Efficacy and Harms of the Hypoglycemic Agent Pramlintide in Diabetes Mellitus

Nancy J. Lee, PharmD
Susan L. Norris, MD, MPH
Sujata Thakurta, MPA

Department of Medical Informatics and Clinical Epidemiology, Oregon Health & Science University, Portland, Oregon

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 (HbA_{1c}) levels in one trial. Pramlintide was somewhat more effective than placebo in patients using conventional insulin therapy, with a between-group difference in HbA_{1c} levels of 0.2% to 0.3% (2 studies). In patients with type 2 diabetes, pramlintide was more effective at reducing HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} 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.

Ann Fam Med 2010;8:542-549. doi:10.1370/afm.1174.

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.[1] 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

Conflicts of interest: none to report

CORRESPONDING AUTHOR

Susan L. Norris, MD, MPH
Department of Medical Informatics and Clinical Epidemiology
Oregon Health & Science University
3181 SW Sam Jackson Park Rd
Mail Code BICC
Portland, OR 97239
norriss@ohsu.edu

glucose, enhancing satiety by slowing gastric emptying, enhancing hepatic glycogen synthesis, and inhibiting elevations in glucagon concentrations.[2] 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/drugeffectiveness) 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.[3,4] Qualitative assessment and synthesis was undertaken by comparing and contrasting outcomes across studies in the context of the characteristics of the study population, pramlintide dosage, use of concurrent hypoglycemic therapies, follow-up intervals, and study design and quality. Meta-analysis was planned if there was minimal heterogeneity of various characteristics across included studies.

RESULTS

Our searches identified 166 citations; of these, 7 randomized controlled trials (RCTs),[5-11] 3 companion articles,[12-14] and 4 pooled analyses[15-18] fulfilled inclusion criteria. We also identified 2 unpublished trials (study #137-117 and #137-123) from the FDA medical and statistical reviews.[19,20] Because we were unable to identify relevant comparative observational studies to evaluate adverse events not reported in RCTs, we searched for large, noncomparative observational studies and identified 2 that fulfilled inclusion criteria.[21,22] We did not find any good-quality systematic reviews.

Table 2 summarizes the characteristics of included placebo-controlled RCTs. None of the studies of type 1 or type 2 diabetes included children, and none of the trials was longer than 52 weeks' duration. We identified no head-to-head studies. Because of limited evidence and the clinical heterogeneity of patient populations, dosages, and follow-up intervals, meta-analyses were not conducted.

The included trials were of fair[5,6,9] or fair-to-poor[7,8,10] quality. The limitations that led to these quality assessments were fairly uniform across studies and included (1) lack of adequate descriptions of methods of randomization and allocation concealment; (2) reporting of the studies as double-blind without specifying precisely who was blinded; (3) unclear handling of missing data and dropouts, making it impossible to determine whether full application of intention-to-treat analyses was per-

Table 1. Study Eligibility Criteria

Component	Description
Population	Adults and children with type 1 or type 2 diabetes
Intervention	Pramlintide for FDA- and non-FDA-approved indications
Compared agent	Other hypoglycemic agent or placebo
Long-term health outcomes	All-cause mortality, micro- or macrovascular disease, quality of life, complications related to diabetes
Intermediate outcomes	Glycemic control: HbA_{1c}, fasting plasma glucose, postprandial glucose; change in weight; time to treatment failure
Harms-related outcomes	Withdrawals due to all causes, withdrawals due to adverse events, overall adverse events, major adverse events
Study design	For efficacy/effectiveness: randomized controlled clinical trials, good-quality systematic reviews
	For harms and subgroups: randomized controlled clinical trials, good-quality systematic reviews, population-based comparative cohort or case-control studies
Excluded	Trials <12 weeks' duration; abstracts, posters, and conference proceedings with limited information for quality assessment

FDA = Food and Drug Administration; HbA_{1c} = glycated hemoglobin.

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	Study Sample at Baseline (Mean): Age, y Male, % White, %	Duration of Diabetes, y	HbA_{1c}, % Weight, kg	Total Daily Insulin Dose Units	Pramlintide Dose and Titration Schedule
Type 1 diabetes							
Whitehouse et al, 2002,[10] Fair-poor	480	52	40.3 55.0 94.0	16.8	8.8 75.3	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 80.0	MDI: 65.1 CSII: 47.8	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 77.1	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	8.5 103.0	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 78.5	12.3	9.2 NR	57.9	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 96.9	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% CI)	*P* Value	Change in PPG, mg/dL	*P* Value	Change in Weight, kg	*P* Value
Edelman et al, 2006,[5] 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 qid	−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	.027[b]
Pramlintide, 60 µg qid	−0.34	.001[b]	NR	–	−0.4	.04[b]
Placebo	−0.04		NR	–	+0.8	

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 HbA_{1c} levels with pramlintide than placebo at 26 and 52 weeks, with between-group differences in HbA_{1c} of 0.2% and 0.3%, respectively. The largest reductions in HbA_{1c} (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 HbA_{1c} levels and clinical assessment.[10] Patients who continued pramlintide the second year maintained their reduction in HbA_{1c} 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 RCT[7] 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/m^2 who used pramlintide showed small changes in weight (range, −0.5 kg to +0.2 kg), whereas patients with a BMI of ≥27 kg/m^2 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 HbA_{1c}, 7.0% to 8.5%),[18] pramlintide lowered HbA_{1c} 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 HbA_{1c} 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

Table 4. Outcomes of Placebo-Controlled Trials of Pramlintide in Type 2 Diabetes

Trial, Duration	Change in HbA_{1c} 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	<.05[a]	−24.4	<.001[a]	−1.6	<.001[a]
Placebo	−0.36		−0.4		+0.7	
Ratner et al, 2002,[8] 52 wk						
Pramlintide, 75 µg tid	−0.50	>.05[a]	NR		−0.5	<.001[a]
Pramlintide, 150 µg tid	−0.60	<.001[a]	NR		−1.4	<.001[a]
Placebo	−0.20		NR		+1.0	
Hollander et al, 2003,[6] 52 wk						
Pramlintide, 90 µg bid	−0.35		NR		−0.5	
Pramlintide, 120 µg bid	−0.62	<.001[b]	NR		−1.25	<.003[b]
Placebo	−0.22		NR		+0.6	

HbA_{1c} = 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.

(Tables 2 and 4).[6,8,9] Patients using glargine (a basal insulin without pronounced peak effects) dosed to target fasting plasma glucose, with or without oral hypoglycemic agents,[9] had significantly greater improvement in HbA_{1c} levels with pramlintide than placebo at 16-weeks ($P < .05$). The percentage of patients achieving HbA_{1c} levels of ≤7% or a ≥0.5% reduction was not significantly different between groups (pramlintide, 54%; placebo, 45%).[9] Pramlintide at higher dosages (120 µg twice daily[6] and 150 µg 3 times daily[8]) reduced HbA_{1c} 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 HbA_{1c} levels of >8.5% showed a larger change in HbA_{1c} levels at 16 weeks (–1.19%) than persons with baseline HbA_{1c} levels of ≤8.5% (–0.36%).[9]

Postprandial glucose was lowered more with pramlintide than with placebo ($P < .001$) as was fasting plasma glucose at the 16-week follow-up[9] (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.[8,9]

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 ($P < .001$).[6,8,9] Changes in weight and HbA_{1c} levels were evaluated in overweight and obese patients (BMI >25 kg/m^2) in a post hoc pooled analysis of persons with type 2 diabetes using insulin.[15] At 26 weeks, pramlintide 120 µg twice daily lowered both HbA_{1c} levels and weight more than placebo (between-group change in HbA_{1c} level, –0.41%; and weight, –1.8 kg; both $P < .001$). 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/m^2 or >40 kg/m^2) 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).[6,15]

One study in type 2 diabetes had an active comparison group: Riddle and colleagues[11] 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 HbA_{1c} 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 $P < .001$).

Only 1 study in type 2 disease examined patient-reported outcomes,[23] based on the trial by Riddle and colleagues discussed above.[9] 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 HbA_{1c} 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.[17] Black and Hispanic patients had higher baseline HbA_{1c} 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%).[6,8,9] 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.[6,8,9]

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)[5,7,10] and type 2 diabetes. In a 2-year, open-label extension study in type 1 disease,[10] 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%,

Table 5. Frequency of Adverse Events in Placebo-Controlled Studies of Pramlintide in Type 1 Diabetes

Trial	Any Nausea %	Severe Nausea %	Any Anorexia[a] or Reduced Appetite %	Severe Anorexia or Reduced Appetite %	Any Vomiting %	Severe Vomiting %
Edelman et al, 2006[5]						
Pramlintide	48.5-95.1[b]	4.0-7.3	6.9-14.6	0.0	11.9-17.1	2.4-5.9
Placebo	36.1	0.7	2.0	0.0	6.1	0.7
Whitehouse et al, 2002[10]						
Pramlintide	46.5	6.2	17.7	2.5	11.5	2.1
Placebo	21.9	1.7	2.1	0.0	8.0	0.4
Ratner et al, 2004[7]						
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

[a] Anorexia was defined as decreased appetite, early satiety or gastric fullness, loss of appetite, or no appetite.
[b] 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[a] Mean No. (SE)		
	Weeks 0-4	Weeks 0-29	Weeks 26-52
Edelman et al, 2006[5]			
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[10]			
Pramlintide, 30 or 60 µg tid-qid	2.12 (0.35)	–	0.43 (0.07)
Placebo	1.04 (0.24)[b]	–	0.52 (0.08)[b]
Ratner et al, 2004[7]			
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)

qid = 4 times daily; SE = standard error; tid = 3 times daily.
[a] 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.
[b] Event rates were calculated after excluding 1 patient in the placebo group who reported >100 episodes of severe hypoglycemia.

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 67.6%; placebo, 47.2% to 70.6%).[8,9] 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 trials[5,7,10] 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),[6,8] 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]

DISCUSSION

Pramlintide improved HbA_{1c} 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 HbA_{1c} levels and weight occurred during the initial 6 months of treatment and then deteriorated with time. Pramlintide's greatest effect on HbA_{1c} 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.[24] Publication bias, whereby studies with positive results are more likely to be published than negative studies, is always of concern in systematic reviews. Because we identified so few studies in our review, tools for examining the potential for publication or small sample bias are not particularly useful.[25,26] Authors from all trials included in our review had financial ties with the manufacturer of pramlintide. Empiric evidence has shown that trials funded or affiliated with the pharmaceutical industry tend to favor the industry-sponsored therapy.[27,28] There is also the potential for selective outcome reporting in both trials and pooled analyses.[29] Pooled analyses were included to provide data on subgroups not otherwise found in single RCTs; however, results from such analyses should be 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 HbA_{1c} 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[18] suggested that pramlintide was effective in improving HbA_{1c} 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 HbA_{1c} levels are small, incremental improvements in HbA_{1c} 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.

To read or post commentaries in response to this article, see it online at http://www.annfammed.org/cgi/content/full/8/6/542.

Key words: Pramlintide; amylin; systematic review; diabetes mellitus

Submitted May 6, 2009; submitted, revised, March 4, 2010; accepted May 10, 2010.

Funding support: This manuscript was the result of work performed for the Drug Effectiveness Review Project, which is a collaboration of 15 organizations, mainly state Medicaid agencies. The funder played no role in drafting this manuscript or in the decision to publish the study findings.

Acknowledgments: The authors gratefully acknowledge Arkady Mak, MD, PhD (independent contractor); and Judith Logan, MD, MS; Andrew Hamilton, MS, MLS; and Theresa Nguyen, all of Oregon Health & Science University.

References

1. Turner RC, Cull CA, Frighi V, Holman RR; UK Prospective Diabetes Study (UKPDS) Group. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). *JAMA*. 1999;281(21):2005-2012.
2. Weyer C, Fineman MS, Strobel S, et al. Properties of pramlintide and insulin upon mixing. *Am J Health Syst Pharm.* 2005;62(8):816-822.
3. Khan KS, ter Riet G, Glanville J, Sowden AJ, Kleijnen J, eds. *Undertaking Systematic Reviews of Research on Effectiveness: CRD's Guidance for Those Carrying Out or Commissioning Reviews.* CRD report number 4 (2nd ed). York: NHS Centre for Reviews and Dissemniation (CRD); 2001.
4. Harris RP, Helfand M, Woolf SH, et al.; Methods Work Group, Third US Preventive Services Task Force. Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev Med*. 2001;20(3)(Suppl):21-35.
5. Edelman S, Garg S, Frias J, et al. A double-blind, placebo-controlled trial assessing pramlintide treatment in the setting of intensive insulin therapy in type 1 diabetes. *Diabetes Care.* 2006;29(10):2189-2195.
6. Hollander PA, Levy P, Fineman MS, et al. Pramlintide as an adjunct to insulin therapy improves long-term glycemic and weight control in patients with type 2 diabetes: a 1-year randomized controlled trial. *Diabetes Care.* 2003;26(3):784-790.
7. Ratner RE, Dickey R, Fineman M, et al. Amylin replacement with pramlintide as an adjunct to insulin therapy improves long-term glycaemic and weight control in Type 1 diabetes mellitus: a 1-year, randomized controlled trial. *Diabet Med*. 2004;21(11):1204-1212.
8. Ratner RE, Want LL, Fineman MS, et al. Adjunctive therapy with the amylin analogue pramlintide leads to a combined improvement in glycemic and weight control in insulin-treated subjects with type 2 diabetes. *Diabetes Technol Ther.* 2002;4(1):51-61.
9. Riddle M, Frias J, Zhang B, et al. Pramlintide improved glycemic control and reduced weight in patients with type 2 diabetes using basal insulin. *Diabetes Care.* 2007;30(11):2794-2799.
10. Whitehouse F, Kruger DF, Fineman M, et al. A randomized study and open-label extension evaluating the long-term efficacy of pramlintide as an adjunct to insulin therapy in type 1 diabetes. *Diabetes Care.* 2002;25(4):724-730.
11. Riddle M, Pencek R, Charenkavanich S, Lutz K, Wilhelm K, Porter L. Randomized comparison of pramlintide or mealtime insulin added to basal insulin treatment for patients with type 2 diabetes. *Diabetes Care.* 2009;32(9):1577-1582.
12. Kovatchev BP, Crean J, McCall A. Pramlintide reduces the risks associate`d with glucose variability in type 1 diabetes. *Diabetes Technol Ther.* 2008;10(5):391-396.
13. Marrero DG, Crean J, Zhang B, et al. Effect of adjunctive pramlintide treatment on treatment satisfaction in patients with type 1 diabetes. *Diabetes Care.* 2007;30(2):210-216.
14. Peyrot M, Rubin RR. How does treatment satisfaction work?: Modeling determinants of treatment satisfaction and preference. *Diabetes Care.* 2009;32(8):1411-1417.
15. Hollander P, Maggs DG, Ruggles JA, et al. Effect of pramlintide on weight in overweight and obese insulin-treated type 2 diabetes patients. *Obes Res.* 2004;12(4):661-668.
16. Hollander P, Ratner R, Fineman M, et al. Addition of pramlintide to insulin therapy lowers HbA1c in conjunction with weight loss in patients with type 2 diabetes approaching glycaemic targets. *Diabetes Obes Metab.* 2003;5(6):408-414.
17. Maggs D, Shen L, Strobel S, Brown D, Kolterman O, Weyer C. Effect of pramlintide on A1c and body weight in insulin-treated African Americans and Hispanics with type 2 diabetes: a pooled post hoc analysis. *Metabolism.* 2003;52(12):1638-1642.
18. Ratner R, Whitehouse F, Fineman MS, et al. Adjunctive therapy with pramlintide lowers HbA1c without concomitant weight gain and increased risk of severe hypoglycemia in patients with type 1 diabetes approaching glycemic targets. *Exp Clin Endocrinol Diabetes.* 2005;113(4):199-204.
19. US Food and Drug Administration. Pramlintide Medical Review. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/21-332_Symlin%20Injection_medr.PDF. Accessed Dec 15, 2009.
20. US Food and Drug Administration. Pramlintide Statistical Review. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/21-332_Symlin%20Injection_statr.PDF. Accessed December 15, 2009.
21. Aronne L, Fujioka K, Aroda V, et al. Progressive reduction in body weight after treatment with the amylin analog pramlintide in obese subjects: a phase 2, randomized, placebo-controlled, dose-escalation study. *J Clin Endocrinol Metab.* 2007;92(8):2977-2983.
22. Karl D, Philis-Tsimikas A, Darsow T, et al. Pramlintide as an adjunct to insulin in patients with type 2 diabetes in a clinical practice setting reduced A1C, postprandial glucose excursions, and weight. *Diabetes Technol Ther.* 2007;9(2):191-199.
23. Peyrot M, Rubin RR, Polonsky WH. Diabetes distress and its association with clinical outcomes in patients with type 2 diabetes treated with pramlintide as an adjunct to insulin therapy. *Diabetes Technol Ther.* 2008;10(6):461-466.
24. Moher D, Pham B, Lawson ML, Klassen TP. The inclusion of reports of randomised trials published in languages other than English in systematic reviews. *Health Technol Assess.* 2003;7(41):1-90.
25. Terrin N, Schmid CH, Lau J. In an empirical evaluation of the funnel plot, researchers could not visually identify publication bias. *J Clin Epidemiol.* 2005;58(9):894-901.
26. Terrin N, Schmid CH, Lau J, Olkin I. Adjusting for publication bias in the presence of heterogeneity. *Stat Med.* 2003;22(13):2113-2126.
27. Als-Nielsen B, Chen W, Gluud C, Kjaergard LL. Association of funding and conclusions in randomized drug trials: a reflection of treatment effect or adverse events? *JAMA.* 2003;290(7):921-928.
28. Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *BMJ.* 2003;326(7400):1167-1170.
29. Chan A-W, Hro'bjartsson A, Haahr HT, Gotzsche PC, Altman DG. Empirical evidence of selective reporting of outcomes in randomized controlled trials. *JAMA.* 2004;291(20):2457-2465.