

Therapies for Diabetes: Pramlintide and Exenatide

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The American Diabetes Association currently recommends an A1C goal of less than 7 percent. However, many patients are unable to achieve this goal by using oral drug combinations or diet and exercise, leaving insulin as the only treatment option. In most cases, insulin is initiated later in therapy because of its inconvenience and adverse effects (e.g., weight gain, hypoglycemia, possible role in atherogenesis). Although insulin effectively helps patients attain glucose goals, the search for new agents continues. Two injectable agents, pramlintide and exenatide, were approved in 2005 for the treatment of diabetes. Pramlintide, indicated for use in patients with type 1 and 2 diabetes, is a synthetic analogue of human amylin that acts in conjunction with insulin to delay gastric emptying and inhibit the release of glucagon. Exenatide, a glucagon-like peptide-1 mimetic, has multiple mechanisms for lowering glucose levels, including the enhancement of insulin secretion, and is indicated for use in patients with type 2 diabetes. Clinical trials have shown that both agents reduce, by a statistically significant degree, A1C levels (0.3 to 0.7 percent more than placebo), fasting plasma glucose levels, and body weight (3 to 5 lb [1.4 to 2.3 kg]). No studies have examined their effects on diabetic complications, cardiovascular disease, or overall mortality. Pramlintide and exenatide may help make glycemic goals more attainable. (*Am Fam Physician* 2007;75:1831-5. Copyright © 2007 American Academy of Family Physicians.)

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Over the past few years, several new products have become available for the treatment of diabetes, and insulin has been modified (i.e., changed its duration of action) and made available for inhaled use. Pramlintide (Symlin) and exenatide (Byetta), injectable drugs that utilize the alternative hormones amylin and glucagon-like peptide-1 (GLP-1), respectively, have been approved for the management of diabetes. These agents may help make glycemic goals more attainable. *Table 1*¹⁻⁴ presents dosing information and possible adverse effects for pramlintide and exenatide. *Table 2* lists the sites of action for the therapies.

Issues with Insulin Therapy

The 2006 American Diabetes Association (ADA) guideline recommends a general A1C goal of less than 7 percent; a higher goal may be appropriate in young children, older patients, patients with comorbid conditions, or patients in whom hypoglycemia poses a significant risk.⁵ Patients with type 2 diabetes are usually instructed on lifestyle modifications with or without oral therapy to manage the disease. In most patients, these treatment modalities eventually are not adequate to achieve glucose control because of declining

beta cell function and increasing insulin resistance in the liver and muscle tissue.⁶ If blood sugar cannot be controlled with oral medications, insulin has been the alternative treatment. Insulin, however, is not favored by many patients and physicians because of the therapy's inconvenience, the need for frequent blood sugar monitoring, and the risk of weight gain and hypoglycemia.⁷

Although studies have shown that insulin, used alone or in combination with oral agents, helps reduce A1C levels,^{8,9} the U.K. Prospective Diabetes Study found no significant reduction in macrovascular complications with intensive insulin therapy compared with sulfonylurea therapy or diet.¹⁰ The introduction of pramlintide and exenatide has given physicians additional treatment options to help improve glucose control.

Pramlintide

Pramlintide is an injectable, synthetic analogue of human amylin, a hormone secreted by the beta cells in response to increased glucose levels. Amylin production is minimal or absent in patients with type 1 diabetes and reduced in patients with type 2 diabetes.^{2,11} Pramlintide acts in conjunction with insulin to delay gastric emptying and inhibit the release of glucagon.¹¹ The suppression of

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	Evidence rating	References
Pramlintide (Symlin) has been shown to cause a statistically significant weight loss and reduction in A1C levels when used in conjunction with insulin, metformin (Glucophage), or a sulfonylurea.	B (weight loss) C (other outcomes)	2, 11-14
Exenatide (Byetta) has been shown to cause a statistically significant weight loss and reduction in fasting plasma glucose, postprandial glucose, and A1C levels when used in conjunction with metformin or a sulfonylurea.	B (weight loss) C (other outcomes)	17-20

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 1754 or <http://www.aafp.org/afpsort.xml>.

these processes slows the rate of glucose absorption, causing decreased postprandial glucose levels.¹² Pramlintide is indicated for patients with type 1 diabetes who take mealtime insulin and in patients with type 2 diabetes who have uncontrolled glucose levels despite optimal therapy with mealtime insulin, metformin (Glucophage), or a sulfonylurea.

Randomized controlled trials (RCTs) have shown that pramlintide has favorable effects on body weight and A1C levels. In one RCT, 656 patients with type 2 diabetes and a mean A1C level of 9.1 percent were given pramlintide (60, 90, or 120 mcg [10, 15, or 20 units] twice a day) or placebo. Patients who received the highest dose had a 0.62 percent ($P < .05$) reduction in A1C and a mean weight loss of 3 lb,

Table 1. Overview of Pramlintide and Exenatide Therapy for Diabetes

Dosing		Incidence of adverse effects in patients with type 2 diabetes (%)*	Cost per month†
Type 1 diabetes	Type 2 diabetes		
Pramlintide (Symlin)¹			
Starting dosage: 15 mcg (2.5 units) SC immediately before major meals, increased by 15 mcg every three to seven days as tolerated Target dose: 60 mcg (10 units)	Starting dosage: 60 mcg SC immediately before major meals, increased to target dose in three to seven days as tolerated Target dose: 120 mcg (20 units)	Nausea: 28.0 Headache: 13.0 Anorexia 9.0 Abdominal pain: 8.0 Vomiting: 8.0 Severe hypoglycemia (i.e., patient needed assistance from another person): 4.7 Severe hypoglycemia requiring medical assistance: 0.4	120 mcg three times a day: \$382
Exenatide (Byetta)³			
Not indicated	Starting dosage: 5 mcg twice a day within one hour before morning and evening meals Target dose: 10 mcg twice a day after one month of therapy if goals are not achieved	Nausea: 44.0 Diarrhea: 13.0 Vomiting: 13.0 Dizziness: 9.0 Headache: 9.0 Dyspepsia: 6.0 Hypoglycemia (exenatide plus sulfonylurea): 14.4 (5 mcg), 35.7 (10 mcg) Hypoglycemia (exenatide plus metformin [Glucophage]): 4.5 (5 mcg), 5.3 (10 mcg)	5 mcg twice a day: \$176 10 mcg twice a day: \$207

SC = subcutaneously; FDA = U.S. Food and Drug Administration.

*—Pramlintide adverse effects are from long-term trials of patients with type 2 diabetes who are taking pramlintide in conjunction with insulin. Exenatide adverse effects are for all dosages.

†—Estimated cost to the pharmacist based on average wholesale prices (rounded to the nearest dollar) in Red Book. Montvale, N.J.: Medical Economics Data, 2006. Cost to the patient will be higher, depending on prescription filling fee.

Information from references 1 through 4.

1 oz (1.4 kg), compared with a 0.25 percent reduction in A1C and a mean weight gain of 1 lb, 5 oz (0.6 kg) in the placebo group.¹³ There were no significant differences in A1C levels and weight gain between the placebo group and patients who received lower doses of pramlintide.¹³

A double-blind RCT showed a small but statistically significant reduction in A1C levels in patients who received pramlintide (30 or 60 mcg four times a day or 60 mcg three times a day) when compared with placebo (0.51 to 0.58 percent versus 0.27 percent reduction).¹⁴ Long-term studies support findings that the administration of pramlintide with mealtime insulin leads to a statistically significant weight loss and a modest reduction in A1C levels.^{2,11} Although some data suggest that the weight loss may be transient, studies of a longer duration are warranted to confirm this effect.¹²

Comments

A U-100, 0.3-mL syringe is recommended for administration; micrograms must be converted to units to ensure a correct dose; nausea (more commonly reported in type 1 patients²) is dose-dependent and appears to resolve over time; must be given in conjunction with insulin therapy; FDA pregnancy category C; should be given to nursing mothers only if the benefits of use outweigh the risks; safety and effectiveness in children have not been determined

Nausea and vomiting can be reduced by slowly titrating the dose⁴; not recommended for patients with a creatinine clearance less than 30 mL per minute (0.50 mL per second), for children, or for patients with severe gastrointestinal disease

Table 2. Sites of Action for Pramlintide (Symlin) and Exenatide (Byetta)

Site	Action
Brain	Improves satiety
Liver	Inhibits glucagon release
Pancreas	Stimulates insulin release and beta cell proliferation and differentiation (exenatide only)
Stomach	Slows gastric emptying

Severe hypoglycemia can occur approximately three hours after insulin and pramlintide are administered concurrently.^{1,11} Long-term clinical trials have shown that approximately 8 percent of patients with type 2 diabetes who use pramlintide for up to three months experience a severe hypoglycemic episode for which they require assistance from another person.¹ The incidence decreases as patients continue therapy.¹ It is recommended that mealtime insulin be reduced by 50 percent when pramlintide is initiated; and that to reduce hypoglycemia, pramlintide be taken with a meal that includes at least 250 calories or contains more than 30 g of carbohydrates.¹ Insulin and pramlintide should not be mixed because of possible compatibility issues.¹²

Pramlintide (U.S. Food and Drug Administration pregnancy category C) should be given to nursing mothers only if the benefits of use outweigh the risks. Its safety and effectiveness in children have not been determined. Because pramlintide delays gastric emptying, it should not be used with drugs that have similar effects. In addition, pramlintide should be given one hour before or two hours after the administration of medications that require rapid absorption for effectiveness (e.g., analgesics).¹ Patients should be carefully selected because of the risk of hypoglycemia, complexity of dosing and administration, and cost.¹⁵

No studies have evaluated whether pramlintide reduces the risk of micro- or macrovascular complications of diabetes or overall mortality. Adding pramlintide to existing therapy may allow patients to maintain or slightly decrease their current insulin doses while minimizing weight gain. Pramlintide can be used in patients with type 1 or 2 diabetes and must be used with insulin, whereas exenatide is contraindicated in patients with type 1 diabetes.

Exenatide

Exenatide, a GLP-1 mimetic, is a synthetic form of exendin-4 (a 39-amino acid peptide). In its natural form, exendin-4 is derived from the saliva of the Gila monster, a species of venomous lizard.¹⁶ GLP-1 is secreted from L cells in the intestine in response to food intake and triggers the secretion and synthesis of insulin from the pancreas.⁴ Exenatide exhibits actions similar to mammalian GLP-1,

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including glucose-dependent enhancement of insulin secretion, suppression of glucagon secretion, promotion of beta cell proliferation and differentiation and neogenesis, improvement in satiety, and delay in gastric emptying.

Exenatide is indicated for patients with type 2 diabetes who have failed to achieve glycemic control despite adequate therapy with metformin, a thiazolidinedione, a sulfonylurea, or a combination of these agents. Exenatide has not been studied in conjunction with other hypoglycemic agents (including insulin)¹⁶ and, therefore, is contraindicated in patients with type 1 diabetes.

Studies have shown that exenatide reduces, by a statistically significant degree, at least one of the following end points: body weight and fasting plasma glucose, postprandial glucose, and A1C levels.¹⁶⁻²⁰ One study compared a combination of sulfonylurea and exenatide with placebo in patients who had an average baseline A1C level of 8.6 percent.¹⁹ In the combination group, patients taking a 10-mcg dose of exenatide had a 0.86 percent reduction in A1C, and patients taking a 5-mcg dose of exenatide had a 0.46 percent reduction in A1C (adjusted $P \leq .0002$ for pairwise comparisons). Patients in the placebo group had a 0.12 percent increase in A1C.¹⁹ Another study compared a combination of metformin and exenatide with placebo; patients had

Pramlintide can be used in patients with type 1 or 2 diabetes and must be used with insulin, whereas exenatide is contraindicated in patients with type 1 diabetes.

an average baseline A1C level of 8 percent. Patients taking a 10-mcg dose of exenatide had a 0.78 percent reduction in A1C, and patients taking a 5-mcg dose of exenatide had a

0.40 percent reduction in A1C (adjusted $P \leq .0002$ for pairwise comparisons); patients in the placebo group had a 0.08 percent increase in A1C.²⁰

A 26-week, open-label RCT compared exenatide with insulin glargine (Lantus); patients had an average baseline A1C level of 8.3 percent. The absolute reduction in A1C was similar between the exenatide and insulin glargine groups (1.16 and 1.14 percent, respectively).²¹ Patients in the insulin glargine group gained weight, whereas patients treated with exenatide had a statistically significant weight loss (mean: 4 lb, 3 oz [1.9 kg]).²¹ Patients taking exenatide had less nocturnal hypoglycemia but a much greater incidence of nausea, vomiting, and diarrhea.²¹

The incidence of hypoglycemia appears to be greater in patients taking exenatide in conjunction with a sulfonylurea; therefore, sulfonylurea needs to be reduced when

exenatide is added to therapy. There have been no hypoglycemic episodes reported in patients taking exenatide in conjunction with metformin. Because exenatide delays gastric emptying and may alter the rate and extent of absorption of certain drugs, doses of exenatide should be given at least one hour after the administration of drugs that are dependent on threshold concentrations for effectiveness (e.g., oral contraceptives, antibiotics).³

The use of exenatide is limited because it is indicated only in patients taking metformin, a sulfonylurea, and/or a thiazolidinedione. A high incidence of gastrointestinal adverse effects and cost may also limit its use. There is insufficient evidence to determine the value of exenatide in patients with A1C levels higher than those represented in the studies; furthermore, no studies have shown that exenatide reduces diabetic complications, cardiovascular complications, or mortality. Additional studies are needed to determine exenatide's value and role in therapy.

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