making adjustments. It is not useful to measure before 3 months because HbA1c shows trends over the last 3 months.

Fructosamine is getting some attention as a value to be monitored, however, there are no guidelines. Fructo-samines are glycosylated serum proteins including albumin, so instead of just the red blood cells being glycosylated, we are looking at other proteins. It shows glycemic control over the last 1 to 2 weeks, so it may help assess short-term changes instead of having to wait 3 months to see if HbA1c is decreasing.

Plasma glucose is the hallmark of diabetes control — it is reproducible, it is what most of the money in monitoring is going toward. It is important to know whether we are looking at plasma or whole blood because there can be as much as a 15% difference in actual readings depending on what measurement you get.

PREVENTION AND MANAGEMENT OF DIABETIC COMPLICATIONS

- Blood pressure should be measured at every visit, and patients should know their goals: <130 /80 mm Hg.
- Lipid panels should be done at diagnosis and annually (more often as needed). LDL should be <100 mg/dL; triglycerides <150 mg/dL; HDL >40 mg/dL for men and >50 mg/dL for women.
- Patients should have nephropathy screening with annual tests for the presence of microalbuminuria and be treated with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers.
- Patients should have a dilated eye exam upon diagnosis and then annually year after.
- Patients should have a comprehensive annual foot exam and a visual inspection of the feet at each exam.

NEW MEDICATIONS

Exenatide. Two GI peptides have been established as incretins, one is glucagons-like peptide-1 (GLP) and the other one is glucose-dependent-insulinotropic peptide (GIP). Both are released with food, and they augment glucose-dependent insulin secretion. The incretins are insulinotropic in nondiabetic patients, so they cause insulin to be secreted. GLP specifically acts on beta-cell function to affect insulin secretion, and it also affects alpha cells to reduce the secretion of glucagon. It delays gastric emptying and causes satiety, which is one of the reasons we see weight loss with these drugs. Together, this promotes a lowering of blood glucose levels after meal ingestion in diabetic patients (Figure 4).

The incretin effect is severely impaired in patients with diabetes. First-phase insulin secretion — which diabetes

Insulin Preparations		Onset (hrs)	Peak (hrs)	Duration (hrs)
Ultra-short Acting	Insulin Lispro	0.25	0.5-1.5	2-5
	Insulin Aspart	0.25	1-3	3-5
Rapid Acting	Insulin Glulisine	0.25	0.5-1.5	1-2.5
Short acting	Insulin injection Regular	0.5-1	1.5-4	8-12 (5-8)
	Intermediate acting	Isophane Insulin Suspension (NPH)	1-1.5	4-12 (6-12)
Long Acting	Insulin Glargine	1.1	5*	18-24
	Insulin Detemir	0.8-2	6*	Up to 24

Figure 5. A comparison of insulin preparations.

patients do not have — is essentially attributed to the incretin effect. Diabetic patients do not respond to GIP, which might account for some of the abnormality in meal-induced insulin secretion in these patients. Diabetic patients also have a decreased sensitivity to GLP-1, but we can induce a response if we give them a supraphysiologic amount.

In addition to the acute effects of the incretins in controlling blood glucose, they may also have a chronic effect on beta cells. Several studies have demonstrated the positive effect of GLP-1 on beta-cell and it appears that GLP-1 has a negative effect on apoptosis.

Analogues of GLP-1 have been derived to make it therapeutically useful and extend its half-life. Exenatide is derived from the saliva of the Gila monster (exanatide [Byetta; Eli Lilly and Company, Indianapolis]). Another drug of this type, liraglutide (Novo Nordisk), is in phase 3 clinical trials.

Exenatide subcutaneous injection is indicated as adjunctive therapy to improve glycemic control in patients with type 2 diabetes who are taking metformin, a sulfonylurea or a combination, but have not achieved adequate control. The mechanism of action is as described with regard to GLP-1. Hypoglycemic episodes associated with exenatide are higher when used in combination with metformin or sulfonylurea. It can cause dizziness, jittery feelings and headaches. The GI side effects are quite significant in some patients, however, the weight loss associated with the agent is not dependent on nausea and vomiting. We have seen aminogenicity with this agent, so we need to watch for those reactions.

Pramlintide. Pramlintide (Symlin; Amylin Pharmaceuticals, San Diego) is an adjunct for type 1 diabetic patients who use mealtime insulin therapy and have failed to reach desired glucose control. This is the first noninsulin treatment for type 1 diabetes. It is also



Figure 6. The inhalation device is not something you want to carry in your pocket.

used in type 2 patients who use mealtime insulin therapy and have failed to achieve desired glucose control, with or without concomitant use of metformin or a sulfonyleurea.

It is a synthetic analog of the naturally occurring pancreatic hormone amylin. Amylin is also located in the beta cells and is released at the same time as insulin. It slows the rate of gastric emptying, suppresses glucagons and modulates brain appetite function to produce satiety. So it is similar in mechanism of action to exenatide.

There is a black box warning for a significant hypoglycemic reaction when it is coadministered with insulin, as indicated. Alone, it does not cause hypoglycemia. Another reaction is local hypersensitivity at the injection site.

New insulins. There is also a new long-acting insulin detemir (Levemir; Novo Nordisk). This is not a “me-too” insulin, but an attempt to mimic basal insulin secretion. It uses recombinant technology and its long duration of action is due to self-aggregation as well as albumin binding in the plasma and injection site. It is released into the bloodstream at a constant rate, and therefore it is peakless. There are no data with regard to how much albumin a patient must have for the agent to bind with, but this is a hypothetical concern.

This insulin is recommended for administration starting in the evening and increasing to twice a day dosing if the predinner target is not reached. This is the first peakless basal insulin that lasts from 12 to 24 hours. That may be a large spread of time and it is patient variable, so the key is try once a day and if the patient is not controlled you go to twice a day.

Insulin glulisine (Apidra; Aventis) is basically a “me-too” drug. Consider this equally efficacious and its profile superimposable on that of lispro (Humalog; Eli Lilly and

Company). Patients with diabetes should be able to switch from any rapid-acting insulin to insulin glulisine on a unit-per-unit basis. Figure 5 is a comparison of insulin preparations.

Inhalable insulin (Exubera; Pfizer) has been approved by the US Food and Drug Administration and will soon be available. Essentially, it will first be released to physicians who see many patients, for example, those at the large centers and major institutions. By June 2007, the company will start releasing it to the general public. It might still be a while before we see it being used.

The actual inhalation device is large, it is not something you want to carry in your pocket (Figure 6). It is a dry powder form of insulin, and it come in 1-mg and 3-mg blister unit doses that you insert into the device. It is administered 10 minutes before mealtime. The onset of activity is comparable to rapid-acting insulin, so this can replace mealtime boluses. Its duration of action is similar to subcutaneous regular insulin — it starts working in 15 minutes and can last 6 hours.

Inhaled insulin should not be used in smokers or those who have smoked in the last 6 months. It is not recommended in patients with chronic lung diseases or poorly controlled or unstable lung disease.

SUMMARY

Our patients with diabetes should also be taking aspirin, ACE inhibitors, beta-blockers and statins. They must have their blood pressure, microalbumin, eyes and feet monitored.

In summary, type 2 diabetic patients without a markedly elevated fasting plasma glucose should start on sulfonyleurea or metformin. Our second agent is the other one that we did not start with. If two agents fail, we can add a third or go to bedtime insulin. Fifteen or 20 years after diagnosis, most patients are going to be on some form of insulin, whether it be BIDS therapy or total replacement. The new insulin analogs (rapid acting) are not much different, so you have three to choose from. The question is: Can inhaled insulins replace rapid-acting insulins?

New classes of drugs may improve beta-cell function, which is fantastic for diabetes, and we have seen weight loss over an extended period of time. The bottom line is control blood glucose however you can. ■

1. Painter NA. New and standard treatments options for patients with type 2 diabetes. Presented at the American Association of Diabetes Educators' 33rd Annual Meeting and Exhibition. Aug. 9-13, 2006. Los Angeles.
2. American Diabetes Association. Standards of medical care in diabetes. IV. Prevention/delay of type 2 diabetes. *Diabetes Care*. 2006;29(Suppl 1):S7-8.
3. UKPDS Group. U.K. prospective diabetes study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. *Diabetes*. 1995;44:1249-1258.
4. American Diabetes Association. Clinical practice recommendations. *Diabetes Care*. 2006;29(Suppl 1).

CME QUESTIONS

Circle the most appropriate answer in the "ANSWER SECTION" on the following page.

1. What are management goals in type 2 diabetes?
 - a. obtain tight glucose control
 - b. minimize or eliminate symptoms
 - c. prevent acute metabolic complications
 - d. delay or minimize microvascular complications
 - e. reduce the rate of morbidity and mortality from macrovascular disease
 - f. all of the above
2. What are the ADA glycemic goals?
 - a. HbA1c 7.0% and postprandial glucose of <90 mg/dL
 - b. HbA1c <6.0% and preprandial fasting glucose of 160 mg/dL
 - c. HbA1c <7.0% and preprandial fasting glucose of 90 mg/dL to 130 mg/dL
 - d. HbA1c <8.0% and a preprandial fasting glucose of 150 mg/dL
3. Lifestyle changes are important in all treatment regimens.
 - a. true
 - b. false
4. Which of the following is NOT a sulfonylurea?
 - a. glipizide
 - b. glyburide
 - c. metformin
 - d. glimepiride
5. Which of the following are NOT indicated as first-line therapy?
 - a. sulfonylureas
 - b. biguanides
 - c. thiazolidinediones
 - d. meglitinides
6. Which of the following is NOT symptom of hypoglycemia?
 - a. sweating
 - b. anxiety
 - c. elevated enhanced mood
 - d. lightheadedness
7. Which of the following are associated with metformin?
 - a. lactic acidosis
 - b. gastrointestinal distress
 - c. contraindicated in patients aged >80 years
 - d. should not be used in patients with CHF
 - e. all of the above
8. Weight gain is a significant side effect of thiazolidinediones.
 - a. true
 - b. false
9. Which of the following are indications of insulin as initial therapy in type 2 diabetes?
 - a. pregnancy
 - b. glucose >300 mg/dL
 - c. ketonuria
 - d. patient desire to start insulin
 - e. all of the above
10. What is considered the hallmark of assessing glycemic control?
 - a. urine test
 - b. self-monitored glucose testing
 - c. HbA1c
 - d. fructosamine

REGISTRATION/EVALUATION FORM: NEW AND STANDARD TREATMENT OPTIONS FOR TYPE 2 DIABETES

To obtain AMA/PRA category 1 credit, you must:

- Read the learning objectives and the CME article and complete the self-assessment test.
- Photocopy and complete this registration/evaluation form and record your test answers in the Answer Section below.
- Send the Registration/Evaluation form to **The Dulaney Foundation, PO Box 44408, Phoenix, AZ 85064, or fax to 602-508-4893.**
- Retain a copy of your test answers. Your answer sheet will be graded, and if you achieve a passing score of 70% or better, you will receive a CME credit letter awarding AMA/PRA category 1 credit within 4 weeks. If you do not achieve a passing score, you will be notified and offered the opportunity to complete the activity again.

ANSWER SECTION

Circle the best answer for each question on page 47.

1. A B C D E F 2. A B C D 3. A B 4. A B C D 5. A B C D
6. A B C D 7. A B C D E 8. A B 9. A B C D E 10. A B C D

REGISTRATION FORM

First name _____ Last name _____ Degree (MD, PhD) _____

Specialty _____

Institution or practice name _____

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Telephone _____ Fax _____ E-mail address _____

The processing fee has been underwritten by an educational grant from Eli Lilly and Company.

I attest that I have completed this activity as designed and I am claiming ____ (up to 1 credit) AMA/PRA category 1 credit.

Signature _____ Date _____

Credit for this activity is available until October 31, 2007.

The planning and execution of useful and educationally sound continuing education activities are guided in large part by input from participants. Please assist us in evaluating the effectiveness of this activity and make recommendations for future educational offerings by completing this evaluation form. Your response will help ensure that future programs are informative and meet the educational needs of all participants. Please note: CME credit letters and long-term credit retention information will only be issued upon receipt of this completed evaluation. Thank you for your cooperation.

OBJECTIVES

After successful completion of this program, you should be able to:

- | | | | | | |
|--|---|---|---|---|---|
| • identify the prevalence and pathophysiology of type 2 diabetes | 5 | 4 | 3 | 2 | 1 |
| • discuss how to select oral agents as either monotherapy or in combination to achieve desired treatment goals | 5 | 4 | 3 | 2 | 1 |
| • identify appropriate monitoring parameters of antihyperglycemic agents | 5 | 4 | 3 | 2 | 1 |
| • create a combination drug therapy regimen including new therapeutic agents to optimize patient outcomes | 5 | 4 | 3 | 2 | 1 |
- (Please circle the number that is most accurate; 5 represents strongly agree and 1 represents strongly disagree.)

OVERALL EVALUATION

- | | | | | | |
|--|---|---|---|---|---|
| • The information presented increased my awareness/understanding of the subject. | 5 | 4 | 3 | 2 | 1 |
| • The information presented will influence how I practice. | 5 | 4 | 3 | 2 | 1 |
| • The information presented will help me improve patient care. | 5 | 4 | 3 | 2 | 1 |
| • The faculty demonstrated current knowledge of the subject. | 5 | 4 | 3 | 2 | 1 |
| • The program was educationally sound and scientifically balanced. | 5 | 4 | 3 | 2 | 1 |
| • The program avoided commercial bias or influence. | 5 | 4 | 3 | 2 | 1 |
| • Overall, the program met my expectations. | 5 | 4 | 3 | 2 | 1 |
| • I would recommend this program to my colleagues. | 5 | 4 | 3 | 2 | 1 |
- (Please circle the number that is most accurate; 5 represents strongly agree and 1 represents strongly disagree.)

• If you anticipate changing one or more aspects of your practice as a result of your participation in this activity, please provide a brief description of how you plan to do so: _____

• Please provide any additional comments pertaining to this activity (positive and negative) and suggestions for improvements: _____