Efficacy and Harms of the Hypoglycemic Agent Pramlintide in Diabetes Mellitus

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ABSTRACT

PURPOSE We conducted a study to examine the efficacy, effectiveness, and harms of pramlintide as adjunct therapy in adults and children with type 1 or type 2 diabetes.

METHODS We searched multiple bibliographic databases to January 2010, the US Food and Drug Administration Web site, and other sources to identify randomized controlled trials (RCTs) fulfilling inclusion criteria. Syntheses were qualitative because data were too heterogeneous for meta-analysis.

RESULTS Three published RCTs in type 1 diabetes and 4 in type 2 disease fulfilled inclusion criteria. All trials were conducted with adults, and none was longer than 52 weeks. In type 1 diabetes with intensive insulin therapy, pramlintide was as effective as placebo in lowering glycated hemoglobin (HbA1c) levels in one trial. Pramlintide was somewhat more effective than placebo in patients using conventional insulin therapy, with a between-group difference in HbA1c levels of 0.2% to 0.3% (2 studies). In patients with type 2 diabetes, pramlintide was more effective at reducing HbA1c levels than placebo when added to flexibly dosed glargine (without prandial insulin) and when added to fixed-dose insulin therapies, with or without oral hypoglycemic agents (between-group differences in HbA1c were approximately 0.4%). Weight loss was observed with pramlintide in both type 1 and type 2 diabetes, whereas placebo-treated patients tended to gain weight. Pramlintide-treated patients experienced more frequent nausea and severe hypoglycemia compared with patients treated with placebo.

CONCLUSIONS Pramlintide was somewhat more effective than placebo as adjunct therapy for improving HbA1c levels and weight in adults with type 1 diabetes on conventional insulin therapy, or type 2 diabetes and inadequate glycemic control with their current therapies, with between-group differences in HbA1c levels in the range of 0.2% to 0.4%. Further research is needed to determine pramlintide’s durability of hypoglycemic effect, as well as effects on patient-reported outcomes, morbidity, mortality, and long-term harms.

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INTRODUCTION

The progressive nature of diabetes poses major challenges in maintaining optimal glycemic control in patients with type 1 or type 2 diabetes. It is estimated that more than 50% of patients with type 2 diabetes will require more than 1 oral hypoglycemic agent 3 years from diagnosis and that approximately 70% will require combination oral therapy with or without insulin by 6 to 9 years. In an effort to slow disease progression, there has been a concerted effort to develop newer pharmacologic agents with alternate mechanisms of action and minimal harms.

In March 2005, pramlintide, a stable synthetic amylin analogue, was approved by the US Food and Drug Administration (FDA) after more than 20 years of researching human amylin, a neuroendocrine hormone co-secreted with insulin. It is thought that pramlintide, by means of receptors in the central nervous system, complements insulin by targeting postprandial
glucose, enhancing satiety by slowing gastric emptying, enhancing hepatic glycogen synthesis, and inhibiting elevations in glucagon concentrations. As pramlintide is mechanistically different from currently available drug therapies, this hormone potentially has a complementary and novel role in achieving and maintaining glycemic control and weight optimization. Pramlintide is indicated for adjunct therapy in adults with type 1 or type 2 diabetes who use prandial insulin and who have failed to achieve their glycemic goal despite optimal therapy. The purpose of this systematic review is to assess the efficacy, effectiveness, and harms of pramlintide in adults and children with type 1 or type 2 diabetes compared to oral hypoglycemic agents, insulin, or placebo.

METHODS

The participating organizations of the Drug Effectiveness Review Project (http://www.ohsu.edu/drugeffective ness) commissioned this review and developed the review questions and inclusion criteria. We searched MEDLINE (1950 to January 27, 2010), the Cochrane Central Register of Controlled Trials (4th quarter 2009), Cochrane Database of Systematic Reviews (4th quarter 2009), and the Database of Abstracts of Reviews of Effects (1st quarter 2010) for English-language publications in populations with type 1 or type 2 diabetes. The following search terms were used: 196078-30-5, pramlintide, symlin, amylin agonist, and amylin analogue. Our search was supplemented with online searches of Web sites of the FDA, Clinicaltrials.gov, the Canadian Agency for Drugs and Technologies in Health, and the National Institute for Health and Clinical Excellence. Hand searching of reference lists and pharmaceutical company dossiers was also performed.

Two reviewers (N.J.L. and S.L.N.) independently assessed titles and abstracts retrieved from searches and reviewed full-text articles based on uniform application of study eligibility criteria (Table 1). Disagreements were resolved by consensus at each step. One author abstracted study data into a standardized template, which were checked by a second author.

We assessed internal validity of included studies on the basis of randomization, allocation concealment, blinding, similarity of treatment groups at baseline, maintenance of comparable groups, and the use of intention-to-treat analysis. Qualitative assessment and synthesis was undertaken by comparing and contrasting outcomes across studies in the context of the characteristics of the study population, pramlintide dos-
formed in 2 studies\(^5\),\(^8\), and (4) lack of reporting the number of subjects screened and eligible for trial inclusion.

**Type 1 Diabetes**

Three placebo-controlled RCTs compared pramlintide with placebo as adjuncts to either intensive insulin therapy (multiple daily injections or insulin pump)\(^5\) or to therapy with short- and long-acting insulin (Table 3).\(^7\),\(^10\) The trial using intensive insulin therapy reported no significant difference in the reduction in glycated hemoglobin (HbA\(_{1c}\)) levels when comparing pramlintide with placebo at week 29.\(^5\) The other 2 trials\(^7\),\(^10\) showed

### Table 2. Characteristics of Placebo-Controlled Trials of Pramlintide

| Author, Year, Quality | N  | Duration, wk | Age, y Male, % White, % | Duration of Diabetes, y | HbA\(_{1c}\), % | Total Daily Insulin Dose Units | Pramlintide Dose and Titration Schedule |
|-----------------------|----|--------------|--------------------------|-------------------------|--------------|-----------------------------|--------------------------------------|
| **Type 1 diabetes**   |    |              |                          |                         |              |                             |                                       |
| Whitehouse et al, 2002, \(^5\) Fair-poor | 480 | 52 | 40.3 55.0 94.0 | 16.8 8.8 NR | 30 µg tid-qid before meals + flexible-dose insulin. If HbA\(_{1c}\) level decreased by <1%, patients were re-randomized to 30 µg or 60 µg. If change in HbA\(_{1c}\) level was ≥1%, patients continued with 30 µg |
| Edelman et al, 2006, \(^5\) Fair | 296 | 29 | 41.0 45.1 88.7 | 20.0 8.2 MDI: 65.1 | 15 µg and titrated to 60 µg tid-qid before meals + flexible-dose insulin. Patients unable to tolerate maintenance dose had dose lowered to 30 µg or 15 µg. A 30%-50% reduction in prandial insulin was allowed |
| Ratner et al, 2004, \(^7\) Fair-poor | 651 | 52 | 40.5 50.0 90.5 | 18.7 9.0 NR | 60 µg tid-qid or 90 µg tid before meals + fixed-dose insulin. If nausea occurred within 2 wk of study, dose could be lowered by up to 50% for up to 2 wk |
| **Type 2 diabetes**   |    |              |                          |                         |              |                             |                                       |
| Riddle et al, 2007, \(^9\) Fair | 212 | 16 | 55.0 48.8 72.5 | 12.2 8.5 51.0 | 60 µg and titrated to 120 µg bid-tid before meals + flexible-dose glargine + metformin, sulfonylurea, and/or thiazolidinedione |
| Ratner et al, 2002, \(^8\) Fair-poor | 538 | 52 | 56.5 59.0 78.3 | 12.3 9.2 NR | 30 µg, 75 µg, or 150 µg tid before meals + fixed-dose insulin and/or metformin, sulfonylurea |
| Hollander et al, 2003, \(^6\) Fair | 656 | 52 | 56.7 50.0 75.0 | 12.2 9.2 NR | 60 µg tid, 90 µg bid, or 120 µg bid before meals + fixed-dose insulin and/or metformin, sulfonylurea. 60-µg dose study arm was excluded from efficacy analyses |

bid = 2 times daily; CSII = continuous subcutaneous insulin infusion; HbA\(_{1c}\) = glycated hemoglobin; MDI = multiple daily injections; NR = not reported; qid = 4 times daily; tid = 3 times daily.

### Table 3. Outcomes of Placebo-Controlled Trials of Pramlintide in Type 1 Diabetes

| Trial, Duration | Change in HbA\(_{1c}\), Level \(\% (95\% \text{ CI})\) | P Value | Change in PPG, mg/dL | P Value | Change in Weight, kg | P Value |
|-----------------|--------------------------------|---------|----------------------|---------|----------------------|---------|
| **Edelman et al, 2006, \(^6\) 29 wk** | | | | | | |
| Pramlintide, 30 or 60 µg tid-qid | 0.50 (-0.61 to -0.33) | - | -34\(^a\) NR | -1.3 | <.001\(^b\) |
| Placebo | -0.50 (-0.63 to -0.35) | - | -18\(^a\) NR | 1.2 | |
| **Whitehouse et al, 2002, \(^10\) 52 wk** | | | | | | |
| Pramlintide, 30 or 60 µg tid | -0.39 .007\(^b\) NR | - | -0.5 NR | | |
| Placebo | -0.12 NR | - | +1.0 NR | | |
| **Ratner et al, 2004, \(^7\) 52 wk** | | | | | | |
| Pramlintide, 60 µg tid | -0.29 .011\(^b\) NR | - | -0.4 0.027\(^b\) | | |
| Pramlintide, 60 µg qid | -0.34 .001\(^b\) NR | - | -0.4 0.04\(^b\) | | |
| Placebo | -0.04 NR | - | +0.8 NR | | |

HbA\(_{1c}\) = glycated hemoglobin; CI = confidence interval; NR = not reported; PPG = postprandial glucose; qid = 4 times daily; tid = 3 times daily.

\(^a\) Change from baseline to 3 hours postprandial.

\(^b\) Compared with placebo.
significantly greater improvement in HbA1c levels with pramlintide than placebo at 26 and 52 weeks, with between-group differences in HbA1c of 0.2% and 0.3%, respectively. The largest reductions in HbA1c (maximum 0.7%) were observed with pramlintide before week 26, followed by gradual worsening of glycemia to week 52.7,10 Patients in one trial were initially randomized to 60-µg or 90-µg doses of pramlintide.7 During the study, however, unpublished data became available suggesting that the 90-µg dosage was less well tolerated, and this treatment arm was therefore excluded from analysis.

There were few data on pramlintide’s effects on fasting plasma glucose (FPG) or postprandial glucose (PPG). In a small subgroup (77 of 296 patients, 26%) who underwent standardized meal tests, a greater percentage of pramlintide-treated patients achieved a PPG of ≤180 mg/dL (9.9 mmol/L) at each meal (range for different meals, 68% to 71%) than patients treated with placebo (range for different meals, 51% to 61%).5 The mean change in PPG was statistically significant but small in absolute terms: in a post hoc subgroup analysis of patients enrolled in the same study (pramlintide, −8.5 mg/dL; placebo, +13.3 mg/dL; between-group P < .001).12 Changes in total daily insulin dose were small for both pramlintide (range, −12% to +2.3%) and placebo (range, 0.0% to +10.3%).5,7,10

Weight loss was consistently greater in patients using pramlintide (range of mean change across 3 trials, −0.4 kg to −1.3 kg) than placebo (+0.8 kg to +1.2 kg).5,7,10 The largest reductions in weight, up to 1.3 kg, occurred from baseline to weeks 13 to 26, then the net change in weight diminished.7,10

One of these trials also reported an open-label extension whereby all patients received pramlintide 30 µg 4 times daily from weeks 52 to 65, with the option to increase to a 60-µg dosage based on HbA1c levels and clinical assessment.10 Patients who continued pramlintide the second year maintained their reduction in HbA1c level to week 104, while they tended to regain the weight lost in the first year, with a mean loss of 0.5 kg from baseline to week 104.

Only 1 study in type 1 diabetes presented patient-reported outcomes: satisfaction was significantly greater with pramlintide treatment than placebo at 29 weeks of follow-up on 12 of 14 patient-reported outcome measures using a questionnaire developed specifically for this trial.13 More patients reported that pramlintide provided better control of blood glucose, helped with weight loss and appetite suppression, and increased ability to function compared with placebo.

Subgroup analyses based on age, sex, race, and total daily insulin dose were not explored in any of these trials. One RCT7 examined the effects of pramlintide by baseline body mass index (BMI) for 309 of 479 (64%) patients at week 26. Patients with a baseline BMI of ≤23 kg/m² who used pramlintide showed small changes in weight (range, −0.5 kg to +0.2 kg), whereas patients with a BMI of ≥27 kg/m² lost more weight (range, 1.0 kg to 2.0 kg).

In a post hoc pooled analysis that evaluated the addition of pramlintide in patients with good but not optimal glycemic control (baseline HbA1c, 7.0% to 8.5%),18 pramlintide lowered HbA1c levels (placebo-corrected change, −0.3%, P < .001) and weight (placebo-corrected change, −1.8 kg, P < .001). These changes were similar in magnitude to those in patients in the original trials who had a higher baseline HbA1c levels.

### Type 2 Diabetes

Three RCTs compared pramlintide with placebo as adjunct therapy in patients inadequately controlled on insulin with or without oral hypoglycemic agents

| Trial, Duration | Change in HbA1c Level, % | P Value | Change in PPG, mg/dL | P Value | Change in Weight, kg | P Value |
|-----------------|--------------------------|---------|----------------------|---------|----------------------|---------|
| Riddle et al, 2007,9 16 wk | Pramlintide, 60 or 120 µg bid-tid | −0.70 | <.05a | −24.4 | <.001a | −1.6 | <.001a |
| Placebo | −0.36 | NR | +0.7 | |
| Ratner et al, 2002,4 52 wk | Pramlintide, 75 µg tid | −0.50 | >.05a | NR | −0.5 | <.001a |
| Pramlintide, 150 µg tid | −0.60 | <.001a | NR | −1.4 | <.001a |
| Placebo | −0.20 | NR | +1.0 | |
| Hollander et al, 2003,4 52 wk | Pramlintide, 90 µg bid | −0.35 | NR | −0.5 | NR |
| Pramlintide, 120 µg bid | −0.62 | <.001b | NR | −1.25 | <.003b |
| Placebo | −0.22 | NR | +0.6 | |

HbA1c = glycated hemoglobin; bid = 2 times daily; NR = not reported; PPG = postprandial glucose; tid = 3 times daily.

a Compared with placebo.

b Compared with placebo for both dosages combined.
Patients using glargine (a basal insulin without pronounced peak effects) dosed to target fasting plasma glucose, with or without oral hypoglycemic agents, had significantly greater improvement in HbA1c levels with pramlintide than placebo at 16-weeks (P < 0.05). The percentage of patients achieving HbA1c levels of ≤7% or a ≥0.5% reduction was not significantly different between groups (pramlintide, 54%; placebo, 45%). Pramlintide at higher dosages (120 µg twice daily and 150 µg 3 times daily) reduced HbA1c levels significantly more than placebo at 1-year follow-up in patients using fixed-dose insulin, with between-group differences of about 0.4%. Pramlintide-treated patients with baseline HbA1c levels of >8.5% showed a larger change in HbA1c levels at 16 weeks (–1.19%) than persons with baseline HbA1c levels of ≤8.5% (–0.36%).

Postprandial glucose was lowered more with pramlintide than with placebo (P < 0.001) as was fasting plasma glucose at the 16-week follow-up (change from baseline with pramlintide was –28.3 mg/dL and with placebo was –12.0 mg/dL, between-group P value not reported). Both pramlintide and placebo treatment groups required increases in insulin dosage with time, and there were no significant difference in requirements between groups.

Weight consistently increased with placebo and decreased with pramlintide across the 3 trials (Table 4), with between-group differences of 1.5 to 2.5 kg (P < 0.001). Changes in weight and HbA1c levels were evaluated in overweight and obese patients (BMI ≥25 kg/m²) in a post hoc pooled analysis of patients with type 2 diabetes using insulin. At 26 weeks, pramlintide 120 µg twice daily lowered both HbA1c levels and weight more than placebo (between-group change in HbA1c level, –0.41%; and weight, –1.8 kg; both P < 0.001). Only 2% or less of patients in both treatment groups lost 7.5% or more of baseline weight, however. Markedly obese patients (baseline BMI = 35–40 kg/m² or >40 kg/m²) showed the largest change in weight (–2.4 kg and –3.2 kg, respectively). No significant relationship was noted between weight loss and nausea in pramlintide subgroups that reported “ever experiencing nausea” compared with those that “never reported nausea” at week 26 (placebo-corrected change, –2.0 kg compared with –1.6 kg, respectively) or at week 52 (placebo-corrected change, –1.5 kg to –1.1 kg compared with –0.3 kg to –2.0 kg, respectively).

One study in type 2 diabetes had an active comparison group: Riddle and colleagues compared pramlintide 120 µg before major meals with the use of rapid-acting insulin analogues (insulin lispro, aspart, or glulisine) in patients using glargine titrated to a fasting plasma glucose of 70 to 100 mg/dL with or without oral agents (n = 113). This open-label study was rated as fair-poor quality. After 24 weeks of treatment, reductions in HbA1c levels and fasting plasma glucose were similar between groups. Weight increased 4.7 kg in the group receiving rapid-acting insulin compared with no change in weight with pramlintide at 24 weeks (between-group P < 0.001).

Only 1 study in type 2 disease examined patient-reported outcomes, based on the trial by Riddle and colleagues discussed above. In adults using insulin glargine with or without oral hypoglycemic agents, pramlintide was associated with a significant reduction in total distress from diabetes and in the domain of regimen distress, but only in persons who were above the median of distress at baseline. This subgroup analysis appears to have been a performed post hoc and thus should be interpreted with caution.

Analyses of important population subgroups were limited in type 2 diabetes. Larger changes in HbA1c levels and weight were seen with pramlintide in black patients (–0.7% and –4.1 kg, respectively) than white (–0.5% and –2.4 kg, respectively) or Hispanic patients (–0.3% and –2.3 kg, respectively) in a post hoc pooled analysis. Black and Hispanic patients had higher baseline HbA1c levels (range, 9.2% to 9.7%) than white patients (range, 8.9% to 9.1%).

**Adverse Events**

There were no reports of death, or cardiac, hepatic, renal, or drug-related idiosyncratic adverse events in patients in any treatment group in studies of either type 1 or type 2 diabetes. Across type 2 diabetes trials, the rate of withdrawal for any reason was similar for pramlintide and placebo (range, 17.1% to 37.5% vs 15.1% to 30.0%). In type 1 disease, however, pramlintide-treated patients at 30-, 60-, or 90-µg doses had higher rates of withdrawal for any reason (range, 21% to 50%) than with placebo (range, 10% to 33%). In both type 1 and 2 populations, withdrawal resulting from adverse events was higher with pramlintide than with placebo (type 1 range, 5% to 22% vs 2% to 8% with placebo; type 2 range, 3.8% to 18.1% vs 0.9% to 10.3% with placebo). Commonly reported reasons for withdrawal were nausea and hypoglycemia.

Mild-to-moderate nausea, vomiting, and anorexia or reduced appetite were the most commonly reported adverse events and were more common with pramlintide than placebo in both type 1 (Table 5) and type 2 diabetes. In a 2-year, open-label extension study in type 1 disease, patients who continued with pramlintide in the second year reported declining rates of nausea (from 46.5% in the first year to 14.4% in the second year) and anorexia (from 17.7% in the first year to 1.6% in the second year). In type 2 patients, rates of nausea were similar for 16 to 52 weeks of follow-up (range of rates with pramlintide: 16.0% to 31.4%, respectively, compared with placebo, 3.0% to 16.9%).
respectively).6,8,9 As in type 1 disease, nausea occurred more frequently early, within the first 4 weeks of treatment.6,15 Vomiting, anorexia, or reduced appetite were not reported in any of the type 2 diabetes trials.

Severe hypoglycemia (requiring assistance of another person, the administration of glucagon, or the administration of intravenous glucose) was generally reported more frequently with pramlintide than with placebo in both type 1 (Table 6) and type 2 diabetes. In type 2 populations, severe hypoglycemia occurred more frequently with the 120-µg pramlintide dose than with placebo in 2 RCTs,6,9 whereas a third trial reported similar rates between treatment groups.8 On the other hand, rates of mild-to-moderate hypoglycemia in type 2 diabetes were similarly high between treatment groups (range, pramlintide, 43.8% to 70.6%; placebo, 47.2% to 70.6%).6,9 Mild-to-moderate hypoglycemia was more common with the use of rapid-acting insulins (82%) than with pramlintide (55%) in the only active-controlled study identified for this review.11

In all 3 type 1 trials5,7,10 severe hypoglycemia occurred more often during the first 4 weeks of treatment as pramlintide doses were being adjusted. For patients who continued pramlintide therapy for a second year as part of an open-label extension study, the rate of severe hypoglycemia was the same in the second year as the last 26 weeks of the first year (event rate, 0.43 per patient-year).10 Similarly, in type 2 disease, rates of hypoglycemia were higher during first 4 weeks of therapy with pramlintide and then declined in frequency to rates similar to those in placebo-treated patients.6,9 Headache was experienced by slightly more pramlintide- than placebo-treated patients (range, 12.3% to 19.0% compared with 8.0% to 13.2%, respectively),5,8 but neither trial explored whether headaches were related to hypoglycemia.

Two noncomparative observational studies were evaluated for additional information on adverse events but did not provide data in addition to that already reported in RCTs.21,22

| Table 5. Frequency of Adverse Events in Placebo-Controlled Studies of Pramlintide in Type 1 Diabetes |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Trial           | Any Nausea %    | Severe Nausea % | Any Anorexia<sup>a</sup> or Reduced Appetite % | Severe Anorexia or Reduced Appetite % | Any Vomiting %  | Severe Vomiting % |
| Edelman et al, 2006<sup>5</sup> | 48.5-95.1<sup>b</sup> | 4.0-7.3 | 6.9-14.6 | 0.0 | 11.9-17.1 | 2.4-5.9 |
| Pramlintide     | 36.1            | 0.7     | 2.0     | 0.0 | 6.1     | 0.7     |
| Placebo         | 46.5            | 6.2     | 17.7    | 2.5 | 11.5    | 2.1     |
| Whitehouse et al, 2002<sup>10</sup> | 21.9          | 1.7     | 2.1     | 0.0 | 8.0     | 0.4     |
| Pramlintide     | 47.9-59.0       | 5.8-8.5 | 11.0-18.0 | 0.6-1.9 | 9.8-12.0 | 0.6-1.8 |
| Placebo         | 12.0            | 1.3     | 2.6     | 0.0 | 6.5     | 0.6     |

<sup>a</sup> Anorexia was defined as decreased appetite, early satiety or gastric fullness, loss of appetite, or no appetite.

<sup>b</sup> The rate of 95.1% occurred in persons in the pramlintide 30-µg group.

| Table 6. Severe Hypoglycemic Events in Placebo-Controlled Trials of Pramlintide in Type 1 Diabetes |
|-----------------|----------------|----------------|----------------|
| Trial           | Events per Patient-Year* | Mean No. (SE) |
|                 | Weeks 0-4 | Weeks 0-29 | Weeks 26-52 |
| Edelman et al, 2006<sup>5</sup> |          |            |            |
| Pramlintide, 30 µg tid-qid | 0.79 (0.46) | 1.10 (0.25) | –          |
| Pramlintide, 60 µg tid-qid | 0.46 (0.46) | 0.42 (0.09) | –          |
| Placebo         | 0.42 (0.19) | 0.30 (0.06) | –          |
| Whitehouse et al, 2002<sup>10</sup> |          |            |            |
| Pramlintide, 30 or 60 µg tid-qid | 2.12 (0.35) | – | 0.43 (0.07) |
| Placebo         | 1.04 (0.24)<sup>b</sup> | – | 0.52 (0.08)<sup>b</sup> |
| Ratner et al, 2004<sup>4</sup> |          |            |            |
| Pramlintide, 60 µg tid | 3.78 (0.57) | – | 0.74 (0.12) |
| Pramlintide, 60 µg qid | 3.41 (0.55) | – | 0.79 (0.12) |
| Pramlintide, 90 µg tid | 3.91 (0.58) | – | 0.64 (0.12) |
| Placebo         | 0.87 (0.27) | – | 0.45 (0.09) |

<sup>a</sup> Event rates were calculated as the total number of events for all patients on a treatment regimen divided by the total number of patient-years of observation.

<sup>b</sup> Event rates were calculated after excluding 1 patient in the placebo group who reported >100 episodes of severe hypoglycemia.

DISCUSSION

Pramlintide improved HbA<sub>1c</sub> levels by 0.2% to 0.4% compared with placebo in both type 1 and type 2 diabetes populations, except when type 1 was managed...
with intensive insulin treatment, for which there was no significant difference between groups. None of the trials, however, evaluated long-term health outcomes and adverse events to determine whether benefits outweigh risks, and few data are published on patient-reported outcomes. Although weight loss was greater with pramlintide than placebo, the amount lost was relatively small. The largest improvements in HbA1c levels and weight occurred during the initial 6 months of treatment and then deteriorated with time. Pramlintide’s greatest effect on HbA1c levels and weight were observed in obese and overweight patients with type 2 diabetes at 26 weeks of follow-up. We found little evidence to suggest that pramlintide is significantly better than placebo at reducing fasting plasma glucose, postprandial glucose, or total daily insulin dose.

There are a number of potential limitations to this review. The identified studies have relatively short follow-up, and it is unclear whether the positive effects on glycemic control and weight can be sustained beyond 1 year. One-year follow-up is also not sufficient to determine whether there are rare but serious adverse events. This review was confined to English language literature, which may introduce language bias. Publication bias, which can introduce publication and selection bias, was not considered with caution because of the lack of systematic approach to selecting studies for inclusion. In addition, all included trials had potential problems with internal validity, lacking adequate methods of reporting randomization and allocation concealment, and unclear approaches to blinding.

The generalizability of trials included in this review to broader populations is likely limited. Most patients with type 1 or 2 diabetes enrolled in included trials represented highly selected populations: white, middle-aged adults with mean baseline HbA1c levels ranging from approximately 8.0% to 9.0%. All trials excluded patients with pulmonary, cardiovascular, renal, neurologic, or hematologic diseases, or gastrointestinal motility disorders. Data regarding baseline comorbidities, disease severity, and microvascular disease were not reported. Study populations most likely included highly motivated patients who desired to achieve optimal glycemic control and who were willing to add 2 to 4 additional injections to their usual therapy.

Data on subgroups of interest to clinicians were lacking. Whether pramlintide is most useful in populations with moderate or poor control is uncertain. One pooled analysis suggested that pramlintide was effective in improving HbA1c levels in patients with good but not optimal glycemic control. That study pooled data from 3 trials using either fixed-dosed or flexibly dosed insulin; however, and those 2 regimens are too heterogeneous to meaningfully combine, and we suspect that pramlintide would show a larger treatment effect with fixed-dose insulin regimens than with flexibly dosed insulin, as evidenced by our findings in both type 1 and 2 disease.

Pramlintide may have a role in glycemic control in some patients with type 1 or type 2 diabetes. Although improvements in HbA1c levels are small, incremental improvements in HbA1c levels of 0.2% to 0.4% from the addition of pramlintide may ultimately contribute to long-term glycemic control and cardiovascular health when combined with other means of improving glycemic control. The mean duration of diabetes was relatively long in studies of type 2 diabetes (12.2 years), and sulfonylureas are likely no longer effective in these populations. Pramlintide might therefore offer an alternative agent to optimize glycemic control. Although weight loss seen with pramlintide is also relatively small, again, incremental improvements may contribute to overall improvements in cardiovascular risk in type 2 diabetes. The significance of this decrease in weight is uncertain in persons with type 1 diabetes; and it may be an advantage in some patients and a detriment in others depending on their baseline BMI.

Good-quality, long-term evidence evaluating pramlintide’s effects on glycemic control is lacking in broad populations. Larger trials with follow-up longer than 1 year are needed, particularly in patients using a variety of hypoglycemic regimes, patients with comorbidities, and in overweight and obese populations. Long-term observational data on potential harms needs to be gathered to have a more complete picture of the relative benefits and harms of pramlintide compared with the multitude of other hypoglycemic agents. In particular, comparative effectiveness studies are needed that examine long-term health and patient-reported outcomes, with comparisons to other active therapies (not placebo), including flexibly dosed insulin regimens rather than fixed-dose regimens. Glycemic targets should be prespecified in these trials. Furthermore, more data on how pramlintide affects fasting plasma glucose, postprandial glucose, and total daily insulin dose compared with conventional treatments are needed.
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