

## Pramlintide in the Management of Obesity

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**Abstract:** Obesity is a common problem that can lead to numerous comorbid conditions, including Type 2 diabetes. Currently, there are few pharmacologic options available to help obese patients lose weight. Pramlintide is an injectable, amylin analogue that is indicated in patients with Type 1 and Type 2 diabetes for use in conjunction with insulin to improve glycemic control. In addition to helping patients decrease hemoglobin A1c levels, pramlintide has also been shown to minimize weight gain, especially in patients with Type 2 diabetes. Studies have been conducted in various patient types, including those patients without diabetes, and the drug tends to have a positive effect on weight loss. It appears that the drug is well tolerated in patients without diabetes; however, current studies have been conducted in small patient populations. Additional research needs to be carried out to determine if the drug is a viable option for obese patients who have failed to respond to other weight loss products.

**Keywords:** obesity, pramlintide, type 2 diabetes, type 1 diabetes

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Obesity is a significant problem that can lead to multiple co morbid conditions. According to the Centers of Disease Control (CDC), in 2008 only one state, Colorado, had an incidence of obesity less than 20 percent.<sup>1</sup> There are few approved weight loss agents available, which has prompted researchers to look for alternatives to treat obesity. One such product is pramlintide. Pramlintide is an amylin analogue used in the treatment of diabetes. Amylin analogues have been shown to facilitate weight loss in patients with diabetes; therefore, they may be a viable therapeutic option in other patients where weight loss is imperative. This article will focus on the weight loss effect of pramlintide in patients with diabetes, due to the fact that studies in obese patients without diabetes are minimal. However, the available studies in patients without diabetes will be discussed.

## Pramlintide

Pramlintide is classified as an amylin analogue.<sup>2</sup> Amylin is secreted by the B-cells in the pancreas in conjunction with insulin secretion. Like Amylin, pramlintide suppresses hepatic glucagon secretion leading to a decrease in hepatic glucose production. In addition, it also slows gastric emptying, resulting in a decrease in the amount of glucose that enters the circulation postprandially. It also may promote a feeling of satiety, leading to a reduction in caloric intake.<sup>3</sup> Pramlintide is administered subcutaneously and has a bioavailability of 30%–40%. Peak plasma levels are achieved within 20 minutes after injection and the half-life is approximately 48 minutes. The duration of effect is 3 hours and the product is primarily eliminated in the urine; however, dosage adjustments in patients with renal insufficiency are not required. Pramlintide must be given in conjunction with insulin; however, it cannot be mixed with insulin and should be given in a site that is away from the concomitant insulin injection site. The initial dose in patients with Type 2 diabetes is 60 mcg, just prior to meals, titrating after 3–7 days to 120 mcg. When initiating therapy all insulin doses should be decreased by 50% to avoid hypoglycemia.

## Clinical Efficacy

The main focus of this clinical efficacy section is to highlight the weight reduction effects of amy-

lin replacement with pramlintide therapy. For this purpose, the primary emphasis is placed on trials evaluating pramlintide use in patients with both type 1 and type 2 (insulin-treated and noninsulin-treated) diabetes as well as in obese non-diabetic patients. Pramlintide is currently only indicated for use in patients with diabetes as adjunct therapy who are using mealtime insulin and have not achieved optimal blood glucose control even with increasing insulin treatment.<sup>4</sup>

## Pramlintide Use in Patients with Type 1 Diabetes

Only about 10% of type 1 patients achieve target A1c levels; however, intensification of insulin therapy is usually accompanied by an increased incidence of hypoglycemia and weight gain.<sup>5</sup> To date there have been three clinical trials<sup>6–8</sup> and a pooled analysis<sup>9</sup> evaluating pramlintide's efficacy in type 1 diabetes patients, which are summarized in Table 1. Long-term clinical trials ranging from 29 to 52 weeks have demonstrated a statistically significant weight loss in type 1 patients. A 29-week dose escalation study evaluated pramlintide doses ranging from 15 mcg to 60 mcg administered with meals on changes in weight associated with reduction in A1c.<sup>8</sup> Doses were titrated by 15-mcg weekly based on whether patients reported the occurrence of nausea. Patients treated with pramlintide plus insulin achieved a significant reduction in mean body weight ( $-1.3 \pm 0.30$  kg) when compared to those patients treated with placebo plus insulin ( $+1.2 \pm 0.24$  kg). A 52-week study also demonstrated reduction in weight with the addition of pramlintide to insulin therapy in type 1 diabetes patients.<sup>7</sup> The efficacy portion of the clinical trial evaluated two dosages of pramlintide, 60 mcg with meals and 60 mcg four times daily in addition to insulin therapy. Patients treated with pramlintide in addition to insulin experienced a significant reduction in body weight as compared to placebo plus insulin treated patients. An additional long-term study, published only in abstract, concluded that the addition of pramlintide to insulin therapy improved glucose and weight control in patients with type 1 diabetes.<sup>10</sup>

A randomized study documented weight loss in subjects randomized to treatment with pramlintide

**Table 1.** Type 1 DM Table focusing on mean change in body weight from baseline.

Reference #	n	Patient population	Design	Duration	Dose	Change in weight	Significance	Severe hypoglycemia <sup>a</sup>
6	480	T1DM	R, DB, parallel study	52 wk with open enrollment extension to an additional 1 year	30 to 60 mcg qid	Double Blind Study: weight loss in Tx group (-0.5) Open Label Extension: Tx group gained weight, Placebo group lost weight during open enrollment tid: -0.4 kg qid: -0.4 kg P: 0.8	At Week 13, 26 and 52 p < 0.001	30 mcg: 0.43 ± 0.07 <sup>b</sup> 60 mcg: 1.24 ± 0.12
7	651	T1DM	R, DB, PC, parallel-group, MC	52 wk	60 mcg tid, 60 mcg qid or 90 mcg tid	tid: -0.4 kg qid: -0.4 kg P: 0.8	p = 0.027 p = 0.40	tid: 0.74 ± 0.12 <sup>c</sup> qid: 0.79 ± 0.12 <sup>c</sup> 90 mcg: 0.64 ± 0.12 <sup>c</sup> P: 0.45 ± 0.09 <sup>c</sup>
9	477	T1DM with A1c 7% to 8.5%	Pooled analysis	16 to 26 weeks	30 to 60 mcg tid or qid	1.8 kg	p ≤ 0.0001	Tx: 1.4 P: 1.86
8	296	T1DM	R, DB, PC, dose escalation	29 wk	15 mcg tid up to 60 mcg tid in 15 mcg increments	-1.3 +/- 0.3 kg	p < 0.0001	Tx: 0.57 ± 0.09 P: 0.3 ± 0.06

<sup>a</sup>Hypoglycemia as per DCCT trial definition; <sup>b</sup>event rate per year/standard deviation; <sup>c</sup>week 26 thru 52.

**Abbreviations:** R, randomized; DB, double blind; PC, placebo controlled; MC, multicenter; P, placebo group; Tx, treatment group.



added on to insulin therapy.<sup>6</sup> In the 52-week open-label extension portion of the study, addition of pramlintide to the patients previously randomized to placebo resulted in a progressive reduction in mean body weight similar to that seen in patients originally randomized to pramlintide. By week-65 of the open-label extension, patients in both groups achieved similar changes in weight loss, but those patients originally randomized to the pramlintide treatment group tended to regain weight after this week. The lack of a placebo-control group during the open-label extension does make it difficult to determine if this was significant.

A pooled analysis was performed to determine the safety and efficacy of pramlintide as adjunctive therapy in type 1 diabetes patients.<sup>9</sup> This analysis concluded that the addition of pramlintide to insulin therapy aided these patients in reaching glycemic targets without experiencing weight gain or additional risk of hypoglycemia.

### **Pramlintide Use in Patients with Type 2 Diabetes**

Table 2 evaluates the clinical studies which added pramlintide therapy to pre-existing insulin regimens in type 2 diabetes patients. The parameters outlined in the table include the reference, number of subjects, patient population, study design, study duration, dose of pramlintide administered during the trial, the mean change in body weight from baseline, the significance, and severe hypoglycemia incidence rates.<sup>11-15</sup>

To date, there have been three long-term clinical trials conducted to evaluate the use of pramlintide in insulin-treated type 2 diabetes patients.<sup>11,12,16</sup> These studies have shown that initiating pramlintide as an adjunct to insulin therapy augments overall blood glucose control, while abating weight gain and severe hypoglycemia, both of which are typically associated with titrating insulin doses. The three long-term clinical studies also showed statistically significant weight reduction at varying pramlintide doses and dosing regimens. Most notably, these studies also documented that the decrease in A1c levels was found unrelated to the extent of weight reduction reported. The subjects randomized in these clinical trials are representative of a typical US type 2 diabetes patient population due to their broad range of baseline glycemic control and body weight.

A pooled post hoc analysis of two long-term clinical trials<sup>12,16</sup> was conducted. The post hoc analysis looked at the potential weight reduction effects of pramlintide therapy in overweight and obese insulin-treated type 2 diabetes patients.<sup>13</sup> They pooled patients with an entry BMI > 25 kg/m<sup>2</sup> to determine the effectiveness of pramlintide 120 µg twice daily given before meals in reducing body weight. Results from this analysis showed that roughly three times the number of pramlintide-treated patients exhibited a ≥5% decrease in body weight compared to the placebo group (9% vs. 3%,  $p = 0.0005$ ) as well as an associated decrease in total daily insulin use ( $r = 0.39$ ,  $p < 0.0001$ ). Therefore, this analysis concluded that pramlintide as adjunct therapy could be a potential treatment option for overweight and obese insulin-treated type 2 diabetes patients desiring weight reduction along with resultant decreases in total daily insulin doses.

Maggs et al carried out a pooled post hoc analysis of two long-term clinical trials previously discussed in this section.<sup>14</sup> This post hoc analysis evaluated the effects of varying pramlintide doses and dosing regimens in Caucasian, African American and Hispanic insulin-treated type 2 diabetes patients. Patients were pooled according to their ethnicity to determine changes from baseline to week 52 in body weight. Results illustrated a reduction in weight for the pramlintide-treated patients regardless of ethnicity (placebo-corrected treatment effect at week 52: -2.6 kg,  $p < 0.0001$ ). This study demonstrates that there are no distinct differences between African Americans and Hispanics when compared to Caucasians regarding results of pramlintide treatment, and that each of the three ethnic groups included were positively affected by pramlintide's ability to decrease body weight.

A dose-escalating clinical study was conducted to assess various pramlintide doses and dosing regimens in basal insulin-treated type 2 diabetes patients.<sup>15</sup> These subjects did not reach desired glycemic control with insulin glargine alone or in combination with oral anti-diabetic agents (metformin, sulfonylurea, and/or thiazolidinedione). Mealtime insulin was not used during the clinical trial, so the findings from the study can be used to determine the effectiveness of pramlintide in patients using only a regimen of basal insulin. This trial reported two co primary endpoints, first the change in A1c from

**Table 2.** Type 2 DM Table focusing on mean change in body weight from baseline.

Reference #	N	Patient population	Design	Duration	Dose	Change in weight	Significance	Severe hypoglycemia <sup>a</sup>
11	538	Insulin-treated T2DM	R, DB, PC, MC, dose-ranging clinical study	52 weeks	30 µg tid, 75 µg tid, or 150 µg tid	30 µg: -0.5, -0.6 and -0.5 75 µg: -0.5, -0.6 and -0.5 150 µg: -1.5, -1.4 and -1.3	p < 0.05	30 µg: 4.1% 75 µg: 2.2% 150 µg: 2.8% P: 1.5%
12	656	Insulin-treated T2DM	R, DB, PC, MC, parallel-group clinical study	52 weeks	60 µg tid, 90 µg bid, or 120 µg bid	90 µg: -0.7* and -0.5 kg 120 µg: -1.1* and -1.4* kg	*p < 0.05	90 µg: 0.1 ± 0.03 120 µg: 0.3 ± 0.05 P: 0.3 ± 0.05
13	498	Insulin-treated T2DM	Pooled post hoc analysis	26 weeks	120 µg bid	-1.8 kg (Avg difference from placebo grp at week 26)	p < 0.0001	Did not report
14	410	Caucasian, African American and Hispanic insulin-treated T2DM	Pooled post hoc analysis	52 weeks	120 µg bid or 150 µg tid	-2.6 kg *Caucasian: -2.4 kg African American: -4.1 kg Hispanic: -2.3 kg	*p < 0.0001	Tx: 43% P: 40%
15	212	Basal insulin-treated T2DM	R, DB, PC, MC, dose-escalating clinical study	16 weeks	60 or 120 µg bid/tids	-1.6 ± 0.3 kg	p < 0.0001	Tx: 44% P: 47%

<sup>a</sup>Hypoglycemia as per DCCT trial definition.

**Abbreviations:** R, randomized; DB, double blind; PC, placebo controlled; MC, multicenter; P, placebo group; Tx, treatment group.





baseline to week 16 as well as a dichotomous composite endpoint evaluating the number of patients meeting all of the following at week 16: 1)  $A1c \leq 7\%$  or an  $A1c$  reduction from baseline  $\geq 0.5\%$ , 2) mean daily postprandial glucose (PPG) increments  $\leq 40$  mg/dL, 3) no weight gain, and 4) no severe hypoglycemia. A greater number of pramlintide-treated patients than placebo group patients reached the composite endpoint (25% vs. 7%,  $p < 0.001$ ). Weight loss was noted in the pramlintide treatment group compared to the placebo group ( $-1.6 \pm 0.3$  kg vs.  $+0.7 \pm 0.3$  kg,  $p < 0.0001$ ), and no severe hypoglycemia was reported. The results from this clinical trial concluded that glycemic and weight control were improved by utilizing pramlintide in patients with type 2 diabetes who were previously uncontrolled on basal insulin alone or in combination with oral antidiabetic agents. However, due to this clinical study's relatively short duration of length (only 16 weeks), other related trials need to be conducted for these results to be considered definitive and clinically relevant.

According to the 6 clinical trials reviewed,<sup>11-16</sup> adding pramlintide to varying insulin regimens in insulin-treated type 2 diabetes patients could potentially help these patients achieve weight loss. It appears adding pramlintide as adjunct therapy to insulin may facilitate glycemic and weight control for these patients at the expense of increasing the amount of injections these patients receive each day, but without increasing the risk of severe hypoglycemia.

### **Pramlintide Use in Obesity**

To date, there have been two clinical trials conducted to assess the anti-obesity properties of amylin replacement with varying doses of pramlintide in patients with diabetes.<sup>17,18</sup> They specifically note pramlintide's effect on satiety and food intake in regard to the magnitude of resultant weight loss. Between the two studies, the patient populations evaluated include obese and nonobese insulin-treated type 2 diabetes patients, obese noninsulin-treated type 2 diabetes patients, and obese, healthy, patients.

A single-center, randomized, double-blind, placebo-controlled, 2-period crossover study was performed to determine the effect of a single dose of pramlintide 120  $\mu$ g on satiety and food intake.<sup>17</sup> Subjects randomized were either male obese or nonobese insulin-treated type 2

diabetes patients ( $n = 14$ ) or male obese nondiabetic patients ( $n = 16$ ). After an overnight fast, the pramlintide or placebo dose was administered, and was followed by a standardized preload meal which was to be ingested within 3 minutes. The preload meal consisted of about 189 kcal, 6 g protein, 36 g carbohydrate and 3 g fat. Then one hour after the pramlintide or placebo dose was administered, subjects were offered an unlimited buffet meal for the next 45 minutes. The buffet included sandwiches, fruit, yogurt, fruit salad, custard, juice and coffee. Energy intake, meal duration and hunger ratings were analyzed. For the insulin-treated type 2 diabetes patients, the total energy intake was  $829 \pm 72$  kcal in the placebo group and  $627 \pm 75$  kcal in the pramlintide group. There was a reduction of  $202 \pm 64$  kcal or by about  $23\% \pm 8\%$  ( $p < 0.01$ ) for the insulin-treated type 2 diabetes patients. For the obese, nondiabetic patients, the total energy intake was  $1,128 \pm 81$  kcal in the placebo group and  $958 \pm 100$  kcal in the pramlintide group. There was a reduction of  $170 \pm 68$  kcal or by about  $16\% \pm 6\%$  ( $p < 0.02$ ) for the obese nondiabetic patients. There was not a statistically significant difference between the study groups in regards to meal duration, feelings about hunger, or feelings of fullness. During this trial, there were no reports of hypoglycemia. The results of this trial propose that pramlintide may be linked to a reduction in caloric intake which elicits weight reduction. However, this study only included a small sample size and other further studies are warranted at this time.

A randomized, double-blind, placebo-controlled, multicenter, phase 2, dose-escalating clinical trial was conducted to assess the anti-obesity effect of increased doses of pramlintide in obese subjects either with noninsulin-treated type 2 diabetes or without diabetes.<sup>18</sup> There were 204 patients randomized to either the placebo group ( $n = 67$ ) or the pramlintide treatment group ( $n = 137$ ). This four phase study consisted of a 1-week lead in period with placebo, a 4-week period where the pramlintide dose was increased, a 12-week maintenance period, and an 8-week follow up period. Pramlintide treatment was initiated at 60  $\mu$ g three times daily before meals and increased in 30  $\mu$ g increments every 3 days to a maximum daily dose of 240  $\mu$ g. Lifestyle modification was not used during the study. Eighty-eight percent of patients reached a dose of 240  $\mu$ g three times daily, and 8% reached a dose of 180  $\mu$ g three times daily. In contrast



to placebo-treated patients who did not experience a significant weight loss, 31% of patients in the treatment group experienced a  $\geq 5\%$  weight loss at week 16 ( $p < 0.001$ ). At the end of the study, participants received a questionnaire in which the majority of the pramlintide treatment group responded that they thought the medication helped them control their weight and appetite, and that they believed the benefits of the medication outweighed any problems with the injections. They also noted that the medication made them feel better. Even though the pramlintide doses used in the study were higher than the recommended dose for patients with diabetes, the most common side effects were nausea (38%) and injection site events (43%). Also, there were no reports of moderate to severe hypoglycemia, only mild episodes noted (8%). This study suggests that higher pramlintide doses are well tolerated in obese patients.

Further research may broaden the patient population in which amylin replacement with pramlintide therapy could be utilized as well as possibly treating obesity in otherwise healthy patients.

### Studies in Other Patient Types

Although the majority of clinical trials are conducted in patients with diabetes, a few trials have investigated the use of pramlintide in healthy patients. One study was conducted in 411 obese subjects without diabetes, BMI between 30 and 50 kg/m<sup>2</sup> and waist circumference  $>102$  cm for men and  $>88$  cm for women.<sup>19</sup> The patients were enrolled in an initial 4 month, randomized, double-blind, placebo-controlled, dose-ranging study and assigned to receive placebo three times per day or pramlintide 120, 240, or 360 mcg two or three times daily. At the end of 4 months, patients continued their pre-assigned treatment dose for an additional 8 months if they did not significantly deviate from the protocol and agreed to the continuation. Patients also participated in an individualized, lifestyle intervention program throughout the trial. At the end of 4 months, weight loss in the placebo group averaged 2.8  $\pm$  0.8 kg compared to an average range of 3.8  $\pm$  0.7 to 6.1  $\pm$  0.8 kg in the treatment arms. Those patients taking 120 mcg 3 times per day and 360 mcg 2–3 times per day achieved statistically significant reductions in weight. In addition, waist circumference also decreased in a number of the groups. Nausea was the most common side effect reported, with incidence increasing

in proportion to dosing increases; however, in most cases nausea subsided with continued use of the drug. At 12 months, 40% of patients treated with pramlintide 120 mcg three times a day and 43% of those treated with 360 mcg twice a day experienced a  $\geq 10\%$  weight loss compared to 12% in the placebo group.

A few other studies have been conducted; however, the number of patients in these studies is minimal. A single-center, randomized, double-blind, placebo-controlled, cross-over study was conducted in fifteen healthy, normal weight subjects.<sup>20</sup> Subjects were exposed to a buffet meal test on two occasions. Subjects were instructed to fast overnight and the next morning were given pramlintide 30 mcg or placebo followed by a standardized pre-load meal. One hour later they were offered a buffet meal at which time caloric intake and meal duration were measured. Subjects given pramlintide had a reduced total caloric intake of 221  $\pm$  101 kcal ( $p = 0.05$ ) as compared to placebo at the buffet meal. Meal duration was reduced by 5.1  $\pm$  1.4 minutes ( $p < 0.005$ ) for patients taking pramlintide when compared to placebo. The study indicates that pramlintide may have an effect on quantity of food intake and duration of meals; thereby, adding to the evidence that pramlintide may affect satiety.

### Safety

The most common adverse event of pramlintide reported in clinical trials of type 1 and type 2 diabetes patients as well as obese patients without diabetes were gastrointestinal related. The incidence is higher when starting therapy with pramlintide and may be reduced with gradual titration. Nausea was the most common event cited in clinical trials, but anorexia and vomiting were also reported.<sup>2,4</sup> Nausea does have a high rate of recurrence, and is the primary reason for subject withdrawal in pramlintide treated patients during long-term controlled trials.<sup>21</sup>

A barrier to diabetic patients maintaining tight glycemic control, A1c of 6.5% to 7%, is fear of hypoglycemia. Prescribing information for pramlintide does contain a boxed warning stating that pramlintide has been associated with an increased risk of insulin-induced severe hypoglycemia in type 1 patients. This event is likely seen within three hours following the injection of pramlintide,<sup>4,21</sup> but clinical studies have demonstrated that pramlintide does



not alter the counter-regulatory hormonal response to insulin-induced hypoglycemia.<sup>22,23</sup> Hypoglycemia is the leading cause of serious adverse events reported in both type 1 diabetes trials (9% pramlintide vs. 4% placebo) and type 2 diabetes trials (2% pramlintide vs. 1% placebo).<sup>21</sup> The occurrence of hypoglycemia in pramlintide treated patients was most common during the first month.<sup>4</sup> The incidence of severe hypoglycemia is reported in Table 1 and Table 2. Severe hypoglycemia was defined per the Diabetes Control and Complications Trials as “an event requiring the assistance of another person, including aid in ingesting an oral carbohydrate, administering a glucagon injection or intravenous glucose”<sup>24</sup> in seven of the trials reviewed.

## Place in Therapy

Based on the information obtained from these studies, pramlintide may be an option for patients needing pharmacologic assistance for weight loss; however, further research needs to be conducted to determine efficacy in obese patients without diabetes. There are several drawbacks to the use of pramlintide, including the fact that it is an injectable medication. The medication does cause nausea in many patients which may lead to discontinuation of the drug. In the studies conducted, nausea was frequent; however, it subsided over time with continued use. Symlin is available as a SymlinPen<sup>®</sup> in strengths of 60 mcg and 120 mcg and as a multi-dose vial. The cost of the pen is as follows: SymlinPen<sup>®</sup> 120(2 syringes, 2.7 ml each), \$293.93, which may limit its use for certain patients.<sup>25</sup> The cost of a multi-dose vial is less expensive, 0.6 mg/ml (5 ml, \$189.74); however, it requires a conversion from mcg to units in order to use an insulin syringe. The conversion could attribute to medication errors.

There are very few therapeutic options for the management of obesity. Since obesity can attribute to and worsen numerous other medical conditions, it is important to identify products to help patients lose weight. Pramlintide is a relatively new product that deserves further study in order to determine if it is a viable option for the treatment of obesity.

## Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under

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