THE JOURNAL OF FAMILY PRACTICE

Diabetes drug update: How 4 new options stack up

3 new agents and a new delivery system for insulin

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Practice recommendations

- Inhaled insulin, a short-acting insulin for type 1 and type 2 diabetes, is comparable with traditional subcutaneous regimens in terms of hemoglobin A_{1c} and postprandial glucose reductions. It can also reduce the number of daily injections (**B**).
- Exenatide, which is indicated for type 2 diabetes in those uncontrolled on a sulfonylurea or metformin, provides a modest reduction in A_{1c} and fasting glucose and is best suited for those whose A_{1c} is within 1% of their goal. Among its advantages: weight loss and the potential to slow the progression of the disease (**B**).
- Sitagliptin is indicated for type 2 diabetes alone or in combination with metformin or a thiazolidinedione. It provides A_{1c} reductions that are comparable to exenatide and does not have high rates of gastrointestinal side effects. It may also improve beta-cell function (**B**).
- Pramlintide, which is indicated for type 1 or type 2 diabetes uncontrolled with mealtime insulin, provides modest reductions in A_{1c} and postprandial glucose—although it's more effective for those with postprandial hyperglycemia. It may reduce insulin dose requirements and the associated weight gain (**B**).

Strength of recommendation (SOR)

- **A** Good quality patient-oriented evidence
- **B** Inconsistent or limited-quality patient-oriented evidence
- **C** Consensus, usual practice, opinion, disease-oriented evidence, case series

The battle over glycemic control begins when you write out that first script for a patient for a sulfonylurea, metformin, or insulin. But it continues during every encounter thereafter, as you monitor your patient's progress, adjust dosages, and take advantage of new pharmacologic options. Recently, that list of options has expanded by 4: Three are new classes of agents, and the fourth is essentially a new delivery system for insulin. Inhaled insulin (Exubera) was approved by the Food and Drug Administration in January 2006, exenatide (Byetta) in April 2005, sitagliptin (Januvia) in October 2006, and pramlintide (Symlin) in March 2005 (**TABLE 1**).

Staying abreast of new agents like these is essential if we are ever going to get the upper hand on a disease that in 2002 affected 18.2 million people.[1] This review provides an at-a-glance summary of the key aspects of each agent, followed by a topline summary of their advantages and disadvantages.

Exubera: A new twist on insulin

The first dry powder inhaled insulin, which can be used in lieu of rapid- or short-acting injectable insulins, is now available. The question is: How does it stack up? Inhaled insulin has been studied in several clinical trials in both type 1 and type 2 diabetes (**TABLE 2**).[2–8] In type 1

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TABLE 1

New therapeutic options for diabetes

DRUG	INDICATIONS	DOSE	COST (AWP)*
Insulin, inhaled powder (Exubera)	Type 1 or type 2 diabetes mellitus	Administer 2–3 times a day just prior to meals. Dose (mg) = weight (kg) X 0.05 mg/kg. Calculated dose should be rounded down to nearest whole milligram	Kit (includes inhaler plus 270 1 - and 3-mg doses): $180 Combination pack (180 1- and 3-mg doses): $134 Combination pack (270 1- and 3-mg doses): $168
Exenatide (Byetta)	Adjunct therapy for type 2 diabetes uncontrolled with metformin or sulfonylurea	Initial: 5 mcg sc twice daily. May be increased to 10 mcg sc twice daily after 1 month (max dose)	5 mcg: $176.40/month 10 mcg: $207.00/month
Sitagliptin (Januvia)	Type 2 diabetes as monotherapy or in combination with metformin or thiazolidinedione	100 mg orally once daily	$174.96/month
Pramlintide (Symlin)	Adjunct therapy for type 1 or type 2 diabetes in uncontrolled patients using mealtime insulin (with or without sulfonylurea or metformin in type 2 diabetes)	**Type 1 diabetes:** Initial: 15 mcg sc prior to each meal. Titrate to 30-60 mcg prior to each meal as tolerated. **Type 2 diabetes:** Initial: 60 mcg sc prior to each meal. Titrate to 120 mcg sc prior to each meal.	$95.40/month

AWP = average wholesale price; sc = subcutaneously

*Cost from *Red Book Update* 2006; 25(9) (Montvale, NJ: Thomson PDR; 2006).

FAST TRACK

With inhaled insulin, the risk of hypoglycemia is the same or less than that of subcutaneous insulin

diabetes it's been combined with NPH insulin or ultralente insulin and compared with subcutaneous regimens of regular insulin with NPH insulin or ultralente insulin.[2,3,6] These studies showed a similar decrease in glycosylated hemoglobin (Hb A_{1c}) and 2-hour postprandial glucose between the inhaled and subcutaneous regimens. No studies comparing inhaled insulin powder containing regimens with subcutaneous regimens utilizing rapid acting insulin have been published.

In type 2 diabetes, inhaled insulin powder has been studied in combination with ultralente insulin, a sulfonylurea, and metformin.[4,5,7,8] For patients with uncontrolled type 2 diabetes on a sulfonylurea or metformin, the addition of inhaled insulin powder has been shown to reduce A_{1c} by 1.9% to 2.3%.[4,8] When combined with ultralente in type 2 diabetes, reductions in A_{1c} were comparable with traditional subcutaneous insulin regimens.

In addition, a few studies have looked at patient satisfaction with inhaled insulin. The findings: Inhaled insulin powder was linked to better satisfaction, convenience, ease of use, and social comfort in type 1 and 2 diabetes when compared to entirely subcutaneous regimens.[6,9,10]

Not an option for smokers or those with pulmonary disease

The most common side effects of inhaled insulin include hypoglycemia, weight gain, cough, and bitter taste. The risk of hypoglycemia appears to be about the same or less than that seen with subcutaneous insulin.[2] The same is true for weight gain, based on limited data.[11] Other potential concerns include the formation of insulin antibodies. Antibody formation is higher with inhaled insulin than with subcutaneous insulin, but the clinical significance at this point is not clear.[12]

TABLE 2

Inhaled insulin studies

STUDY	TYPE	DESIGN	A_{1c} CHANGE FROM BASELINE (%)
Skyler (2001)[3]	Type 1	RCT, 12 weeks	–0.6 (INH); –0.8 (INJ)
Weiss (2003)[4]	Type 2	RCT, 12 weeks INH + preexisting OHA vs preexisting OHA	–2.3 (INH + OHA) –0.1 (OHA)*
Quattrin (2004)[2]	Type 1	RCT, 6 months INH + U vs R + NPH	–0.2 (INH + U) –0.4 (R + NPH)
Hollander (2004)[5]	Type 2	RCT, 6 months INH + U vs R + NPH	–0.7 (INH + U) –0.6 (R + NPH)
Rosenstock (2004)[6]	Type 1 or type 2	RCT, 12 weeks INH + U vs conventional split/mixed regimen	**Type 1 diabetes:** –0.69 (INH + U) –0.85 (split/mixed) **Type 2 diabetes:** –0.61 (INH + U) –0.79 (split/mixed)
DeFronzo (2005)[7]	Type 2	RCT, 3 months INH vs rosiglitazone	–2.3 (INH) –1.4 (rosiglitazone)
Rosenstock (2005)[8]	Type 2	RCT, 12 weeks INH alone, INH + OHA, or OHA alone (all after OHA failure)	–1.4 (INH alone) –1.9 (INH + OHA) –0.2 (OHA alone)

A_{1C}, glycosylated hemoglobin; RCT, randomized controlled trial; INH, inhaled insulin; INJ, injected insulin; OHA, oral hypoglycemic agent; U, ultralente; R, regular insulin; NPH, NPH insulin

*$P<.05$

The drug's effect on lung function is also an issue. Inhaled insulin powder should not be used in patients who smoke (or those who have quit within the past 6 months) or who have underlying pulmonary disease. Smoking increases the drug's absorption and can lead to hypoglycemia.[13] The safety and efficacy of inhaled insulin in patients with underlying pulmonary disease remains unclear. Some short-term studies in those without underlying pulmonary disease found no effects on pulmonary function, while others showed a decline in lung function.[2–5]

The manufacturer reports that in trials lasting less than 2 years, both individual patients on inhaled insulin or a comparative agent experienced a decrease in pulmonary function.[14] Forced expiratory volume in 1 second (FEV_1) declined by ≥20% in 1.5% of inhaled insulin treated patients and in 1.3% of those on another agent. Carbon monoxide diffusing capacity (DL_{CO}) decreased by ≥20% in 5.1% of those on inhaled insulin and 3.6% of those on a comparative agent. Thus, the manufacturer recommends a baseline spirometry (FEV_1) and possibly DL_{CO}. The manufacturer does not recommend the use of inhaled insulin if FEV_1 or DL_{CO} is <70% predicted.

A patient's pulmonary function should be assessed after 6 months on the drug and then annually thereafter. Should FEV_1 decline by ≥20% from baseline or pulmonary symptoms develop while on therapy, you'll need to discontinue the inhaled insulin. Two longer-term trials of up to 4 years in duration did not show any significant effect on pulmonary function.[15,16]

A convenience with a price tag

Inhaled insulin powder is available in single-dose 1-mg and 3-mg blister packs and should be used no more than 10 minutes

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Should FEV_1 decline by ≥20% from baseline or pulmonary symptoms develop, you'll need to stop inhaled insulin

TABLE 3

Exenatide studies

VARIABLE	BUSE (2004)[17]	DEFRONZO (2005)[18]	KENDALL (2005)[19]
BASELINE DATA			
Number of patients	377	336	733
Age (yrs)	55	53	55
BMI (kg/m²)	33	34	34
A_{1c} (%)	8.6	8.2	8.5
FPG (mg/dL)	184	172	180
Concomitant therapy	Sulfonylurea	Metformin	Sulfonylurea + metformin
RESULTS—CHANGE FROM BASELINE			
A_{1c} (%)	5 mcg dose: –0.5 10 mcg dose: –0.9	5 mcg dose: –0.4 10 mcg dose: –0.8	5 mcg dose: –0.6 10 mcg dose: –0.8
FPG (mg/dL)	5 mcg dose: –5.4 10 mcg dose: –10.8	5 mcg dose: –7.2 10 mcg dose: –10.1	5 mcg dose: –9 10 mcg dose: –11
Weight (kg)	5 mcg dose: –0.9 10 mcg dose: –1.6	5 mcg dose: –1.6 10 mcg dose: –2.8	5 mcg dose: –1.6 10 mcg dose: –1.6

BMI, body mass index; A_{1c}, glycosylated hemoglobin; FPG, fasting plasma glucose.

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Because of pulmonary function concerns, injectable insulins may be a safer alternative to inhaled insulin

before meals. To administer the insulin, the patient breathes out, inhales the dose, and then holds his breath for 5 seconds. The patient will, however, need to load each dose.

Each milligram of the inhaled insulin is equivalent to 2 to 3 units of regular subcutaneous insulin. Inhaled insulin powder is a bolus insulin that targets postprandial glucose and thus can be used in place of rapid- or short-acting injectable insulins.

Patients with type 1 diabetes will require an injectable basal insulin (intermediate or long acting) in conjunction with the inhaled insulin. In type 2 diabetes, inhaled insulin can be used in conjunction with a basal insulin or oral therapy. In patients who are currently using an injectable bolus insulin, the package insert contains a dose conversion table. Initial doses can also be estimated based on weight.

Inhaled insulin may reduce the number of daily insulin injections to 1 to 2 times a day, and that could translate into improved patient compliance, although this has not been directly evaluated. The cost of Exubera is significantly higher than traditional subcutaneous insulin. An Exubera kit costs $180, which includes an inhaler and 270 1 mg and 3 mg doses.

The take-home message is... While inhaled insulin offers comparative efficacy to subcutaneous regimens, there's a potential for short-term decreases in pulmonary function. The long-term effects are largely unknown. As a result, rapid or short-acting injectable insulins may be a safer alternative. Inhaled insulin's role in type 2 diabetes is less clear at this time. In patients with type 2 disease, it would be an option when considering the addition of insulin. However, there's limited data on using inhaled insulin in place of an oral agent.

Exenatide (Byetta): From the mouths of (gila) monsters

Exenatide is synthetic exendin-4, originally isolated from the saliva of the gila monster lizard. It binds to and activates the pancreatic GLP-1 (glucagon like peptide-1) receptor resulting in an increase in insulin secretion from beta

Glycemic control with an eye toward cardiovascular risk

In 2002 diabetes affected 18.2 million individuals, or 6.3% of the US population.[1] The prevalence is expected to double within the next 20 years along with significant increases in cardiovascular disease.[1]

There are 2 theories as to how diabetes increases cardiovascular mortality.[35,36] The first suggests that beta-cell dysfunction and subsequent failure leads to elevated glucose that causes an increase in oxidative stress, and thus leads to cardiovascular disease. The second theory suggests that insulin resistance causes endothelial dysfunction along with inflammation and fibrinolysis and this leads to cardiovascular disease. It's likely that both of these theories are at work, since we know that elevated blood glucose levels can lead to elevated insulin levels and insulin resistance can cause beta-cell dysfunction.

The research on the diabetes/CVD link is intriguing. For instance, there is data suggesting that insulin sensitizing agents may have a positive effect on cardiovascular disease.[37] In addition, trials are being conducted between sulfonylureas and thiazolidinediones to evaluate reductions in CVD.[38] It may not be long before reducing cardiovascular morbidity and mortality becomes a goal of treatment in the management of our patients with diabetes.

cells in the presence of hyperglycemia. It also suppresses glucagon secretion, slows gastric emptying, and decreases food intake. Its use is limited to type 2 diabetes; it has no role in the management of type 1 diabetes.

Three large placebo-controlled trials evaluated the use of exenatide as adjunct therapy to a sulfonylurea or metformin in patients unable to achieve glycemic control (**TABLE 3**).[17–19] Hemoglobin A_{1c} was reduced by 0.4% to 0.6% with 5 mcg twice daily and 0.8% to 0.9% with 10 mcg twice daily. The effects on fasting plasma glucose were less impressive, though not surprising due to the drug's mechanism of action.

One other trial compared exenatide, 10 mcg twice daily, to insulin glargine, one daily dose titrated to achieve fasting glucose less than 100 mg/dL in patients with type 2 diabetes uncontrolled on a sulfonylurea and metformin, which represents a relatively common clinical scenario.[20] The reduction in A_{1c} after 26 weeks was comparable between the 2 groups (1.11% for both).

Exenatide was more effective at reducing postprandial glucose, while glargine more effectively reduced fasting glucose. Weight increased by an average of 1.8 kg in the glargine group and decreased by 2.3 kg with exenatide. Rates of symptomatic hypoglycemia were similar between the 2 groups. Gastrointestinal symptoms were more common in the exenatide group, including nausea (57.1% vs 8.6%), vomiting (17.4% vs 3.7%), and diarrhea (8.5% vs 3%). This led to a significant difference in the number of subjects who withdrew from the study (19.4% for exenatide vs 9.7% for glargine). It's important to note that the mean baseline A_{1c} values were only moderately elevated (8.2% in exenatide vs 8.3% in glargine) and thus not representative of those with very poor control.

One other research finding is worth mentioning here. GLP-1 administration has been shown to result in beta-cell proliferation and increased beta-cell mass in animals and *in vitro* studies.[21] Thus, in theory, exenatide could slow the progression of type 2 diabetes. However, long-term studies are needed to address this.

Bad news: Transient nausea
Good news: Unrelated weight loss

Nausea is the most common side effect and occurs in 36% to 39% of patients

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Exenatide was more effective at reducing postprandial glucose, while glargine more effectively reduced fasting glucose

with the 5-mcg dose and 45% to 50% of those with the 10-mcg dose, although it's usually transient.[17–19,22] Exenatide results in a moderate reduction in weight (approximately 2–4 pounds), which does not appear to be related to the adverse gastrointestinal effects. There's a risk of mild to moderate hypoglycemia when exenatide is used with a sulfonylurea, which is most likely due to the effects of the sulfonylurea.

Exenatide reportedly results in low levels of antibodies in approximately 40% of patients but had no affect on glucose control.[22] About 6% of patients may develop high antibody levels, which could result in a diminished response.[22]

Exenatide is dispensed as a injection pen containing a 30-day supply of medicine. The patient will need to administer it subcutaneously in the thigh, abdomen, or upper arm no more than 60 minutes before morning and evening meals. The cost of exenatide is substantially higher than sulfonylureas, metformin, or insulin but comparable with pioglitazone and rosiglitazone.

The take-home message is... Exenatide is not currently recommended for use as initial therapy in type 2 diabetes. In clinical trials, exenatide 10 mcg twice daily achieved A_{1c} reductions of about 1%. Oral agents typically produce reductions of 1% to 2%, although the effects of combining oral agents may not always be additive.[23,24]

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Exenatide is best suited for those whose A_{1c} is within 1% of their treatment goal

At this point, exenatide is best suited for those whose A_{1c} is within 1% of their treatment goal, especially in those unable to take another oral agent or insulin (eg, due to renal or hepatic impairment or congestive heart failure) and those who have elevated postprandial glucose. Otherwise, adding an oral agent or insulin would likely produce the best results.

Sitagliptin (Januvia): It, too, focuses on GLP-1

Sitagliptin (Januvia), the first drug in a new class of agents called dipeptidyl-peptidase-4 (DPP-4) inhibitors, was just approved in October 2006 for the treatment of type 2 diabetes. This drug, like exenatide, focuses on the actions of GLP-1. Active GLP-1 is rapidly degraded by the DPP-4 enzyme. Inhibiting this enzyme results in an increased concentration and prolonged action of GLP-1.

There are some key differences between DPP-4 inhibitors and GLP-1 agonists such as exenatide. Specifically, DPP-4 inhibitors do not appear to have significant rates of nausea and vomiting, can be given orally, have no effect on gastric emptying, and are weight neutral. Limited evidence suggests that, like GLP-1 agonists, they may also improve chronic beta-cell function.[25] Side effects include stuffy or runny nose and sore throat, upper respiratory infection, and headache.

Published studies are sparse at this point. One dose finding study randomized 552 patients to one of five treatments: placebo, sitagliptin (25, 50, or 100 mg once daily), or 50 mg twice daily. Baseline A_{1c} ranged from 5.8% to 10.4% and after 12 weeks of treatment, the sitagliptin 100 mg once daily group had the largest reduction in A_{1c}. Reductions were dependent on baseline A_{1c}: Those with a baseline A_{1c} <7%, 7% to 8.5%, or 8.5% to 10% had reductions of 0.4%, 0.6%, and 0.8%, respectively.[26]

Renal patients require a change in dose

The recommended dose of sitagliptin is 100 mg by mouth once a day as monotherapy or in combination with metformin or a thiazolidinedione. You'll need to reduce the dose in those patients with renal impairment.

The take-home message is... This newest class of medications exhibits some potential advantages and disadvantages when compared to the GLP-1 agonists. On the plus side, it does not appear to cause nausea and vomiting and can be given orally. On the downside, it has no effect on gastric emptying, which means

TABLE 4

Pramlintide studies

STUDY	TYPE OF DIABETES	DESIGN	A_{1c} CHANGE FROM BASELINE (%)	PPG CHANGE FROM BASELINE (MG/DL)
Fineman (1999)[30]	Type 1	DB, PC, 26 wk	–0.2* (60 mcg 3x/day) –0.1 (90 mcg 2x/day) –0.1 (90 mcg 3x/day) 0.1 (placebo)	NA
Gottlieb (1999)[31]	Type 2	DB, PC, 26 wk	–0.3 (90 mcg 2x/day) –0.4 (90 mcg 3x/day) –0.4* (120 mcg 2x/day) –0.1 (placebo)	NA
Nyholm (1999)[32]	Type 1	DB, PC, 4 wk	NA	–126 (1-hr) –72 (2-hr) (30 mcg 4x/day)
Whitehouse (2002)[27]	Type 1	R, DB, PC, 52 weeks	–0.39* (30–60 mcg 4x/day) –0.12 (placebo)	NA
Ratner (2002)[28]	Type 2	R, DB, PC, 52 weeks	–0.3 (30 mcg 3x/day) –0.5 (75 mcg 3x/day) –0.6* (150 mcg 3x/day) –0.2 (placebo)	NA
Hollander (2003)[29]	Type 2	R, DB, PC, 52 weeks	–0.35 (90 mcg 2x/day) –0.62*(120 mcg 2x/day) –0.22 (placebo)	NA
Levetan (2003)[33]	Type 1	R, DB, PC, 4 weeks	NA	–79.2 (1-hr) –64.8 (2-hr) (30 mcg 3x/day)
Ratner (2004)[34]	Type 1	R, DB, PC, 52 weeks	–0.29* (60 mcg 3x/day) –0.34* (60 mcg 4x/day) –0.04 (placebo)	NA

A_{1c}, glycosylated hemoglobin; PPG, postprandial glucose; DB, double-blind; PC, placebo-controlled; R, randomized; NA, not accessed.

*$P<.05$ vs placebo.

it may not reduce postprandial glucose as much. In addition, it does not cause weight loss (although it does not cause weight gain either).

Pramlintide (Symlin): Shoring up deficiencies

Pramlintide is a synthetic analog of human amylin, a neuroendocrine hormone secreted by pancreatic beta cells. Amylin works in concert with insulin to suppress postprandial glucagon secretion and slow carbohydrate absorption by delaying gastric emptying. Amylin is cosecreted with insulin so patients with type 1 diabetes have an absolute deficiency of amylin while those with type 2 diabetes have a progressively declining production. Thus, pramlintide may be used in either type of diabetes.

In clinical trials, pramlintide produced modest reductions in A_{1c} (0.1–0.62%) and more impressive reductions in postprandial glucose (64.8–126 mg/dL) in adults with type 1 or 2 diabetes (**TABLE 4**).[27–34] In addition, it has been shown to minimize insulin dose increases and the weight gain associated with insulin.[27,29–31,34]

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On the plus side: sitagliptin doesn't appear to cause nausea and it can be given orally

What's in the pipeline

Inhaled insulin, exenatide, sitagliptin, and pramlintide are exciting developments in the management of diabetes. They offer potential advantages over currently available therapies, but also have their share of limitations. As we gain further experience with them, their roles may increase.

Other agents are also on the horizon and worth noting. Vildagliptin (Galvus), a DPP-4 inhibitor, is expected to become available shortly. Another drug, liraglutide, a synthetic GLP-1 analog with a longer half-life than exenatide, is currently in phase III trials. A long-acting exenatide, given once weekly, is in phase II trials.

Time will tell as to how these agents—both the recently approved ones and those in the pipeline—will aid in our battle against diabetes. What is clear is that our arsenal will continue to grow, and we we'll continue to make inroads—one patient encounter at a time.

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While pramlintide offers a different approach to postprandial glucose, it doesn't appear to offer distinct advantages

Nausea is a factor, as is slowed gastric emptying

The most common adverse effects include nausea, vomiting, and anorexia. Rates of nausea in studies have ranged from 9.5% to 59% with most cases being mild to moderate in nature and resolving in 2 to 8 weeks.[27–29]

Pramlintide in itself does not cause hypoglycemia, however when administered with insulin, it does increase the risk of insulin-induced hypoglycemia. Pramlintide should not be used in patients with gastroparesis since it slows gastric emptying. Pramlintide should not be mixed with insulin in the same syringe as there is insufficient data to support the safety of doing so. Thus, it may increase the number of daily injections for patients.

Pramlintide may also interfere with agents that stimulate gastric motility and slow the absorption of other drugs. The manufacturer recommends separating the administration of analgesics and pramlintide by 1 to 2 hours since coadministration could delay the analgesic onset.

Starting pramlintide means reductions elsewhere

Pramlintide is supplied as a 5 mL vial containing 0.6 mg/mL. Immediately prior to each major meal, the patient will need to administer it subcutaneously into the abdomen or thigh (arm administration is not recommended due to varying absorption). When initiating pramlintide in a patient, you'll need to reduce the patient's rapid/short insulin (including fixed-mixed insulin such as 70/30) by 50%.

In type 1 diabetes, the pramlintide dose may be increased in 15-mcg increments, provided that the patient has not experienced clinically significant nausea for at least 3 days and his glycemic goals are not met. In type 2 diabetes, the initial pramlintide dose may be doubled, provided that the patient has not experienced clinically significant nausea for 3 to 7 days and his glycemic goals are not met. In either case, should the increase in dose result in intolerable nausea, you may need to drop the dose back to the previous dose.

The take-home message is... While pramlinitide offers a different approach (as compared with insulin) to lowering postprandial glucose, there is no evidence that it offers any distinct advantage to the patient. Thus, it may be best to simply increase the premeal insulin dose. Should continued weight gain be a major concern, then pramlintide could play a role as adjunct therapy to mealtime insulin. Further studies evaluating quality of life and patient acceptance are needed. ■

Disclosure

The authors have no financial conflicts of interest to report.

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FAST TRACK

In the pipeline:

- **Vildagliptin (Galvus) may be available soon**
- **Liraglutide, in phase III trials**
- **Long-acting exenatide, in phase II trials**