Drug Class Review

Newer Drugs for the Treatment of Diabetes Mellitus

Final Report

August 2008

The Agency for Healthcare Research and
Quality has not yet seen or approved this report.

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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INTRODUCTION

Diabetes mellitus (diabetes) is a chronic and insidious disease affecting more than 20 million Americans, approximately 7% of the population.[1] Of those diagnosed, 90-95% have type 2 diabetes, while 5-10% have type 1 diabetes. Type 1 diabetes is characterized by autoimmune destruction of beta cells of the pancreas resulting in absolute insulin deficiency. Type 2 diabetes encompasses a heterogeneous group of disorders characterized by slow progressive loss of beta cell function and mass leading to variable degrees of insulin resistance, impaired insulin secretion, and increased hepatic glucose production. Among the counterregulatory hormones, higher glucagon levels relative to insulin also plays a significant role in the pathogenesis and management of type 2 diabetes, making optimal control difficult to maintain.

The 2008 American Diabetes Association treatment guidelines recommend achieving and maintaining an A1c goal of <7% in nonpregnant patients with the caveat that less stringent goals may be appropriate for certain populations, all the while maintaining minimal hypoglycemia in order to prevent micro- and perhaps macrovascular outcomes.[2] Insulin is the treatment for type 1 diabetes. Pharmacologic options for type 2 diabetes have primarily included sulfonylureas, biguanides, thiazolidinediones, meglitinides, alpha-glucosidase inhibitors, and insulin. Because of the progressive nature of diabetes, practitioners and patients experience challenges in reaching and sustaining American Diabetes Association goals. In fact, it is estimated that more than 50% of persons with type 2 diabetes will require more than one oral hypoglycemic agent after 3 years of diagnosis and approximately 70% will require combination oral therapy with or without insulin 6 to 9 years from diagnosis.[3]

Within the last 1 to 2 years, three new antihyperglycemic agents have been approved: pramlintide, exenatide, and sitagliptin (Table 1). These agents offer mechanisms of glycemic control beyond that of "traditional" oral agents and insulin by targeting alternate gluco-regulatory receptors and hormones such as amylin, glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic peptide (GIP), and dipeptidyl peptidase-4 (DPP-4).

Amylin is a neuroendocrine hormone co-secreted with insulin from beta cells in response to elevated blood glucose concentrations and complements the actions of insulin. GLP-1 and GIP are secreted by L-and K-type cells in the intestinal tract in response to a combination of endocrine and neural signals initiated by the entry of food into the gut. Secretion of GLP-1 and GIP enhance insulin release. Both endogenous GLP-1 and GIP are rapidly degraded by the proteolytic enzyme DPP-4.

Table 1. Characteristics of pramlintide, exenatide, and sitagliptin

Drug **Drug class** **Brand name** **(Manufacturer)** **Approval date** **Country**	**Dosage** **How supplied**	**FDA indications** **Mono- or combined therapy**	**Contraindications** **Precautions** **Pregnancy category**	**Dose adjustments** **Monitoring**
Pramlintide Amylinomimetic/amylin agonist Symlin® (Amylin) March 2005 US	DM1: Initiate at 15 mcg subQ before major meals (≥30 g of carbohydrate) and titrate by 15 mcg every 3 days to 30 or 60 mcg/meal as tolerated. If nausea persists at the 45 or 60 mcg dose, may decrease to 30 mcg. DM2: Initiate at 60 mcg subQ before major meals and increase every 3-7 days to 120 mcg/meal as tolerated. If nausea persists at the 120 mcg dose, may decrease to 60 mcg. Supplied as Symlin Pen™ 60 or 120 prefilled pen, or as a 5 mL vial containing 600 mcg/mL.	Adjunctive therapy in DM1, DM2, adults only, who use prandial insulin and failed desired glucose control despite optimal therapy (+/- SU and/or metformin in DM2). Patients who meet any of the following criteria should NOT be considered: Poor compliance with current insulin regimen and with self-blood glucose monitoring, A1c >9%, recurrent severe hypoglycemia, requires use of drugs that stimulate gastrointestinal motility, pediatric patients	Contraindications: Hypersensitivity to pramlintide or its components, confirmed diagnosis of gastroparesis, hypoglycemia unawareness. Precautions: Pramlintide should not be mixed with any type of insulin. Pregnancy category: C	Decrease rapid- or short-acting insulins, including fixed-mix insulins (such as 70/30) by 50% to reduce the risk of hypoglycemia. Patients should monitor blood glucose and A1c frequently. Recent blood glucose monitoring data, history of hypoglycemia, current insulin regimen, and body weight should be reviewed prior to use.
	Mechanism of action: The exact mechanism of action is unclear but it appears to affect the rate of postprandial glucose appearance by slowing gastric emptying, suppressing glucagon secretion (not normalized by insulin alone), which leads to suppression of endogenous glucose output from the liver, and regulating food intake due to centrally-mediated modulation of appetite.			

Table 1. Characteristics of pramlintide, exenatide, and sitagliptin

Exenatide Incretin mimetic/GLP-1 analog Byetta® (Amylin) April 2005 US	5 mcg BID subQ before a meal, can be increased to 10 mcg BID subQ before a meal after 1 month. Supplied as 5 mcg 1.2 mL prefilled pen and 10 mcg 2.4 mL prefilled pen	DM2, adults only, in patients taking metformin, SU, or TZD with inadequate glycemic control Combined therapy with metformin +/-SU, SU, TZD +/- metformin	Contraindications: Hypersensitivity to exenatide or any of its components Precautions: Not a substitute for insulin in insulin-requiring patients, type 1 diabetes, diabetic ketoacidosis, acute pancreatitis, anti-exenatide antibodies, end-stage renal disease, severe renal impairment, severe gastrointestinal disease, hypoglycemia Pregnancy category: C	Decrease SU dose to reduce risk of hypoglycemia; monitor hypersensitivity
	Mechanism of action: The exact mechanism is unclear but appears to have acute effects on pancreatic beta cell responsiveness to glucose and leads to insulin release only in the presence of elevated glucose concentrations. Exenatide improves fasting and postprandial glycemic control by suppressing elevated glucagon levels from alpha-cells of the pancreas, and delaying gastric emptying time while increasing the sensation of satiety by mimicking the actions of GLP-1 in the gut and through stimulation of GLP-1 receptors located in the central nervous system and vagus nerve.			
Sitagliptin Incretin enhancer/DPP-4 enzyme inhibitor Januvia® (Merck) October 2006 US, Canada	100 mg once daily with or without food. Available as 100 mg, 50 mg, or 25 mg tablets	Mono- or as add-on therapy in DM2, adults only, inadequately managed on diet and exercise. Combined therapy with metformin +/- SU, SU, TZD	Contraindications: Hypersensitivity to sitagliptin or its components Precautions: Dose adjustment is recommended in patients with renal insufficiency and failure Pregnancy category: B	Decrease sitagliptin dose to 50 mg if CrCl 30-50 mL/min and decrease dose to 25 mg if CrCl <30 mL/min, or on dialysis. SU dose may need to be decreased if frequent hypoglycemia occurs.
	Mechanism of action: Inhibits the degradation of endogenous GLP-1 and glucose-dependent insulinotropic peptide (GIP), thereby prolonging their half-lives and concentrations. It is unclear whether sitagliptin has clinically relevant effects on prolonging gastric emptying time or reducing satiety. It appears that sitagliptin may exhibit a flat dose-response curve at 100 mg/d.			

Abbreviations: AMP, adenosine monophosphate; BID, twice daily; CrCl, creatinine clearance; DM1, type 1 diabetes; DM2, type 2 diabetes; FDA, US Food and Drug Administration; GLP-1, glucagon-like peptide-1; SC, subcutaneous; SU, sulfonylureas; TZDs, thiazolidinediones.

Scope and Key Questions

The purpose of this review was to compare the effectiveness and harms of newer diabetes medications for persons with diabetes mellitus. The key questions for this review were developed with input from experts in the fields of endocrinology and internal medicine. The Oregon Evidence-based Practice Center wrote preliminary key questions and identified the populations, interventions, outcomes of interest, and the eligibility criteria for studies. The key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project. The participating organizations of the Drug Effectiveness Review Project were responsible for ensuring that the scope of the review reflected the populations, drugs, and outcome measures of interest to clinicians and patients in their constituencies. The participating organizations approved the following key questions to guide this review:

Pramlintide: Key Questions

1. For children and adults with type 1 diabetes does pramlintide differ in efficacy, effectiveness, or harms in achieving glycemic control when added to prandial insulin compared with conventional insulin therapy?
2. For children and adults with type 2 diabetes does pramlintide differ in efficacy, effectiveness, or harms in achieving glycemic control when added to prandial insulin compared with conventional insulin therapy with or without concurrent oral hypoglycemic agents?
3. Are there subgroups of patients for which pramlintide is more or less suitable than other hypoglycemic agents?

Exenatide: Key Questions

1. For children and adults with type 2 diabetes does exenatide differ in efficacy, effectiveness, or harms in achieving glycemic control compared with other hypoglycemic agents as monotherapy or combined therapy?
2. For children and adults with type 2 diabetes, does exenatide differ in efficacy, effectiveness, or harms in achieving glycemic control when added to other hypoglycemic agents compared with conventional insulin therapy?
3. Are there subgroups of patients for which exenatide is more or less suitable than other hypoglycemic agents?

Sitagliptin: Key Questions

1. For children and adults with type 2 diabetes does sitagliptin differ in efficacy, effectiveness, or harms in achieving glycemic control compared with placebo?
2. For children and adults with type 2 diabetes does sitagliptin differ in efficacy, effectiveness, or harms in achieving glycemic control as monotherapy compared with other hypoglycemic agents or when added as part of combined therapy?
3. Are there subgroups of patients for which sitagliptin is more or less suitable than other hypoglycemic agents?

Note: Inhaled insulin (Exubera®) was included in the key questions posted for public comment in August 2007. When in October 2007 Pfizer announced that it would no longer provide the inhaled powder for use, the medication was removed from these key questions. According to Pfizer, the decision to remove Exubera® was voluntary and was not based on safety or efficacy problems but on lack of demand for the drug.

METHODS

Literature Search

To identify relevant citations we searched Ovid MEDLINE®, Ovid MEDLINE® IN-Process (1950 to April Week 3, 2008), Cochrane Database of Systematic Reviews®, Cochrane Central Register of Controlled Trials®, and the Database of Abstracts of Reviews of Effects (3rd quarter 2007) using search terms for included drugs, indications, and study designs. Electronic database searches were supplemented by hand searches of reference lists of included studies and reviews. In addition, we searched the US Food and Drug Administration (FDA) Center for Drug Evaluation and Research, the Canadian Agency for Drugs and Technologies in Health, and the National Institute for Health and Clinical Excellence web sites for medical or statistical reviews and technology assessments. Finally, we searched dossiers of published and unpublished studies submitted by pharmaceutical companies. (See Appendix A for complete search strategies.) All citations were imported into an electronic database (Endnote® v.9.0).

Study Eligibility

All citations were reviewed for inclusion using the criteria shown in Table 2. Two reviewers independently assessed titles and abstracts of citations identified from literature searches. Full-text articles of potentially relevant citations were retrieved and assessed for inclusion by two reviewers, and disagreements were resolved by consensus. Results published only in abstract form (such as a conference proceeding) were not included, because they typically provided insufficient detail for adequate quality assessment.

Table 2. Study inclusion and exclusion criteria

Included populations
• Adults and children • Type 1 and type 2 diabetes mellitus
Excluded populations
• Gestational diabetes and Type 1 and type 2 diabetes mellitus in pregnancy
Subgroups of interest
• Demographic characteristics (age, race, and sex) • Concomitant medications and drug-drug interactions • Comorbidities such as obesity and cardiovascular disease • History of hypoglycemic episodes • Baseline A1c • Drug specific-subgroups: pramlintide, renal insufficiency; exenatide, renal insufficiency; and sitagliptin, renal and hepatic insufficiency
Included health outcomes
• All-cause mortality • Microvascular disease: chronic kidney disease including renal dialysis, renal transplantation, and end-stage renal disease; retinopathy including proliferative retinopathy and blindness; and peripheral neuropathy • Macrovascular disease: cardiovascular events, cardiovascular mortality, stroke or transient ischemic attack, coronary heart disease, cardiovascular procedures, and extremity amputation • Other complications of diabetes: lower extremity ulcers • Quality of life including treatment satisfaction

• Other: hospitalization and medical visits related to diabetes care
Included intermediate outcomes
• Glycemic control: fasting glucose, post-prandial glucose, and A1c • Change in weight • Time to treatment failure
Included safety and harms outcomes
• Overall adverse events • Withdrawals due to adverse events • Major adverse events including but not limited to diabetic ketoacidosis and non-ketotic hyperosmolar coma • Specific adverse events including but not limited to hypoglycemia, liver toxicity, liver function abnormalities, gastrointestinal effects, adverse changes in lipid concentrations, and weight gain • Adverse events specific to drug class: DPP-4 inhibitors, infection and neoplasm including cancer; amylinomimetics, neoplasm including cancer
Included study designs
• All studies (efficacy, effectiveness, and harms) were required to have ≥12 weeks of follow-up, the minimum study duration needed to adequately assess change in glycemic control. • Studies evaluating health outcomes*:* randomized controlled trials of cross-over or parallel group design, good-quality systematic reviews, observational studies reporting health outcomes such as: cohort studies with a comparison group and case-control studies. • Studies evaluating intermediate outcomes*:* randomized controlled trials of cross-over or parallel group design and good-quality systematic reviews • Studies evaluating harms*:* randomized controlled trials, controlled clinical trials, population-based comparative cohort studies focused on adverse events, case-control studies, reports from voluntary adverse event reporting systems, and good-quality systematic reviews

Data Abstraction

The following data were abstracted by one reviewer and reviewed by a second: study design; setting and population characteristics (including sex, age, ethnicity, and diagnosis); eligibility and exclusion criteria; interventions (dose and duration); comparisons; numbers screened, eligible, enrolled, and lost to follow-up; method of outcome ascertainment; and results for each outcome. We recorded intention-to-treat results when reported.

For included systematic reviews, we abstracted the searched databases, study eligibility criteria, numbers of studies and patients represented, characteristics of included studies, data synthesis methods, and main efficacy and safety results.

Validity Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria listed in Appendix C. These criteria are based on the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (UK) criteria.[4, 5] We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intention-to-treat analysis. We considered methods to meet criteria for intention-to-treat analysis if outcomes for at least 95% of participants were analyzed according to the group to which they were originally assigned. We considered total attrition of ≥15% in any of the treatment arms to be excessive.

Trials that had fatal flaws were rated poor quality. Trials that met *all* criteria were rated good quality and the remainder rated fair quality. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses: The results of some fair-quality studies are *likely* to be valid, while others are only *probably* valid. A poor-quality trial is not valid; the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs. A fatal flaw is reflected by failing to meet *combinations* of items of the quality assessment checklist that work together to suggest a potential for bias.

We assessed the quality of systematic reviews using pre-defined criteria developed by Oxman and Guyatt (See Appendix C). These included adequacy of literature search and study selection methods, methods of assessing validity of included trials, methods used to combine studies, and validity of conclusions.

Data Synthesis

A qualitative analysis of the available evidence or lack of evidence was undertaken. We constructed evidence tables (included as a separate document) showing the study characteristics, quality rating, and results for all included studies.

Pooled estimates of effect sizes were estimated by meta-analysis using random-effects models.[6] Results from each study were stratified by dose level of the drug intervention arms (high and low doses). Weighted mean differences between drug and control were calculated for outcomes (percent change in A1c, weight loss, fasting plasma glucose, and post-prandial glucose). Risk ratios between drug and control were pooled for withdrawals and adverse events. Forest plots for both weighted mean difference and risk ratio were created to visually inspect the data.[7] The Q-statistic and the I^2 statistic (the proportion of variation in study estimates due to heterogeneity) were calculated to assess heterogeneity between the effects from pooled studies.[8, 9] Publication bias was examined using funnel plots to check for asymmetry with respect to precision and magnitude of effect.[10] All analysis was done using "R statistical environment" software and Forest plots were generated using RevMan.[11, 12]

Peer Review and Public Comment

Original Drug Effectiveness Review Project reports are independently reviewed and commented upon by three to five peer reviewers. Peer reviewers are identified through a number of sources, including but not limited to members of professional societies, acknowledged experts in a particular field, authors figuring prominently in the published literature, and persons recommended by the Drug Effectiveness Review Project participating organizations. A list of peer reviewers for Drug Effectiveness Review Project reports is available on the Drug Effectiveness Review Project website (www.ohsu.edu/drugeffectiveness).

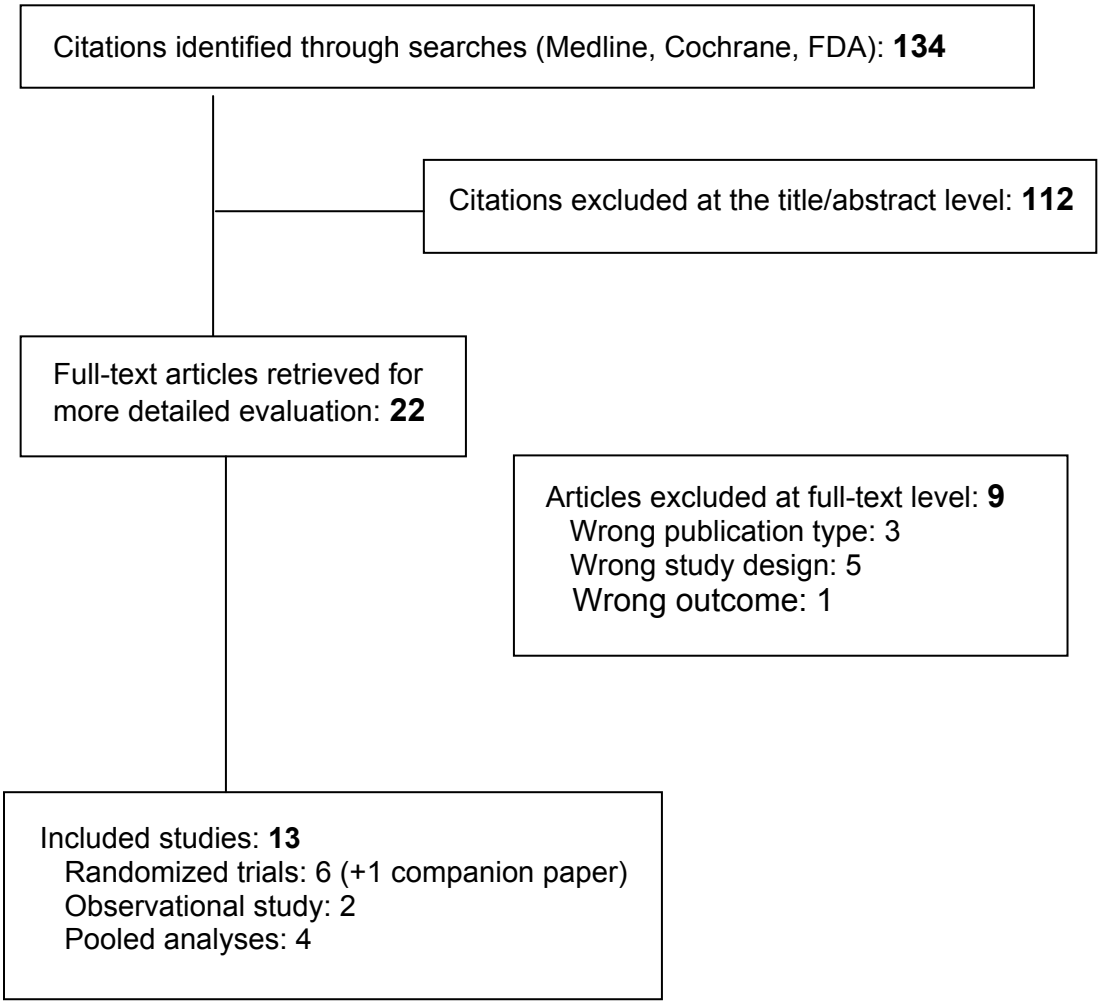
The Drug Effectiveness Review Project process allows for a two-week public comment period prior to finalization of the report. Draft reports are posted on the Drug Effectiveness Review Project website and interested individuals or organizations can submit comments. Comments received from peer reviewers are considered and revisions made accordingly. Public comments are discussed with the Drug Effectiveness Review Project participating organizations and then a determination is made as to what revisions are appropriate.

RESULTS

Pramlintide

We identified 134 citations from our literature search (Figure 1). Six randomized controlled trials (with 1 companion paper) and 4 pooled analyses fulfilled inclusion criteria. No comparative cohort or case-control studies reporting long-term benefits or harms were identified. Details of included studies are found in Evidence Tables 1-3 and quality assessment in Evidence Table 4. Trials excluded upon review of the full text are listed in Appendix D. In the FDA Medical and Statistical Reviews, 6 relevant trials were identified, of which 4 were published and already included in our review. The remaining two trials could not be found in the published literature. No good quality systematic reviews of pramlintide were identified for inclusion.

Figure 1. Literature search results for pramlintide



Summary of Evidence for Pramlintide

Key Question 1. For children and adults with type 1 or type 2 diabetes, does pramlintide differ in efficacy, effectiveness, and in harms for achieving glycemic control when added to prandial insulin compared to conventional insulin therapy?

Type 1 diabetes

Evidence in children

- No data on children were reported, although children were eligible for study enrollment in 2 included trials.

Long-term health outcomes and adverse events

- No studies evaluated long-term health outcomes or adverse events and none were longer than 52 weeks in duration.

Efficacy and harms

- A1c was either slightly improved or no different with the addition of pramlintide 30 or 60 mcg/meal to a flexible-dose insulin regimen compared with placebo plus flexible-dose insulin regimen over 29 weeks[13] (between-group difference: 0.0%) and 52 weeks[14] (between-group difference: 0.27%, *P*-value, not reported) of treatment.
- When pramlintide 60 mcg 3 or 4 times a day was added to fixed-dose insulin therapy, A1c decreased from baseline by 0.29% to 0.34% ($P<0.01$), with no significant effect in the placebo group 0.04% at 52 weeks of follow-up.[15]
- Patients randomized to receive pramlintide in addition to insulin lost slightly more weight from baseline (range: -0.4 to -1.3 kg) than compared with those receiving placebo plus insulin in a fixed- or flexible-dose setting, who experienced slight weight gain (range: +0.8 to +1.2 kg) over 29 and 52 weeks.
- Groups receiving pramlintide in addition to fixed- or flexible-dose insulin therapy exhibited larger overall rates of withdrawal (range across studies: 20-42% compared with 10-33%) and withdrawals due to adverse events (range across studies: 5-20% compared with 2-8%) than groups receiving placebo plus insulin.
- Adverse events including nausea, vomiting, anorexia, and reduced appetite were more commonly reported with the use of pramlintide plus insulin than with placebo plus insulin.
- Severe hypoglycemia occurred more frequently with pramlintide plus insulin during the first 4 weeks of treatment compared with placebo plus insulin. Rates of severe hypoglycemia declined once pramlintide doses stabilized but continued to remain slightly higher than with placebo plus insulin at up to 52 weeks of follow-up.

Type 2 diabetes

Evidence in children

- Children and adolescents ≤ 18 years were not included in any of the published studies on effectiveness, efficacy, or harms.

Long-term health outcomes and adverse events

- No studies evaluated long-term health outcomes or adverse events and none were longer than 52 weeks in duration.

Efficacy and harms

- Pramlintide 90 mcg or 120 mcg added to fixed- or stable doses of insulin decreased A1c by 0.13% to 0.4% and weight by 1.1 kg to 1.85 kg (placebo-corrected differences) at 52 weeks compared with placebo and insulin.[16, 17]
- At 16 weeks the addition of pramlintide to glargine (without prandial insulin) reduced A1c by 0.34% and weight by 2.3 kg (placebo-corrected differences) relative to placebo plus glargine in a flexible-dose setting.[18]
- Both pramlintide- and placebo-treated subjects exhibited similar rates of withdrawal and withdrawal due to adverse events.
- The most commonly reported adverse event was nausea, which occurred more frequently with pramlintide plus insulin than with placebo plus insulin especially during the first 4 weeks of treatment and declined thereafter.
- Severe hypoglycemia occurred more frequently with pramlintide 150 mcg 3 times a day added to insulin than with insulin plus placebo during the first 4 weeks of treatment. Rates of hypoglycemia after 4 weeks were similar among treatment groups.

Table 3. Characteristics of pramlintide placebo-controlled trials in adults with type 1 diabetes

Author, year Country Quality	Sample size (N) Follow-up (weeks)	Age (years) (SD)[a] % Male[a] % White[a] % Hispanic[a] Diabetes[a] duration (years)	Baseline values: A1c (%) (SD)[a] Weight (kg)[a] BMI (kg/m^2)[a] Total daily insulin dose (units)[a] Glycemic goals prespecified?	Interventions	Combination therapy
Whitehouse, 2002 US Fair-Poor	480/342 52	40.3-40.4 (11.6-12.1) 55 92-96 NR 16.5-17.1 (10.0-10.5)	8.7-8.9 (1.3-1.5) 75.0-75.6 (13.8-13.3) 25.2-25.8 (3.3-3.5) NR NR	Pramlintide: 30 mcg, 60 mcg QID, before meals + insulin Insulin: No restrictions on use (flexible dosing)	Treatment arms received the addition of pramlintide to insulin while the comparator arm received placebo in addition to insulin
Ratner, 2004[15] US, Canada Fair-Poor	651/479 52	39.2-41.9 (12.8-13.6) 47-53 89-92 NR 18.2-19.2 (10.5-11.4)	8.9-9.0 (0.9-1.1) 75.8-78.3 (14.5-15.8) 26.3-26.8 (4.1-4.9) NR NR	Pramlintide: 60 mcg TID, 60 mcg QID, 90 mcg TID, before meals + insulin Insulin: Dose adjustments not encouraged (fixed-stable dosing) Note: Efficacy results from 90-mcg arm were excluded after another trial indicated that this dose exhibited an adverse tolerability profile	Treatment arms received the addition of pramlintide to insulin while the comparator arm received placebo in addition to insulin
Edelman, 2006[13] US Fair	296/295 29	41 (12-14) 36.6-53.5 85.4-92 NR 19-21 (12)	8.1-8.2 (0.7-0.8) 77-83 (13-18) 27-28.1 (3.8-4.9) MDI: 63.7-66.4 (26.5-35.1) CSII: 45.9-49.6 (17.5-23.3) Yes	Pramlintide: 30 mcg, 60 mcg, TID-QID, before meals +insulin Insulin: No restrictions on use (flexible dosing)	Treatment arms received the addition of pramlintide to insulin while the comparator arm received placebo in addition to insulin

[a] Data presented are the range across treatment groups for mean and standard deviation.
Abbreviations: CSII, Continuous subcutaneous insulin infusion; MDI, Multiple daily injections; NR, not reported; SD, standard deviation; TID, three times daily; QID, four times daily.

Detailed Assessment of Pramlintide in Type 1 Diabetes

Key Question 1. For children and adults with type 1 diabetes, does pramlintide differ in efficacy, effectiveness, or harms in achieving glycemic control when added to prandial insulin compared with conventional insulin therapy?

Details of the three included placebo-controlled trials are presented in Table 3 and glycemic control results are presented in Table 4. None of these trials were similar enough for efficacy data to be pooled. This section reports key details of individual studies.

Flexible-dose insulin

In a fair-quality trial the addition of pramlintide 30 mcg or 60 mcg 3 or 4 times a day with meals to a flexible-dose insulin regimen did not significantly improve A1c (-0.5% vs. -0.5%; Table 4). The comparison group was patients receiving a combination of short- and long-acting insulin plus placebo adjusted to achieve specified glycemic targets over 29 weeks.[13] According to the study investigators, a greater percentage of pramlintide-treated patients who self-monitored blood glucose concentrations achieved post-prandial glucoses below the American Diabetes Association targets for all three meals compared with those on insulin plus placebo (breakfast: 68% compared with 51%; lunch: 71% compared with 61%; dinner: 70% compared with 58%, $P<0.0001$ for each meal compared with placebo). Pramlintide-treated patients lost slightly more weight than insulin-only patients (-1.3 kg compared with +1.2 kg). Pramlintide-treated patients also exhibited slightly larger reductions in total daily insulin doses (-12% of total daily dose from baseline) than patients using insulin plus placebo (+1% of total daily dose from baseline) by the end of 29 weeks. In the initial 4 weeks of treatment however, more pramlintide-treated patients decreased their prandial insulin doses than compared with patients on insulin plus placebo (-28% of prandial insulin dose vs. -8% of prandial insulin dose). During the remainder of the trial, patients in both treatment arms required dose increases to their basal insulin regimen (pramlintide, +3% of basal insulin dose vs. placebo, +10% of basal insulin dose).

All patients received stable doses (±10% change from baseline) of intensive insulin therapy using multiple daily injections or continuous insulin infusion before enrolling in the study. Patients were mainly middle-aged and white and had long-standing type 1 diabetes. Mean baseline A1c was 8.1%. A 30%-50% reduction in mealtime insulin was recommended before starting pramlintide to avoid hypoglycemic events.

A patient survey examined whether subjects in this study *believed* that pramlintide added to insulin provided marked benefits compared with placebo plus insulin.[19] A significantly greater proportion of subjects receiving pramlintide believed their study medication provided them with more control over their blood sugar, weight, appetite, and ability to function than compared with those in the insulin plus placebo arm. However, more pramlintide-treated patients believed their study medication "had side effects that would keep me from using it on a long-term basis" relative to those randomized to the placebo plus insulin arm.

The authors of this study stratified the results by insulin delivery method (multiple injections or continuous infusion). Patients using placebo plus continuously infused insulin were more likely to have lower satisfaction than patients on pramlintide plus insulin delivered by either modality. Because baseline treatment satisfaction data were not presented, this study could not be used to determine whether significant changes in satisfaction occurred over the duration of

the study. Also, the study does not explicitly state that patients participating in the survey remained blinded during the entire survey period.

In a second trial using flexible insulin dosing,[14] the addition of pramlintide 30 mcg or 60 mcg 4 times a day to insulin with each meal was slightly more effective than insulin plus placebo in lowering A1c, weight, and total insulin requirement (Table 4). The change in A1c at week 52 was -0.39% with pramlintide plus insulin and -0.12% with insulin plus placebo (between-group difference: 0.27%, *P*-value, not reported). During the course of the trial, patients from both treatment groups required increases in their total daily insulin dose. The percent change in insulin dose adjustment were statistically significant between pramlintide-treated and insulin plus placebo-treated patients at the end of 52 weeks (+2.3% compared with +10.3%, *P*=0.018); however, the clinical significance of the between-group difference is yet to be determined. A higher proportion of pramlintide-treated patients achieved an A1c of <7% "at any time" at the end of the trial.

This trial was rated fair-poor quality: only 71% of patients completed the 52 weeks of therapy and data from only completers were examined. The total withdrawal rates of 28-29% were similar between the treatments, however, more pramlintide-treated patients discontinued due to adverse events than placebo-treated patients during the study (12.8% compared with 8.0%). Nausea was the most common reason for withdrawal. In addition, the authors reported no further details on insulin dose adjustments than that they were made according to "good medical practices."

Stable insulin dosing

The addition of pramlintide 60 mcg 3 or 4 times a day with meals to fixed or stable background insulin therapy improved A1c by 0.25% and 0.34% compared with 0.04% improvement in the insulin plus placebo group over 52 weeks of therapy.[15] A greater proportion of pramlintide-treated patients achieved the A1c goal of <7% at "any time" and exhibited small decline in total daily insulin doses over the study duration (3-6% decrease in total daily dose of insulin from baseline compared with 0% change). Pramlintide-treated subjects also demonstrated nominal weight loss from baseline (-0.5 kg at 52 weeks, *P*<0.05), which was not seen with placebo (+0.8 kg at 52 weeks, *P*>0.05). This trial was rated fair-poor quality because of high withdrawal rates (>35% in all treatment arms), however a greater proportion of pramlintide-treated patients discontinued due to adverse events (primarily nausea) compared with those in the placebo plus insulin arm (14-20% compared with 3% for adverse events).

This trial began with a 90 mcg dose arm, which was removed from efficacy analysis when another trial (identified as study #137-117 in FDA reviews) revealed an adverse tolerability profile associated with this 90 mcg dose. Specific reasons for "intolerability" with the 90 mcg dose could not be found in either study #137-117 in the FDA documents or from this trial by Ratner and colleagues. Only general sweeping statements were made by Ratner and colleagues: there was 2-fold increase in nausea, vomiting, anorexia and 4-fold increase in severe hypoglycemia event rates associated with pramlintide across the doses compared with placebo. Study #137-117 could not be found in a peer-reviewed publication.

Table 4. Pramlintide in type 1 diabetes

Author, year	A1c[a] (%)						Weight[a] (kg)			Total daily insulin dose[a] (% change)			Percent achieving A1c goal <7%		
	29 weeks						29 weeks			29 weeks			29 weeks		
Edelman, 2006[13]	30/60 TID-QID[b]		PBO				30/60 TID-QID[b]		PBO	30/60TID-QID[b]		PBO	30/60 TID-QID[b]		PBO
	-0.5		-0.5				-1.3		+1.2	-12		+1	NR		NR
	26 weeks			52 weeks			52 weeks			52 weeks			at "any time"		
Whitehouse, 2002[14]	30/60[b] QID		PBO	30/60[b] QID		PBO	30/60[b] QID		PBO	30/60 QID[b]		PBO	30/60 QID[b]		PBO
	-0.58		-0.18	-0.39		-0.12	-0.5		+1.0	+2.3		+10.3	25.0		11.3
Ratner, 2004[15]	60 TID	60 QID	PBO	60 TID	60 QID	PBO	60 TID	60 QID	PBO	60 TID	60 QID	PBO	60 TID	60 QID	PBO
	-0.41	-0.39	-0.18	-0.29	-0.34	-0.04	-0.4	-0.4	+0.8	-3.0	-6.0	0.0	11.0	12.5	3.5

[a] Data represent change from baseline.
[b] Patients received 30 or 60 mcg with meals.
Abbreviations: PBO, placebo; TID, three times daily; QID, four times daily.

Table 5. Adverse events with pramlintide in type 1 diabetes

	Whitehouse 2002[14]		Ratner 2004[15]				Edelman 2006[13]		
	30/60[a] QID	Placebo	60 TID	60 QID	90 TID	Placebo	30 TID-QID	60 TID-QID	Placebo
Mean number of severe hypoglycemia events per patient-year (SE)[b]									
Weeks 0-4	2.12 (0.35)	1.04 (0.24)	3.78 (0.57)	3.41 (0.55)	3.91 (0.58)	0.87 (0.27)	0.79 (0.46)	0.46 (0.46)	0.42 (0.19)
Weeks 26-52	0.43 (0.07)	0.52 (0.08)	0.74 (0.12)	0.79 (0.12)	0.64 (0.12)	0.45 (0.09)	---	---	---
Weeks 0-29	---	---	---	---	---	---	1.10 (0.25)	0.42 (0.09)	0.30 (0.06)
Treatment-emergent adverse events (%)[c]									
Total nausea	46.5	21.9	47.0	47.0	59.0	12.0	95.1	48.5	36.1
Severe nausea	6.2	1.7	8.5	6.8	5.8	1.3	7.3	4.0	0.7
Total vomiting	11.5	8.0	9.8	11.0	12.0	6.5	17.1	11.9	6.1
Severe vomiting	2.1	0.4	1.8	0.6	1.2	0.6	2.4	5.9	0.7
Total anorexia	17.7	2.1	18.0	11.0	16.0	2.6	---	---	---
Severe anorexia	2.5	0.0	1.2	1.9	0.6	0.0	---	---	---
Total reduced appetite	---	---	---	---	---	---	14.6	6.9	2.0
Severe reduced appetite	---	---	---	---	---	---	0.0	0.0	0.0
Total sinusitis	---	---	---	---	---	---	22.0	12.9	8.8
Severe sinusitis	---	---	---	---	---	---	0.0	0.0	0.0

[a] All doses are reported as mcg/meal. 30/60, 30 or 60-mcg arms
[b] Severe hypoglycemia event rates are calculated as the total number of events for all patients on a treatment regimen divided by the total number of patient-years of observation.
[c] Treatment-emergent adverse events with occurrences ≥10% for totals and the incidence in the pramlintide arm is at least twice that of placebo arm.
Abbreviations: TID, three times daily; QID, four times daily.

Harms

Patients receiving pramlintide in addition to insulin had greater rates of withdrawal due to all causes and withdrawal due to adverse events than patients receiving placebo plus insulin. This was found with both fixed- and flexible-dose insulin (see Evidence Table 3). No included trial reported deaths or listed rare adverse events. There were no significant cardiac, hepatic, renal, or drug-related idiosyncratic adverse events observed in any treatment arm. Adverse events reported in the included studies are summarized in Table 5.

Hypoglycemia

During the first 4 weeks of treatment severe hypoglycemia occurred more frequently with pramlintide plus insulin than with insulin plus placebo, with both fixed and flexible insulin regimens. The rate of severe hypoglycemia declined once pramlintide doses were stabilized and not being titrated; however, at weeks 26-52[14, 15] and weeks 0-29[13] the rate of severe hypoglycemia associated with pramlintide was still slightly higher than placebo (event rates 0.42 to 1.10 compared with 0.30 to 0.52) (Table 5). Only 1 trial[13] reported that a 30-50% reduction in prandial insulin was allowed before the use of pramlintide. Even in this study, pramlintide-treated patients exhibited slightly higher rates of severe hypoglycemia than compared with insulin plus placebo-treated patients (Table 5). No trials reported the overall incidence of mild to moderate hypoglycemic episodes. All 3 trials predefined the term "severe hypoglycemia" to mean: those requiring either assistance of another person, the administration of glucagon, or the administration of intravenous glucose.

Nausea and vomiting

A significant proportion of pramlintide-treated patients experienced nausea during the trials: Across trials overall rates of nausea for pramlintide groups ranged from 46% to 95%; for placebo groups, 12% to 36%. Specifically, patients who did not tolerate pramlintide 60 mcg also frequently experienced nausea with the 30 mcg dose, and the highest reported rates of nausea (95%) were in subjects who received 30 mcg 3 times a day.[13] Higher rates of nausea were reported with pramlintide 90 mcg 3 times a day[15] than with lower dosages in the same trial.

Severe nausea was much less common than nausea overall, ranging between 5.8% and 8.5% for pramlintide plus insulin and 0.7% to 1.7% for placebo plus insulin across studies.[13-15]

More than 10% of patients randomized to pramlintide plus insulin experienced vomiting, compared with rates of up to 8.0% with placebo plus insulin. Severe vomiting occurred in up to 2% of patients taking pramlintide compared with 0.4% to 0.7% taking placebo.[13-15]

Of note, 2 of 3 placebo-controlled trials [14, 15] reported that most cases of nausea and vomiting tended to occur within 2-4 weeks of treatment but no actual data were provided to verify these statements.

Anorexia or reduced appetite

Rate of anorexia was significantly more frequent with pramlintide plus insulin (11%-18% across trials) than with placebo plus insulin (approximately 2%). Severe anorexia occurred in <2% of pramlintide patients and no placebo patients.[14,15]

Other adverse events

One trial reported sinusitis at a rate of 14.0% with pramlintide and 8.8% with placebo (P>0.05).[13] Two non-comparative observational studies[20, 21] were also evaluated for rare adverse events and neither reported any additional information.

Key Question 3. Are there subgroups of patients with type 1 diabetes for which pramlintide is more or less suitable than other hypoglycemic agents?

There was insufficient evidence to perform subgroup analyses based on age, sex, race, ethnicity, or baseline A1c in individual studies.

One randomized controlled trial conducted subgroup analyses that were not all prespecified, and one post hoc pooled-analyses was identified.[15, 22] Results from these hypothesis-generating analyses should be used with caution. Further prospective research with larger sample sizes will need to be conducted to verify these findings.

Total daily insulin dose

No studies conducted subgroup analysis evaluating whether pramlintide exhibited differential effects depending on total daily insulin dose.

Stable insulin dose

A1c outcomes were reported for a subgroup with stable insulin dosing (± 10% change in total insulin dose from baseline over 52 weeks).[15] Change in A1c was -0.59% with pramlintide 60 mcg 3 times a day and -0.57% with dosing 4 times a day. These reductions were significantly larger than those noted in the entire study group of -0.29 to -0.34%; however, generalizability of using fixed doses of insulin is limited in clinical practice.

Baseline body mass index

Pramlintide appeared to inhibit weight gain in patients with baseline body mass index ≤ 23 kg/m^2 while producing mild weight loss for patients with body mass index > 23 kg/m^2 (baseline to week 26).[15] Data at 52-week follow-up were not reported.

Baseline A1c < 8%

Data from 3 studies that included patients with baseline A1c between 7% and 8.5% receiving pramlintide 30 mcg or 60 mcg were pooled and reported in a separate publication.[22] Two of the 3 studies were identified and included in our review.[14, 15] The third study was in abstract form and was excluded. The pooled publication reported results up to 26 weeks. In this subgroup, the pooled change in A1c was -0.3% and the change in weight was -1.6 kg (both placebo-corrected; both $P<0.0009$). There was no overall increased risk in hypoglycemia. The improvement in A1c in this pooled subgroup analysis was similar to the change in A1c noted for all subjects (across a range of A1c) in the original studies. Thus, it appears that patients with good but not optimal baseline A1c of 7%-8.5% experienced similar degrees of A1c reduction as the populations included in the original trials, with no increased risk of hypoglycemia at 26 weeks.

Applicability to general populations with type 1 diabetes

The methods for recruiting study subjects were not reported in these trials, and subjects likely represent a highly selected population: Primarily white, middle-aged men and women with mean baseline A1c ranging from 8.1% to 9.0% and diabetes of 16 to 21 years duration. None of the patients had significant cardiovascular or renal disease or problems with gastrointestinal motility. Data regarding baseline comorbidities, disease severity, and existing microvascular disease such as retinopathy or neuropathy were not reported. The population included highly motivated subjects who were willing to add 2 to 4 injections to their daily regimen and who rigorously self-

monitored blood glucose over the course of the study. Study settings were not reported, but they were likely to have been outpatient clinics.

Detailed Assessment of Pramlintide in Type 2 Diabetes

Key Question 2. For children and adults with type 2 diabetes, does pramlintide differ in efficacy, effectiveness, or harms in achieving glycemic control when added to prandial insulin compared with conventional insulin therapy?

Details of the three included placebo-controlled trials are presented in Table 6 and glycemic results in Table 7. None of the trials were pooled due to significant heterogeneity.

Dose-ranging study

The addition of pramlintide 75 mcg/meal or 150 mcg/meal to fixed-dose insulin, with or without oral hypoglycemic agents (metformin or sulfonylureas), improved A1c by 0.3% to 0.4% and weight loss by 1.5 to 2.4 kg (placebo-corrected values)[17] in a population with poorly controlled (A1c 9.0-9.3%) type 2 diabetes over 52 weeks. No significant differences in A1c were observed between two pramlintide doses at the end of the trial: pramlintide 75 mcg (-0.5%) vs. 150 mcg (-0.6%). The largest reductions in A1c (almost 1%) occurred early on at week 13 for those on the 150 mcg dose. A greater percentage of patients taking pramlintide achieved an A1c goal of <7% at "any time" during the study than compared with patients taking placebo (Table 7). Both placebo- and pramlintide-treated patients required increases in their total daily insulin doses during the 52 weeks (change in total daily dose from baseline for pramlintide compared with placebo: pramlintide: +8 to +11% vs. placebo: +15%, *P*-value, not reported).

This trial was rated fair-poor quality based on a high withdrawal rate (~30%) which were similar for placebo, pramlintide 30 mcg and 75 mcg groups. Those randomized to pramlintide 150 mcg dose exhibited largest rates of total withdrawal and withdrawal due to adverse events (37.5% and 18%).

Stable insulin dosing

During the course of this one fair-quality trial,[16] results from another study (identified as study #137-123 in the FDA reviews) found that pramlintide 60 mcg was less effective than compared with higher doses. As a result, efficacy and safety information from the 60 mcg arm were excluded from this trial, though safety results should have been reported.

The addition of pramlintide 90 mcg or 120 mcg to fixed or stable doses of insulin with or without oral hypoglycemic agents (metformin or sulfonylureas) gave slightly larger improvements in A1c and weight at 52 weeks than patients randomized to placebo plus fixed-dose insulin (placebo-corrected values for A1c: 90 mcg: -0.13%, 120 mcg: -0.4% and for weight: 90 mcg: -1.1 kg; 120 mcg: -1.85 kg).[16] Effect on A1c was greatest at 26 weeks for both pramlintide groups ($P<0.05$ compared with placebo) and persisted only with the 120 mcg arm at 52 weeks (change in A1c from baseline -0.62%, $P<0.05$). No dose adjustments of baseline insulin or oral hyperglycemic agents were implemented during the study and no specific glycemic targets were reported. Approximately 20-27% of all randomized patients were taking oral hypoglycemic agents at baseline.

Flexible basal insulin dosing

In contrast to the previous study, this short-term fair-quality trial [18] evaluated pramlintide as a pre-meal medication in conjunction with glargine (without prandial insulin) with or without oral hypoglycemic agents (metformin, sulfonylureas, and/or thiazolidinediones). The comparison group was patients on flexible-dose glargine plus placebo. At 16 weeks, the addition of pramlintide to glargine reduced A1c by 0.36% and induced weight loss of 2.3 kg (placebo-corrected values) relative to placebo plus glargine. Pramlintide-treated patients also exhibited larger reductions in post-prandial glucose (change from baseline: -24.4 mg/dL ± 3.6 mg/dL compared with -0.4 mg/dL ± 3.0 mg/dL, $P<0.0001$). There were no significant differences between pramlintide-treated and placebo-treated groups for those achieving A1c <7% (54% compared with 45%) and no significant differences in changes in total daily insulin dose (change from baseline: +11.7 units compared with +13.1 units) following 16 weeks of treatment.

Glargine, a basal insulin without pronounced peak effects, was allowed to be adjusted during the study to achieve prespecified fasting glucose targets once pramlintide doses were stabilized. Patients had diabetes of 10 to 11 years' duration. At baseline A1c was moderately elevated at 8.5%, and patients were using insulin glargine 48 to 54 units per day, with 50% of patients concomitantly taking ≥2 oral hypoglycemic agents and 89% taking at least 1 oral agent.

Table 6. Characteristics of pramlintide placebo-controlled trials in adults with type 2 diabetes

Author, year Country Quality	Sample size (N) Follow-up (weeks)	Age (years) (SD)[a] % Male[a] % White[a] % Hispanic[a] Diabetes duration (years)[a]	Baseline A1c (%) (SD)[a] Weight (kg)[a] BMI (kg/m^2)[a] Total daily insulin dose (units) Glycemic goals prespecified?	Intervention Dosages	Combination therapy
Ratner, 2002[17] US Fair-Poor	538/538 52	55.5-57.5 (8.9-10.8) 56-62 76-81 8-10 11.3-13.3 (7.0-7.8)	9.0-9.3 (1.1-1.2) NR 30.4-31.1 (4.7-5.5) 55.1-60.6 (26.5-29.2) NR	Pram: 30 mcg 75 mcg, 150 mcg TID, before meals + insulin ± OHA Insulin: Dose adjustments not encouraged (fixed-stable dosing)	Stable doses of MET or SU were allowed; doses to remain unchanged
Hollander, 2003[16] US Fair	656/498 52	56.4-57.0 (10.2-10.5) 48-52 73-77 8-13 12.0-12.4 (6.6-7.3)	9.0-9.3 (1.1-1.3) 96.7-97.1 (19.3-23.2) 33.7-34.1 (6.3-7.5) 69-74 NR	Pram: 60 mcg TID, 90 mcg, 120 mcg BID, before meals +insulin ± OHA Insulin: Dose adjustment not encouraged (fixed-stable dosing) Note: 60 mcg arm was excluded after another trial indicated that this dose was less effective than higher doses	Stable doses of MET or SU were allowed; doses to remain unchanged
Riddle, 2007[18] US Fair	212/211 16	55 (9-10) 45.7-51.9 72-73 8-13 12.0-12.4 (6.6-7.3)	8.5 (0.9) 103 (18) 35 (5-6) 48-54 (25-42) Yes	Pram: 60 mcg, 120 mcg, BID-TID +glargine ± OHA Insulin: Glargine only; flexible dosing; titrate to goals	Stable doses of MET, SU, +/-TZD were allowed

[a] Data presented are the range across treatment groups for mean and standard deviation.
Abbreviations: Pram, pramlintide; NR, not reported; OHA, oral hypoglycemic agents; SU, sulfonylureas; MET, metformin; TZD, thiazolidinediones; BID, twice daily; TID, three times daily.

Table 7. Effect of pramlintide in type 2 diabetes

Author, year	Change in A1c from baseline at (%)						Change in PPG from baseline at (mg/dL)			Change in weight from baseline at (kg)			Change in total daily insulin dose from baseline			Percent achieving A1c goal <7%		
	16 weeks						16 weeks			16 weeks			16 weeks			16 weeks		
Riddle, 2007[18]	**60/120 BID-TID**		**PBO**				**60/120 BID-TID**		**PBO**	**60/120 BID-TID**		**PBO**	**60/120 BID-TID**		**PBO**	**60/120 BID-TID**		**PBO**
	-0.7		-0.34				-24.4		-0.4	-1.6		+0.7	+11.7 u		+13.1 u	54.0		45.0
	26 weeks			52 weeks			52 weeks			52 weeks			52 weeks			at “any time”		
Ratner, 2002[17]	**75 TID**	**150 TID**	**PBO**	**75 TID**	**150 TID**	**PBO**	**75 TID**	**150 TID**	**PBO**	**75 TID**	**150 TID**	**PBO**	**75 TID**	**150 TID**	**PBO**	**75 TID**	**150 TID**	**PBO**
	-0.8	-0.79	-0.3	-0.5	-0.6	-0.2	NR	NR	NR	-0.5	-1.4	+1.0	+10.9%	+7.9%	+8.1%	13.4	19.2	11.1
Hollander, 2003[16]	**90 BID**	**120 BID**	**PBO**	**90 BID**	**120 BID**	**PBO**	**90 BID**	**120 BID**	**PBO**	**90 BID**	**120 BID**	**PBO**	**90 BID**	**120 BID**	**PBO**	**90 BID**	**120 BID**	**PBO**
	-0.54	-0.68	-0.3	-0.35	-0.62	-0.22	NR	NR	NR	-0.5	-1.25	+0.6	+2 u	+1 u	+2 u	9.4	12.2	4.1

Abbreviations: PBO, placebo; u, units; BID, twice daily; TID, three times daily.

Table 8. Adverse effects reported with pramlintide

	Ratner 2002[17]			Hollander 2003[16]			Riddle 2007[18]	
	75 TID[a]	150 TID	Placebo	90 BID	120 BID	Placebo	60/120 BID-TID	Placebo
Mean number of severe hypoglycemia events per patient-year (SD)[b]								
Weeks 0-4	---	---	---	0.1 (0.08)	0.9 (0.3)	0.3 (0.20)	---	---
Weeks 26-52	---	---	---	0.0 (0.02)	0.1 (0.05)	0.2 (0.06)	---	---
Weeks 0-52	---	---	---	0.1 (0.03)	0.3 (0.05)	0.3 (0.05)	---	---
Treatment-emergent adverse effects[c] (%)								
Total hypoglycemia	67.6	64.6	70.6	---	---	---	43.8	47.2
Severe hypoglycemia	2.2	2.8	1.5	---	---	---	0.95	0.0
Total nausea	26.5	22.9	16.9	18	16	3	31.4	10.4
Severe nausea	0.7	2.8	1.5				---	---
Nausea during weeks 0-4				31	30	14	---	---
Total headaches	19.1	16.0	13.2	15	17	8	---	---
Total sinusitis	18.4	9.7	8.1	---	---	---	---	---
Total retinal disorder	5.9	10.4	5.1	---	---	---	---	---
Total inflicted injury[d]	13.2	10.4	12.5	---	---	---	---	---
Injection site reactions	---	---	---	---	---	---	0.95	0.94

[a] Doses are expressed in mcg.
[b] Severe hypoglycemia event rates are calculated as the total number of events for all patients on a treatment regimen divided by the total number of patient-years of observation.
[c] Treatment-emergent adverse events with occurrences ≥10% for totals and a 5% higher incidence in the pramlintide arm than placebo arm.
[d] Inflicted injury was not defined.
Abbreviations: BID, twice daily; TID, three times daily.

Harms

Pramlintide-plus-insulin and placebo-plus-insulin groups had similar rates of withdrawal due to all causes and withdrawal due to adverse events (see Evidence Table 3). There was no evidence of cardiac, hepatic, renal, or drug-related idiosyncratic adverse events in patients in any treatment arm of the three randomized controlled trials identified for this review and no deaths were reported. Adverse effects are summarized in Table 8.

Hypoglycemia

Pramlintide-plus-insulin and placebo-plus-insulin groups experienced similar rates of mild-to-moderate hypoglycemia,[17, 18] but pramlintide-treated patients experienced more episodes of severe hypoglycemia. Severe hypoglycemia occurred most with pramlintide 120 mcg during the first 4 weeks of therapy (0.9 events/patient-year compared with 0.3 events/patient-year with placebo).[16] The incidence of severe symptoms declined with continued use of pramlintide, and rates were similar to placebo for weeks 4-26 and 26-52.[16] All 3 trials predefined the term "severe hypoglycemia" to mean: those requiring either assistance of another person, the administration of glucagon, or the administration of intravenous glucose.

Nausea

The incidence of mild-to-moderate and severe nausea was significantly higher with pramlintide 75, 90, 120, and 150 mcg than with placebo plus insulin. Only 1 trial reported data showing that most events occurred within the first 4 weeks of treatment.[16] When metformin use was stratified in one trial, its addition to pramlintide plus insulin appeared to have no significant effect on nausea compared with the larger study population.[16] These trials did not report vomiting or anorexia.

Headache

Higher rates of headache were reported with pramlintide (15% and 17%) than with placebo (8%).[16] In another trial[17] rate of headache was similar among treatment groups, ranging from 13.2% in the placebo-plus-insulin group to 19.1% with pramlintide 75 mcg 3 times a day plus insulin. None of the studies provided enough information to determine whether there were any correlations between the incidence of headaches and hypoglycemic events.

Other adverse events

No trials reported any treatment-emergent adverse events occurring with a frequency of more than 2%-5%. Overall adverse events occurring with a frequency of ≥10% with a minimum 5 percentage point difference between pramlintide- and placebo-treated patients comprised sinusitis, retinal disorder, inflicted injury, and injection site reactions (Table 8).[16, 17]

Higher incidence of retinal disorder was reported with pramlintide 150 mcg than with lower pramlintide doses and placebo.[17] The authors performed detailed medical reviews of these patients with reported retinal disorder and concluded that the increased incidence was likely attributable to preexisting conditions that were not documented at the time of screening.

Key Question 3. Are there subgroups of patients with type 2 diabetes for which pramlintide is more or less suitable than other hypoglycemic agents?

Age, sex, total daily insulin dose, and prior use of oral hypoglycemic agents
None of the randomized controlled trials conducted subgroup analyses evaluating whether pramlintide had differential effects in these populations.

Race and ethnicity
A post hoc analysis[23] of two 52-week trials[16, 17] pooled subjects of various ethnic groups. Black and Hispanic patients tended to have higher baseline A1c (9.2%-9.7%) than white patients (8.9%-9.1%). Pramlintide produced larger reductions in A1c and weight from baseline in black patients (0.7%, 4.1 kg) than white patients (0.5%, 2.4 kg) and Hispanic patients (0.3%, 2.3 kg). Changes in total daily insulin requirement and baseline oral hyperglycemic use were not different among the different races and ethnicities.

Nausea and weight loss and effects of weight on A1c
Weight loss experienced with pramlintide 90 or 120 mcg appeared to be independent of nausea, as weight loss was similar in patients never experiencing nausea (90 or 150 mcg, -1.1 to -1.5 kg) and patients experiencing nausea at anytime (90 or 150 mcg, -0.3 to -2.0 kg).[16] In addition, improvements in A1c observed with pramlintide appeared to be independent of weight lost or gained during the trial (subjects who gained weight, change in A1c -0.29% to -0.53%; subjects who lost weight, change in A1c -0.22% to -0.58%).

A pooled analysis[24] of overweight and obese patients also evaluated whether weight loss associated with pramlintide 120 mcg was influenced by nausea. Like the other, this post hoc subgroup analysis suggested that weight loss was independent of nausea (change in weight in group reporting "never nausea," -1.3 kg; "nausea at anytime," -1.9 kg). None of the studies explored to see if there were any correlations between anorexia and weight loss.

Overweight and obese patients
A post hoc analysis[24] pooled data from two randomized controlled trials comparing pramlintide 120 mcg with placebo when both were added to insulin. At 26-week follow-up overweight and obese (body mass index > 25 kg/m^2) patients receiving pramlintide showed greater reductions in A1c and weight than similar patients receiving placebo. Approximately 2% of overweight and obese patients on pramlintide plus insulin achieved weight loss of ≥10% change from baseline compared with 0% in those on placebo plus insulin. Markedly obese patients (baseline body mass index 35-40 kg/m^2 and >40 kg/m^2) had the greatest weight loss (-2.4 kg and -3.2 kg, respectively).

Baseline A1c
When patients were stratified by baseline A1c,[18] at 16 weeks patients with baseline A1c > 8.5% who received pramlintide plus insulin glargine showed larger improvements in A1c, fasting plasma glucose, and postprandial glucose than patients receiving placebo plus glargine (pramlintide change in A1c -1.19%, fasting plasma glucose -44.4 mg/dL, postprandial glucose -23 mg/dL, and weight -1.0 kg compared with placebo plus glargine A1c -0.69%, fasting plasma glucose -18.4 mg/dL, postprandial glucose +3.2 mg/dL, weight +1.1 kg). Among subjects with lower baseline A1c (≤ 8.5%), improvements in A1c (-0.36%) and weight (-2.0 kg) were also

larger in pramlintide-treated patients than those who took placebo plus glargine. Overall, reductions in A1c were greatest in those with baseline A1c >8.5%.

Another post hoc analysis[25] pooled data from two trials at 26-week follow-up and examined patients with baseline A1c of 7.0% to 8.5%. Pramlintide plus insulin was better than placebo plus insulin for A1c (placebo-corrected change in A1c -0.43, $P<0.0009$) and weight (placebo-corrected change in weight -2.0 kg, $P<0.0003$).

Applicability to general populations with type 2 diabetes

No included trial evaluated the effects of pramlintide in patients whose type 2 diabetes was inadequately managed on combination prandial and basal insulin therapy with or without oral agents. Two studies evaluated pramlintide in patients using fixed-dose insulin. One trial used flexible dosing for insulin glargine only. Hence, results have limited applicability to the broader population using more commonly prescribed insulin regimens.

FDA-approved dosage of pramlintide for type 2 diabetes includes initial therapy of 60 mcg/meal and maintenance therapy of 120 mcg/meal. Only 2 trials examined the 120 mcg dosage.[16, 18] The third included trial was a dose-ranging study that did not use a 120 mcg dose but did include a 75 mcg dose which may be used in clinical practice.[17]

Overall, patients included in these 3 trials represent a highly selected population: mainly white, middle-aged men and women with mean baseline A1c between 8.5% and 9.3% and diabetes of 11-13 years' duration. None of the patients had significant pulmonary, cardiovascular, renal, neurologic, or hematologic diseases or problems with gastrointestinal motility. The study populations probably included highly motivated subjects who desired to achieve optimal glycemic control through the additional 2-4 injections added to their usual regimens of insulin and oral hypoglycemic agent over 16-52 weeks of participation in a trial. Study setting also was not reported in any of the included trials; subjects likely were evaluated in outpatient clinics.

Table 9. Summary evidence table

Type 1 diabetes

Type 1 Diabetes	Quality of evidence	Conclusion
Key Question 1. For children and adults with type 1 diabetes, does pramlintide differ in efficacy, effectiveness, and in harms for achieving glycemic control when added to prandial insulin compared to conventional insulin therapy?		Evidence in children is lacking.
Effectiveness	No available data	-Data are insufficient to determine long-term effectiveness of pramlintide. -No studies assessed long-term health outcomes and none were > 52 weeks in duration.
Efficacy	**Pramlintide with titratable insulin (flexible schedule)** -Fair, 2 RCTs **Pramlintide with fixed or stable doses of insulin** -Fair-Poor, 1 RCT (relevance: Low)	**Pramlintide with titratable insulin** -Evidence on FPG and time to treatment failure is lacking. -One trial showed no significant differences in A1c lowering between those receiving pramlintide+insulin and placebo+insulin (in a setting where insulin was titrated to achieve prespecified glycemic targets) at the end of 29 weeks. -In contrast, one trial showed a small improvement in A1c by 0.27% (placebo-corrected) with pramlintide + insulin compared with placebo + insulin over 52 weeks. -Two trials showed small reductions in total daily insulin dose with those on pramlintide+insulin than compared with those on placebo+insulin (range: 3-12% decrease compared with 0-1% increase). Clinical significance is yet to be determined. -Pramlintide-treated subjects showed more weight loss than insulin-treated subjects, but this was not clinically significant (range: -0.4 kg to -1.3 kg compared with +0.8 kg to +1.2 kg) at 29 or 52 weeks. **Pramlintide with fixed or stable insulin** -Pramlintide produced small reductions in A1c (placebo-corrected: 0.21% to 0.30%) and weight (-1.3 kg) compared with a fixed doses of placebo plus insulin over 52 weeks.
Harms	-Fair-Poor	**For both groups:** -Studies beyond 52 weeks in duration evaluating harms are lacking. -More pramlintide-treated patients withdrew due to adverse effects than

Type 1 Diabetes	Quality of evidence	Conclusion
		insulin-treated patients (5-20% compared with 2-8%). -In general, adjunctive therapy with pramlintide was associated with higher rates of severe hypoglycemia during the initial 4 weeks than insulin alone (event rate: 0.46 to 3.78 compared with 0.42 to 1.04). In one trial where patients were allowed to decrease prandial insulin by 30-50%, rates of severe hypoglycemia were still slightly higher for those on pramlintide+insulin than compared with those receiving placebo+insulin. -There was significantly greater incidence of nausea, vomiting, and anorexia associated with pramlintide therapy than insulin therapy. Two trials mentioned that most of these events occurred within 4 weeks of therapy, however, no actual data were available to verify the statement.
Key Question 2. Are there subgroups of patients for which pramlintide is more or less suitable than other hypoglycemic agents?	-Poor (post hoc analyses and selective outcome reporting)	-No subgroup analyses were conducted on age, sex, race, or total daily insulin usage. -One study showed patients with baseline A1c <8% exhibited similar reductions in A1c than the total population. -One study showed the use of pramlintide prevented weight gain in normal weight populations (BMI < 23 kg/m^2) and assisted weight loss in overweight and obese patients (BMI > 23 kg/m^2).

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; PPG, postprandial glucose; RCT, randomized controlled trial.

Type 2 Diabetes

Type 2 Diabetes	Quality of evidence	Conclusions
Key Question 1. For children and adults with type 2 diabetes, does pramlintide differ in efficacy, effectiveness, and in harms for achieving glycemic control when added to prandial insulin compared to conventional insulin therapy?		No evidence in children.
Effectiveness	No available data	-Data were insufficient to determine long-term effectiveness of pramlintide. -No studies assessed long-term health outcomes and none were > 52 weeks in duration.
Efficacy	**Pramlintide added to titratable doses of insulin glargine with or without oral agents**	-Evidence on FPG and time to treatment failure was lacking. **Added to titratable insulin glargine with or without oral agents)** -Addition of pramlintide to a glargine-

Type 2 Diabetes	Quality of evidence	Conclusions
	-Fair, 1 RCT	only regimen lowered A1c by 0.36% (placebo-corrected values) more than those receiving placebo+glargine over 16 weeks. -Small weight loss was observed with pramlintide, while minimal weight gain was seen with glargine. The results were not clinically significant (-1.6 kg compared with +0.7 kg) over 16 weeks. -Patients in both treatment groups required dose increases to their insulin regiments. There was no significant differences between the groups at the end of 16 weeks (change from baseline: +11.7 units compared with +13.1 units).
	Added to fixed or stable doses of insulin with or without oral agents -Fair-Poor, 2 RCTs (relevance: Low)	**Added to fixed or stable doses of insulin with or without oral agents** - Pramlintide lowered A1c by 0.13%-0.4% compared with placebo (placebo-corrected) over 52 weeks. -Pramlintide-treated patients had larger weight loss than patients not on pramlintide, but these results were not clinically significant (-0.5 to -1.25 kg compared with +0.6 kg) over 52 weeks.
Harms	-Fair-Poor	-Studies beyond 52 weeks in duration evaluating harms are lacking. -There were no significant differences in withdrawal rates between pramlintide+insulin and placebo+insulin treated patients. -Both pramlintide+insulin and placebo+insulin groups exhibited similar rates of mild-moderate hypoglycemia. -More pramlintide+insulin treated patients had greater incidence of severe hypoglycemic events during the first 4 weeks of treatment than those receiving placebo+insulin. -Incidence of nausea was significantly greater for pramlintide + insulin than placebo+insulin treated patients. One trial reported data that showed most events occurring within 4 weeks of therapy. -Headache was reported at a slightly higher rate in patients receiving

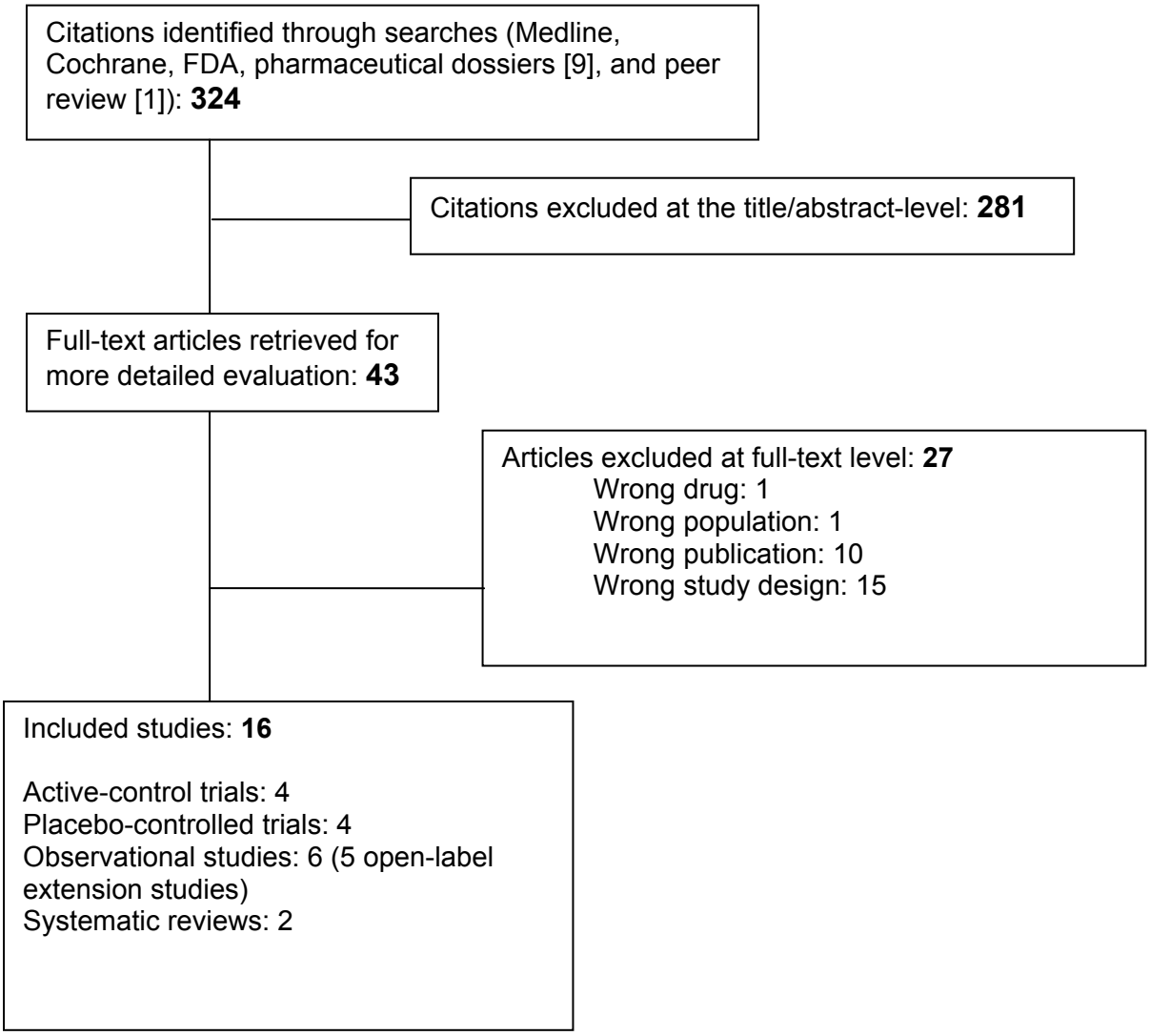
Type 2 Diabetes	Quality of evidence	Conclusions
		pramlintide+insulin compared with those receiving placebo+ insulin. It is unknown whether these events were associated with hypoglycemia. -Neither vomiting nor anorexia was reported.
Key Question 2. Are there subgroups of patients for which pramlintide is more or less suitable than other hypoglycemic agents?	-Poor (post hoc analyses with selective outcome reporting)	-No subgroup analyses were conducted on age, sex, race, or total daily insulin usage. - Black patients may have slightly larger treatment effects with pramlintide than White or Hispanic patients. -The incidence of nausea had no impact on observed weight loss with pramlintide. - Markedly obese subjects (BMI ≥35 kg/m2) had the largest reduction in weight (2-3 kg) but only 1%-2% achieved clinically significant weight loss of ≥ 10% of body weight. -Patients with higher baseline A1c (>8.5%) had larger treatment effects than patients with baseline A1c ≤8.5%.

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; PPG, postprandial glucose; RCT, randomized controlled trial.

Exenatide

We identified 4 RCTs that compared exenatide with conventional insulin therapy, with both groups receiving oral diabetes agents (Table 10 and Evidence Table 1-3).[26-30] In addition we identified 4 placebo-controlled trials (Table 11 and Evidence Table 1-3),[31-34] 5 single-arm open-label extension studies of exenatide,[35-39] one single-arm retrospective cohort study[40] (Table 12 and Evidence Tables 1-4), and two relevant systematic reviews (Evidence Tables 5-6).[41, 42] No studies that met our inclusion criteria compared exenatide to oral diabetes agents used as either monotherapy or combined therapy in adults. We found no studies of exenatide in children. The literature search results are provided in Figure 2, and studies excluded upon review of the full text are listed in Appendix D.

Figure 2. Literature search results for exenatide



Systematic Reviews

Two systematic reviews of exenatide met our inclusion criteria.[41,42] Amori and colleagues[41] published a high-quality review of published and unpublished English-language studies of FDA-approved and unapproved DPP-4 inhibitors (sitagliptin and vildagliptin) and GLP-1 analogs including exenatide. These reviewers derived the following pooled estimates of change from baseline for exenatide compared with placebo (both groups combined with various oral diabetes agents): A1c –1.01% (95% CI -1.18% to -0.84%), fasting plasma glucose -27 mg/dL (95% CI -34 to –20 mg/dL), and weight -1.44 kg (95% CI -2.13 to -0.75 kg). When exenatide was compared with various insulin regimens, the following pooled estimates of change from baseline for exenatide compared with insulin were noted: A1c -0.06% (95% CI -0.22% to 0.10%), fasting blood glucose 13 mg/dL (95% CI -16 to 41 mg/dL), and weight -4.8 kg (95% CI -6.0 to -3.5 kg). Weight loss was dose-dependent and progressive, with no apparent plateau by week 30. Severe hypoglycemia was rare (5/2781 patients who used exenatide) and occurred only when combined with sulfonylurea use. The risk ratio for mild to moderate hypoglycemia with

exenatide compared with placebo was 2.3 (95% CI 1.1 to 4.9). Dose-dependent nausea and vomiting were the most frequently reported adverse events with exenatide (risk ratio nausea compared with any other treatment 2.9 (95% CI 2.0 to 4.2). Withdrawal rates due to gastrointestinal effects were higher with exenatide (4%) than with placebo.

The second review[42] was poor quality (Score ≤ 4 using the Oxman and Guyatt criteria[43]) (see Evidence Table 4) and so was not included in our review.

Summary of Evidence for Exenatide

Key Question 1 and 2. For children and adults with type 2 diabetes, does exenatide differ in efficacy, effectiveness, and in harms for achieving glycemic control when compared to other hypoglycemic agents as monotherapy or combined therapy? or when added to other hypoglycemic agents compared to conventional insulin therapy?

Are there subgroups of patients for which exenatide is more or less suitable than other hypoglycemic agents?

Efficacy

- Active-control trials compared exenatide to insulin, with both groups receiving oral diabetes agents, and demonstrated improved A1c in both treatment groups (range change in A1c exenatide 10 mcg twice daily -1.0% to -1.4%; range insulin -0.9% to -1.4%), with no significant differences between treatments.[27, 28] The substitution of exenatide for insulin did not improve A1c in either group.[26]

- A1c improved more with exenatide than with placebo, both added to various oral agents: between-group difference (exenatide minus placebo): 5 mcg twice daily: -0.6% (95% CI -0.8 to -0.4%); 10 mcg twice daily -1.0% (95% CI, -1.2 to -0.8%)

- Active-control studies demonstrated significant weight loss in exenatide groups compared to weight gain with insulin (between-group difference 4.0 to 5.5 kg). Weight decreased progressively with exenatide combined with oral agents, compared with placebo, but weight change was small (pooled between group difference exenatide 5 mcg twice daily, -0.51 kg, 95% CI -0.89 to -0.13; exenatide 10 mcg twice daily, –1.25 kg, 95% CI –1.90 to –0.61).

- No study examined children or adolescents with type 2 diabetes.

Effectiveness

- Quality of life was examined in only one study. No significant differences were seen between exenatide dosed twice a day and insulin glargine, despite higher rates of gastrointestinal adverse effects with exenatide.

Adverse effects

- Total withdrawals were less with exenatide 5 mcg twice daily than with placebo (relative risk 0.67, 95% CI 0.53 – 0.85); there was no significant difference between placebo and exenatide 10 mcg twice daily.

- Withdrawal rates due to adverse events were higher with exenatide 10 mcg twice a day than with placebo; there were no differences between treatment groups at the 5 mcg twice daily dosing.

- The incidence of hypoglycemia was elevated with exenatide 5 and 10 mcg twice a day compared with placebo but was significant only for the higher dosage (relative risk 2.44, 95% CI 1.09 to 5.49). Rates of hypoglycemia were greatest in subjects taking a sulfonylurea and exenatide compared with placebo plus exenatide. Rates of hypoglycemia were similar between insulin-treated and exenatide groups.

- Nausea and vomiting were the most frequent adverse events among exenatide-treated patients, and rates of these symptoms were significantly higher in the exenatide group than the insulin or placebo groups. Nausea declined after the first 8 weeks of therapy

- There was no evidence of cardiovascular, pulmonary, hepatic, or renal adverse effects across studies, and rates of serious events were similar between treatment groups.

Subgroups

- In one pooled analysis, exenatide was equally efficacious in reducing A1c in patients over and under 65 years of age, and rates of hypoglycemia were similar between these two age groups. There were no other data on subgroups defined by demographic or other characteristics.

Detailed Assessment of Exenatide

Key Question 1 and 2. For children and adults with type 2 diabetes, does exenatide differ in efficacy, effectiveness, and in harms for achieving glycemic control when compared to other hypoglycemic agents as monotherapy or combined therapy? Or when added to other hypoglycemic agents compared to conventional insulin therapy?

Active-control trials

Four open label studies compared exenatide 10 mcg twice a day to insulin therapy (various regimens). All studies used concurrent sulfonylurea and/or metformin in addition to the study treatment regimes (Table 10, Evidence Tables 1-3). Three of these trials were fair-quality noninferiority studies,[27, 28, 30] and one was a fair-to-poor-quality exploratory substitution study.[26] The outcomes in these four trials were too heterogeneous to estimate meaningful pooled effect sizes.

Table 10. Characteristics of exenatide active-controlled trials in adults with type 2 diabetes

Author, year Country Quality	Sample size (N) Follow-up (weeks)	Age (years) (SD)[a] % Male[a] % White[a] % Hispanic[a] Diabetes duration (years)[a]	Baseline A1c (%) (SD)[a] Weight (kg)[a] BMI (kg/m^2)[a]	Intervention	Combination therapy
Barnett 2007 Fair	138 16	54.4-55.3 (1.1-1.2) 45.7 – 48.5 NR 6.6-8.3 (0.6-0.7)	8.89 (0.13) 84.0-85.6(2.0) 30.9-31.3 (0.5)	Exenatide 10 ug BID Insulin glargine	Both groups continued prior MET or SU
Davis, 2007 Fair-poor	51 16	52-54 (8) 56-50 NR NR 10-12 (6-7)	8.0-8.3 (0.9-1.2) 95-102 (17-19) 33-35 (4)	Exenatide: 10 mcg BID Insulin: various	Both groups received MET +/- SU or SU
Heine, 2005 Boye, 2006 Fair	551 26	58-59.8 (8.8-9.5) 55-56.6 79.8-80.5 15-15.6 9.2-9.9 (5.7-6.0)	8.2-8.3(1.0) 87.5-88.3 (16.9 - 17.9) 31.3-31.4 (4.4 - 4.6)	Exenatide: 10 mcg BID Insulin glargine	Both groups received maximum MET and SU
Nauck, 2007 Fair	505 52	58-59 (9) 49-53 NR NR 9.8-10.0 (6.2-6.3)	8.6 (1.0-1.1) 83.4-85.5 (15.6-15.7) 30.4 (4.1)	Exenatide: 10 mcg BID Biphasic insulin aspart	Both groups received MET and SU

[a] Data presented are the range across treatment groups for mean and standard deviation.
Abbreviations: BID, twice daily; MET, metformin; NR, not reported; SD, standard deviation; SU, sulfonylurea.

Efficacy and effectiveness

Heine and colleagues[27] compared once-daily glargine to exenatide twice daily over 26 weeks of follow-up in a noninferiority study, with both groups receiving metformin and a sulfonylurea. Reductions in A1c were 1.11% in both groups (between-group difference 0.017%, 95% CI -0.123 to 0.157%). Fasting plasma glucose decreased in both treatment groups, with a greater reduction with insulin glargine (change in the insulin glargine group - 51.5 md/dL and in the exenatide group -25.7 md/dL; between-group $P<0.001$). Weight increased in the insulin glargine group throughout the trial, with progressive reduction in the exenatide group (weight change -2.3 kg with exenatide, +1.8 kg with insulin glargine; between-group difference -4.1 kg, 95% CI -4.6 to -3.5 kg).

Quality of life was assessed in this trial.[27, 29] A per protocol analysis of 455 of 549 original trial patients revealed no significant differences between the two treatments for measures of symptoms, quality of life, vitality, and treatment satisfaction. These similar outcomes occurred despite an additional injection daily and gastrointestinal adverse events with exenatide.

Another noninferiority study [30] also compared exenatide 10mcg twice daily to insulin glargine, with both groups continuing pre-study single oral agents. Change in A1c at 16 weeks was identical in the two treatment arms (-1.36%, SE 0.09%, within group $P<0.001$). Both exenatide and insulin glargine reduced A1c by a similar amount in patients with baseline A1c ≥ 9% (approximate change -1.8%) and < 9% (change -0.9%).[30]

A third non-inferiority study[28] compared exenatide twice daily with biphasic insulin aspart in patients poorly controlled on sulfonylurea and metformin. The change in A1c was similar between groups (change with exenatide -1.04%, change with insulin aspart -0.89%; between group difference -0.15%, 95% CI -0.32 to 0.01%). Exenatide patients lost weight while insulin-treated patients gained weight (between-group difference -5.4 kg, 95% CI -5.9 to -5.0 kg). Fasting serum glucose decreased in both groups (insulin aspart -1.7 mmol/L; exenatide -1.8 mmol/L).

The fourth active-control trial[26] examined persons with type 2 diabetes who were already using insulin and sulfonylurea and/or metformin. In this small (N=51), exploratory RCT, exenatide 5 and then 10 mcg twice daily was substituted for insulin, while oral agents were continued. Specific glycemic goals were not set. A1c did not change significantly in either group ($P>0.05$) and there was no significant between-group difference in A1c at 12-week follow-up. Exenatide patients noted a decrease in weight (mean weight change -4.2 kg, SD 3.0 kg, $P<0.001$), in contrast to the insulin group (mean weight change +0.5 kg, SD 1.7, $P<0.001$). This study was rated fair-poor quality because of its high and differential withdrawal rate and lack of reporting methods for randomization and allocation.

Adverse effects

Total withdrawals in the exenatide group ranged from 12.0% to 21.3% and in the comparison group from 0% to10.1% in the four active-controlled trials. [26-28, 30] Withdrawals due to adverse events for the exenatide group ranged from 8% to 15% and were less than 1% in the comparison groups. Nausea and vomiting were the most frequent adverse events among exenatide-treated subjects, and rates of these symptoms were significantly higher in the exenatide group than in groups using insulin glargine[27, 30] or other insulin routines,[26,28] with rates of nausea ranging from 33% to 57% in the exenatide groups compared with <1 to 9% with the comparison group receiving insulin.

Overall hypoglycemia rates were similar between groups treated with insulin and with exenatide. [27, 28, 30] Hypoglycemia was particularly common when exenatide (39%) or insulin

(38%) was combined with sulfonylurea and/or metformin;[26] 79% of hypoglycemia cases were associated with sulfonylurea. In a study comparing exenatide and titrated insulin glargine,[30] the overall rate of hypoglycemia with exenatide (14.7%) was not statistically different than that with insulin glargine (25.2%). In subgroup analysis of this study, however, the rate of hypoglycemia in patients who received metformin and exenatide was 2.6% as compared with 17.4% in those receiving insulin glargine (*P*=0.010), whereas the rates of hypoglycemia in patients taking sulfonylureas was similar with exenatide (30.0%) and insulin glargine (34.5%).

Placebo-controlled trials

We identified 4 large, multicenter, fair-quality placebo-controlled trials[31-34] of exenatide as combination therapy (Table 11, Evidence Tables 1-3). Overall, study subjects were fairly homogeneous. Subjects were similar in age (mean 53 to 57 years) and sex (52 to 60% male) with some variation in race and ethnicity. Mean baseline A1c ranged from 7.9% to 8.6% and mean duration of diabetes from 4.9 to 9.4 years.

Table 11. Characteristics of exenatide placebo-controlled trials in adults with type 2 diabetes

Author, year Country Quality	Sample size (N) Follow-up (weeks)	Age (years) (SD)[a] % Male[a] % White[a] % Hispanic[a] Duration of diabetes (years)[a]	Baseline A1c (%) (SD)[a] Weight (kg)[a] BMI (kg/m^2)[a]	Intervention	Combination therapy
Buse, 2004 101 sites in US Fair	377 30	55 (10-11) 57-63 59.7-66.7 18.4-21.7 5.7-6.6 (4.7-6.6)	8.5-8.7 (1.1-1.2) 95-99(18-22) 33-34 (5-6)	5, 10 mcg BID	Maximum SU (but could be decreased by 50% based on hypoglycemic events)
DeFronzo, 2005 82 sites in US Fair	336 30	52-54 (9-11) 51.8-60.2 72.6-79.6 7.3-10.6 4.9-6.6 (4.7-6.1)	8.2-8.3 (1.0-1.1) 100-101(19-22) 34 (6)	5, 10 mcg BID	High dose MET
Kendall, 2005 91 sites in US Fair	733 30	55-56 (9-10) 55.9-59.3 66.4-69.0 15.8-16.6 8.7-9.4 (5.9-6.4)	8.5 (1.0-1.1) 97-99(19-21) 33-34 (5-6)	5, 10 mcg BID	High dose MET + SU
Zinman, 2007 49 sites in Canada, Spain, US Fair	233 16	55.6-56.6 (10.2-10.8) 53.7-57.1 82.1-85.1 NR 7.3-8.2 (4.9-5.8)	7.9 (SE 0.1) 96.9-97.5(18.8-19.0) 34 (5)	10 mcg BID	TZD +/- MET

[a] Data presented are the range across treatment groups for mean and standard deviation.
Abbreviations: BID, twice daily; MET, metformin; SU, sulfonylurea; TZD, thiazolidinedione.

Efficacy and effectiveness

Three very similar studies with overlapping authors compared exenatide to placebo, with both treatment groups taking oral hypoglycemic agents.[31-33] Kendall and colleagues[33] randomized patients to exenatide 5 mcg or 10 mcg or placebo twice daily over 30 weeks. Patients continued their pre-study metformin and a sulfonylurea. A1c decreased in the exenatide arms and steadily increased with placebo (placebo-adjusted change in A1c for exenatide 5 mcg, -0.8%; 10 mcg, -1.0%; $P<0.001$ for both treatment groups versus placebo). Weight decreased progressively in both exenatide arms, more so than in the placebo arm (weight change -1.6 kg, SE 0.2 kg in both exenatide groups; -0.9 kg, SE 0.2 kg with placebo).

In a similarly designed study Buse and colleagues[31] compared exenatide to placebo in patients taking a sulfonylurea. A1c improved in both treatment groups (A1c change with exenatide 5 mcg, -0.46%; 10 mcg, -0.86%) while increasing slightly in the placebo group (between-group $P\leq 0.0002$). Weight decreased more in the exenatide groups (weight change -1.6 kg, SE 0.3) than in the placebo group (weight change -0.6 kg, SE 0.3 kg). DeFronzo and colleagues[32] performed a similar study except that all subjects were taking metformin. The researchers noted very similar improvements in A1c with exenatide 10 mcg (A1c change -0.78%, SE 0.1%) compared with placebo (A1c change 0.08%, SE 0.10%) and also a similar decrease in weight with exenatide.

In a fourth placebo-controlled trial, subjects who were inadequately controlled with a thiazolidinedione (with or without metformin), were randomized to exenatide 10 mcg twice daily or placebo.[34] Exenatide improved A1c (mean between-group difference -0.98, 95% CI -1.21 to -0.74%) and fasting glucose (mean between-group difference -30.5 mg/dL, 95% CI -40.0 to -21.1 md/dL). Exenatide reduced weight but placebo did not (between-group difference -1.51 kg, 95% CI -2.15 to -0.88).

In several placebo-controlled trials of exenatide combined with oral agents, patients with a baseline A1c more than 9.0% achieved greater reductions in A1c than subjects with baseline less than 9.0%.[31, 33, 36] Weight reductions were greater in persons who had higher body mass index at baseline.[35, 38]

These studies were sufficiently homogeneous to obtain pooled estimates of effect (Table 12, Figures 3 and 4) When compared with placebo, exenatide 5 mcg twice daily produced a significant decrease in A1c (pooled effect –0.59, 95% CI –0.79 to –0.40, $P<0.00001$, Figure 3).[31-33] A larger improvement in A1c was noted with exenatide 10 mcg twice daily (pooled effect versus placebo –0.97, 95% CI –1.16 to –0.79, $P<0.00001$).[31-33] Significant improvements were also noted in fasting plasma glucose with exenatide 10 mcg twice daily compared with placebo (pooled effect –1.50 mmol/L, 95% CI –1.85 to –1.15, $P<0.00001$, Table 12, Appendix B).[31-33] Available data were insufficient to conduct meta-analyses on postprandial glucose.

When compared with placebo, exenatide produced a significant decrease in weight (pooled effect exenatide 5 mcg twice daily, -0.51 kg, 95% CI -0.89 to -0.13, $P=0.009$; exenatide 10 mcg twice daily, –1.25 kg, 95% CI –1.90 to –0.61, $P=0.0001$).[31-34] Statistical tests for heterogeneity were not significant ($P>0.05$) for all glycemic control and weight outcomes.

Adverse effects

Based on pooled estimates across the four placebo-controlled trials, total withdrawals were less with exenatide 5 mcg twice daily than with placebo (relative risk 0.67, 95% CI 0.53 to 0.85); there was no significant difference between placebo and exenatide 10 mcg twice daily. Withdrawals due to adverse effects were greater with exenatide 10 mcg twice daily than with

placebo, however, with no significant difference between exenatide 5 mcg twice daily and placebo (See Table 12).

There was no evidence of cardiovascular, pulmonary, hepatic, or renal adverse effects across studies, and rates of serious events were similar between treatment groups. One study reported one subject who withdrew from the exenatide group because of chest pain and a second subject because of an injection site reaction.[34] Two additional treatment-group patients in this study had serious adverse events (chest pain and allergic alveolitis) which did not necessitate study withdrawal.

Nausea, vomiting, and diarrhea were significantly more frequent with treatment at both dosages than in the placebo group (Table 12). Nausea declined after 8 weeks of treatment, although the statistical significance of the trend was not reported.[31-34]There was no correlation between change in body weight and duration[32, 33] or severity[35] of nausea. When the incidence of nausea remained stable, body weight continued to decrease.[39]

The incidence of hypoglycemia was elevated in both dosage groups but was significant only for the higher dosage (relative risk 2.44, 95% CI 1.09 to 5.49). Hypoglycemia and nausea were much more common in the exenatide groups in a study by Buse and colleagues,[31] where all subjects received a sulfonylurea, than in the other three placebo-controlled studies. Rates were particularly high with 10 mcg twice daily dosing. These high rates lead to heterogeneity of the data across studies. Excluding this study from the pooled effect still produced statistically a significant increase in hypoglycemia (RR 1.88, 95% CI 1.29 to 2.75) and nausea (RR 2.28, 95% CI 1.86 to 2.80), but with statistically homogeneous data (chi-square for heterogeneity $P<0.05$) (Table 12). In this trial which reported higher rates of nausea and hypoglycemia [31], no episodes of severe hypoglycemia (requiring third party assistance) were noted. Rates of mild-to-moderate hypoglycemia were reported in 36% of subjects who received exenatide 10 mcg twice daily, 14% with 5 mcg twice daily, and 3% with placebo. All subjects were taking a sulfonylurea titrated to maximum effect dosage during the lead-in period and dosages were reduced if hypoglycemia occurred. High rates of hypoglycemia were also noted in a placebo-controlled trial where all subjects received metformin plus a sulfonylurea.[33] The risk of hypoglycemia was not increased compared with placebo when all subjects received a thiazolidinedione[34] or metformin.[32]

None of these studies included in this report noted cases of acute pancreatitis, however, from the date of the drug's approval through December 2006, the FDA received 30 domestic reports of acute pancreatitis in patients who received exenatide.[44] Median age of patients was 60 years and daily doses ranged from 10-20 mcg. The median time to onset of the symptoms was 34 days (range 4 to 300 days). Median amylase value was 384 IU/L and median lipase value 545 IU/L. Seventy percent of patients required hospitalization. A majority of affected patients (90%) had other risk factors for pancreatitis, including alcohol use or hypertriglyceridemia.

Table 12. Placebo-control trials of exenatide: Meta-analysis

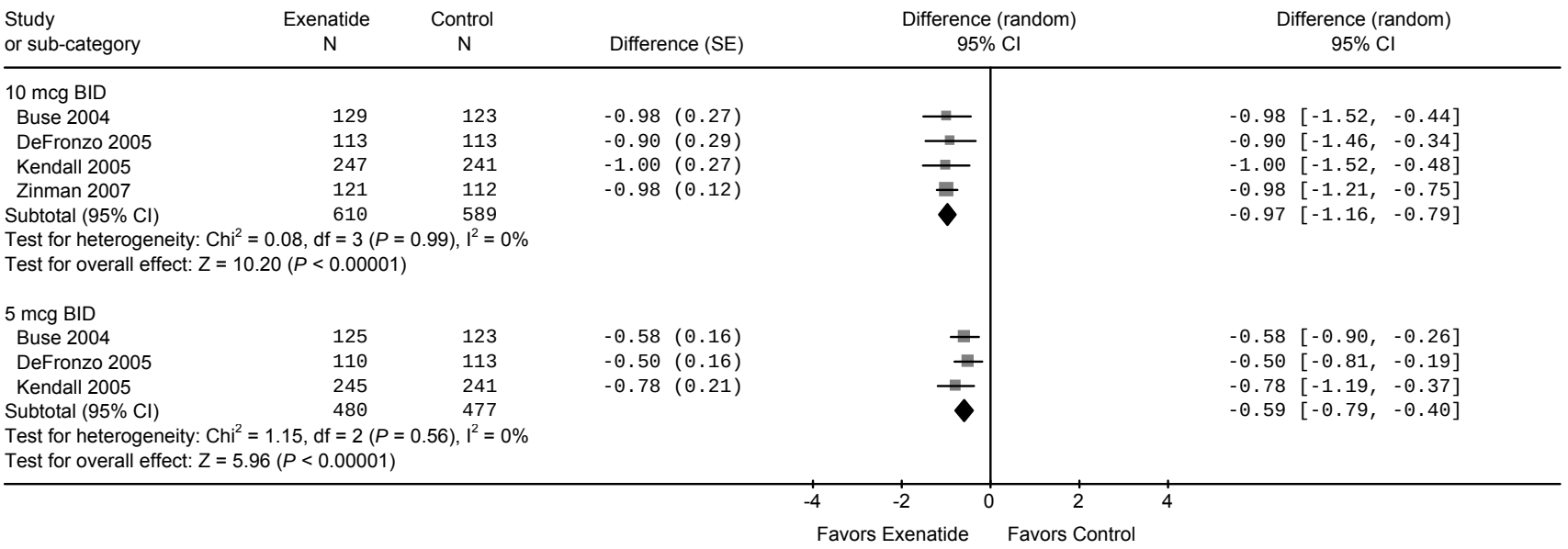
	Exenatide dosage	Outcome	N	Studies included	Pooled analysis					Heterogeneity		
					Measure	Units	Estimate	95% CI	*P* value	I^2	Q	p(Q)
Outcome	10 mcg BID	A1c	4	Buse (2004), DeFronzo (2005), Kendall (2005), Zinman (2007)	WMD	%	-0.97	(-1.16; -0.79)	<0.001	0%	0.08	0.994
		Weight	4	Buse (2004), DeFronzo (2005), Kendall (2005), Zinman (2007)	WMD	kg	-1.25	(-1.90; -0.61)	<0.001	53%	6.41	0.093
		FPG	4	Buse (2004), DeFronzo (2005), Kendall (2005), Zinman (2007)	WMD	mmol/L	-1.50	(-1.85; -1.15)	<0.001	0%	1.33	0.722
	5 mcg BID	A1c	3	Buse (2004), DeFronzo (2005), Kendall (2005)	WMD	%	-0.59	(-0.79; -0.40)	<0.001	0%	1.15	0.563
		Weight	3	Buse (2004), DeFronzo (2005), Kendall (2005)	WMD	kg	-0.51	(-0.89; -0.13)	0.009	10%	2.21	0.331
		FPG	1	Kendall (2005)	WMD	mmol/L	-1.30	(-1.98; -0.62)	<0.001	NA	NA	NA
Withdrawals	10 mcg BID	Total	4	Buse (2004), DeFronzo (2005), Kendall (2005), Zinman (2007)	RR		0.95	(0.63; 1.44)	0.812	74%	11.3	0.010
		Due to AE	4	Buse (2004), DeFronzo (2005), Kendall (2005), Zinman (2007)	RR		3.40	(1.72; 6.73)	<0.001	31%	4.37	0.224
	5 mcg BID	Total	3	Buse (2004), DeFronzo (2005), Kendall (2005)	RR		0.67	(0.53; 0.85)	0.001	0%	1.12	0.571
		Due to AE	3	Buse (2004), DeFronzo (2005), Kendall (2005)	RR		1.64	(0.89; 3.04)	0.113	0%	1.35	0.509
Adverse events	10 mcg BID	Hypoglycemia, any	4	Buse (2004), DeFronzo (2005), Kendall (2005), Zinman (2007)	RR		2.44	(1.09; 5.49)	0.031	78%	13.6	0.004
			3	Excluding Buse (2004)	RR		1.88	(1.29; 2.75)	0.001	9%	2.19	0.334
		Nausea	4	Buse (2004), DeFronzo (2005), Kendall (2005), Zinman (2007)	RR		2.82	(1.86; 4.27)	<0.001	75%	11.8	0.008
			3	Excluding Buse (2004)	RR		2.28	(1.86; 2.80)	<0.001	0%	0.91	0.635
		Vomiting	4	Buse (2004), DeFronzo (2005), Kendall (2005), Zinman (2007)	RR		3.77	(2.30; 6.18)	<0.001	0%	2.71	0.439

Exenatide dosage	Outcome	N	Studies included	Pooled analysis					Heterogeneity		
				Measure	Units	Estimate	95% CI	*P* value	I^2	Q	p(Q)
	Diarrhea	4	Buse (2004), DeFronzo (2005), Kendall (2005), Zinman (2007)	RR		2.35	(1.60; 3.48)	<0.001	0%	0.47	0.925
	Upper respiratory tract infection	2	DeFronzo (2005), Kendall (2005)	RR		0.90	(0.64; 1.26)	0.542	NA	0	1.000
	Headache	3	Buse (2004), Kendall (2005), Zinman (2007)	RR		1.37	(0.84; 2.26)	0.211	0%	0.2	0.905
5 mcg BID	Hypoglycemia, any	3	Buse (2004), DeFronzo (2005), Kendall (2005)	RR		1.77	(0.83; 3.76)	0.139	58%	4.79	0.091
		2	Excluding Buse (2004)	RR		1.43	(0.97; 2.12)	0.075	NA	0.85	0.356
	Nausea	3	Buse (2004), DeFronzo (2005), Kendall (2005)	RR		2.35	(1.35; 4.09)	0.003	80%	10.1	0.006
		2	Excluding Buse (2004)	RR		1.79	(1.41; 2.27)	<0.001	NA	0.5	0.481
	Vomiting	3	Buse (2004), DeFronzo (2005), Kendall (2005)	RR		3.35	(2.01; 5.58)	<0.001	0%	0.09	0.956
	Diarrhea	3	Buse (2004), DeFronzo (2005), Kendall (2005)	RR		1.72	(1.12; 2.66)	0.014	0%	1.08	0.583
	Upper respiratory tract infection	2	DeFronzo (2005), Kendall (2005)	RR		0.82	(0.39; 1.76)	0.616	NA	3.38	0.066
	Headache	2	Buse (2004), Kendall (2005)	RR		1.88	(1.11; 3.19)	0.018	NA	0.86	0.354

Abbreviations: AE, adverse event; BID, twice daily; CI, confidence interval; FPG, fasting plasma glucose; RR, relative risk; WMD, weighted mean difference.

Figure 3. Change in A1c in placebo-controlled studies of exenatide

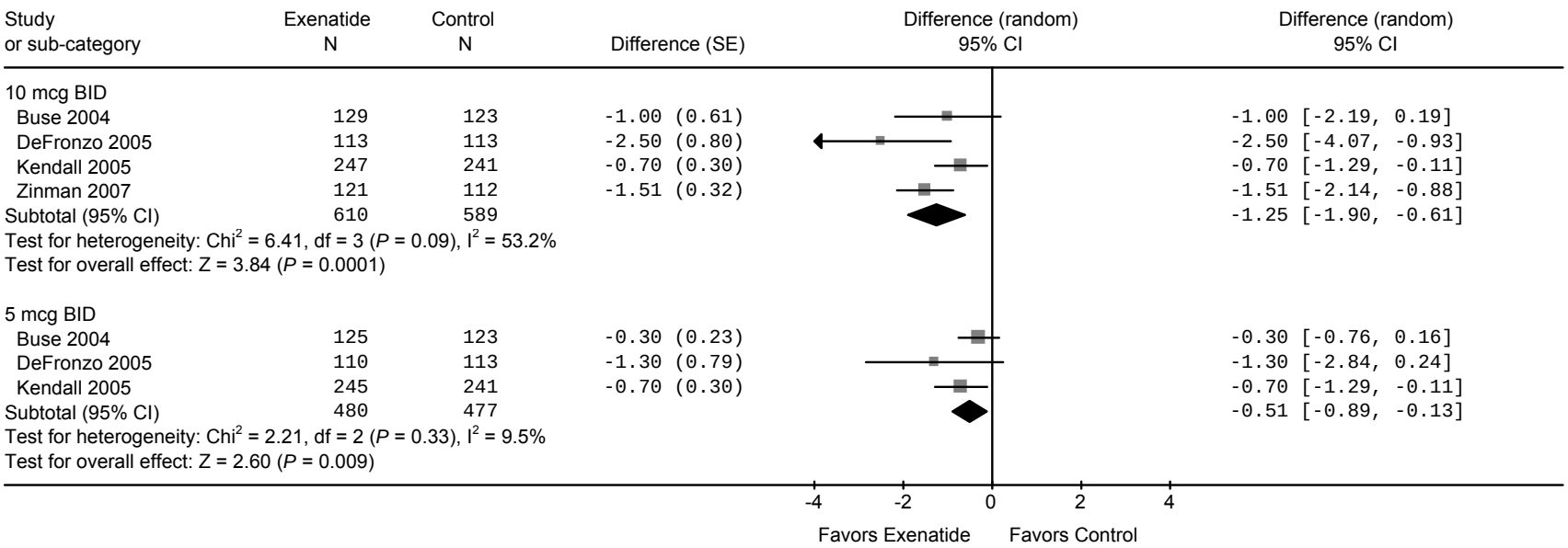
Comparison: A1c (%)
Outcome: Difference from control



Abbreviation: BID, twice daily.

Figure 4. Weight change in placebo-control exenatide studies

Comparison: Weight loss (kg)
Outcome: Difference from control



Abbreviation: BID, twice daily.

Cohort studies

We examined adverse events in cohort studies of exenatide and identified six single-arm open-label extension studies[35-39, 45] and one single-arm retrospective cohort[40] study (Table 13). All of the open label extension studies assessed exenatide 10 mcg twice daily. In these studies, investigators included only subjects who had previously completed a prior study and several studies[35, 38, 39] excluded patients who had received placebo.

An open-label extension study of three of the placebo-controlled primary trials[31-33] included in this report was published in multiple publications with overlapping or identical populations.[35, 36, 38, 39, 45] These publications represented a pooled synthesis of patients continuing in an open-label extension beyond the original 30-week trial comparing exenatide 5 mcg or 10 mcg twice daily to placebo. Subjects from both the placebo and treatment groups were invited to continue on 10 mcg twice daily along with their existing metformin and/or sulfonylurea regimens for a 2-year[36] and then 3-year[45] period. Mild-to-moderate nausea was the most frequently reported adverse event, and 3% of subjects withdrew over the extension period (30 weeks to 2 years) because of nausea. Eight percent of subjects continued to complain of nausea after 2-years of follow-up. Hypoglycemia (of any severity) occurred at a rate of 1 case in 1010 person-years of exenatide treatment. There were no cardiovascular, pulmonary, hepatic, or renal effects attributed to treatment.

Adverse events in subjects completing 3-year follow-up of the open label extension of these three placebo-controlled trials[45] included mild-to-moderate nausea (59%) (5% of subjects withdrew due to nausea over the 3 years), and hypoglycemia (40%) with 2 of 527 subjects withdrawing because of hypoglycemia. Weight progressively decreased over the follow-up period (change from baseline -5.3kg, SE 0.4). A1c reductions seen at 12 weeks were sustained at 3 years (A1c change -1.0%, SE 0.1%). This study population was a select group: only approximately half (46%) of subjects originally enrolled in the three primary trials enrolled in the open-label extension. Of subjects enrolled, only 54% completed the 2-year follow-up and 41% the 3-year follow-up.

An unrelated open-label, extension study[37] ("Study B") of a 28-day trial reported that nausea and vomiting were the most common adverse effects with exenatide 10 mcg twice daily for 26 weeks, but incidence rates were not reported. Approximately ¾ of subjects also received metformin; the other ¼ received diet and exercise only. A retrospective chart review[40] of 200 patients who had used exenatide noted that 13% discontinued treatment due to side effects, including nausea (8%), urticaria (2%), and hypoglycemia (0.5%).

Key Question 3. Are there subgroups of patients for which exenatide is more or less suitable than other hypoglycemic agents?

Only one publication examined subgroups based on demographic characteristics. A pooled analysis[36] of three placebo-controlled trials reported that reductions in A1c were not related to age and that hypoglycemia was not more frequent in subjects ≥ 65 years of age. No primary study examined the efficacy or effectiveness of exenatide in subgroups defined by age or other characteristics.

Applicability of efficacy, effectiveness, and safety data to general diabetes populations

The studies identified for this review are rather homogeneous, relatively small, and may be rather selected, thus applicability to broader diabetes populations may be limited. Study subjects were homogeneous across studies for age, sex, and baseline A1c in both the In the placebo- and active-controlled trials. Significant comorbidities were excluded in the three placebo-controlled studies reporting that characteristic[31-33] and comorbidities were not mentioned in three of the four active-controlled trials.[26, 28, 30]

Most studies reported only the number of subjects randomized, and randomization occurred in all placebo-controlled trials after a run-in of injected placebo. In other words, the number of potential study subjects who did not tolerate twice daily injections and who were therefore not included in the study was usually not reported. Open label extension studies were of highly selected populations who completed the primary study and who volunteered to continue (or start if on placebo) exenatide.

Table 13. Characteristics of exenatide observational studies in adults with type 2 diabetes

Author, Year Country	Sample size (N) Follow-up (weeks)	Age (years) (SD)[a] % Male[a] % White[a] % Hispanic[a] Diabetes duration (years)[a]	Baseline A1c (%)[a] Weight (kg)[a] BMI (kg/m^2)[a]	Intervention	Combination therapy	Primary trial citations
Blonde, 2006 US	974 (551-ITT) 82	55(10) 61 74 12 7(6)	8.4(1.0) 98(20) 34(6)	10 mcg BID	MET +/- SU	Buse, 2004 DeFronzo, 2005 Kendall, 2005
Buse, 2007 US	974 (521-ITT) 104	55(10) 59 74 12 8(6)	8.4(1.1) 99(20) 34(6)	10 mcg BID	NR	Buse, 2004 DeFronzo, 2005 Kendall, 2005
King, 2006 US	200 12	NR	NR	NR	None or various(TZD, SU, MET, insulin)	NA
Nelson, 2007 US	127 30	52(11) 44 76 6 3.9(4.5)	7.5(0.7) 100(19) 35(6)	10 mcg BID	MET or diet/exercise (“Study B”)	NA
Ratner, 2006 US	150 (92 completers) 82	54(10) 69 86 1 5(5)	8.1(1.0) 102(21) 34(6)	10 mcg BID	MET	DeFronzo, 2005
Riddle, 2006 US	518 (222 completers) 82	57(10) 61 75 12 8(6)	8.4(1.0) 99(21) 34(6)	10 mcg BID	SU	Buse, 2004 Kendall, 2005

[a] Data presented are mean (standard deviation).
Abbreviations: BID, twice daily; ITT, intention-to-treat population; MET, metformin; SU: sulfonylurea; TZD, thiazolidinedione.

Table 14. Exenatide summary evidence table

Type 2 Diabetes	Quality of evidence	Conclusion
Key Question 1. For children and adults with type 2 diabetes, does exenatide differ in:		No study examined children or adolescents with type 2 diabetes. No study examined exenatide as monotherapy.
Efficacy and effectiveness for achieving glycemic control when compared to other hypoglycemic agents as monotherapy or combined therapy?	Placebo-controlled trials, both groups receiving oral diabetes agents Glycemic control: Fair quality, 4 RCTs Weight change: Fair quality, 4 RCTs Health outcomes: No data	A1c improved more with exenatide than with placebo, both added to various oral agents: between-group difference (exenatide minus placebo): 5 mcg BID: -0.6% (95% CI -0.8 to -0.4%); 10 mcg BID -1.0% (95% CI, -1.2 to -0.8%) Weight decreased progressively with exenatide combined with oral agents and compared with placebo, but weight change was small (pooled between group difference: exenatide 5 mcg twice daily, -0.51 kg, 95% CI -0.89 to -0.13; exenatide 10 mcg twice daily, –1.25 kg, 95% CI –1.90 to –0.61). No study examined health or quality-of-life outcomes. Exenatide was not compared with other active drugs except insulin.
Efficacy and effectiveness for achieving glycemic control when added to other hypoglycemic agents compared to conventional insulin therapy?	Active-controlled trials, both groups receiving oral diabetes agents Glycemic control: Fair quality, 3 RCTs Weight change: Fair quality, 3 RCTs Health outcomes: Poor quality, 1 RCT	A1c improved in both treatment groups with no significant differences between treatments. The substitution of exenatide for insulin did not improve A1c in either group. Exenatide produced significant weight loss compared to weight gain with insulin (difference 4-5.5 kg). Quality of life was examined in only one study, with no significant differences between exenatide and insulin glargine despite higher rates of gastrointestinal adverse effects with exenatide.
Harms for achieving glycemic control when compared to other hypoglycemic agents as monotherapy or combined therapy? **Harms** for achieving glycemic control when added to other hypoglycemic agents compared to conventional insulin therapy?	Nausea: Good quality, 7 RCTs Hypoglycemia: Good quality, 7 RCTs Severe, long-term, or idiosyncratic adverse events: Fair, most data from less than 30-week follow-up.	Total withdrawal rates were higher with exenatide than with insulin treatment or placebo. Withdrawal rates due to adverse events were higher with exenatide 10 mcg BID than with placebo; there was no difference between treatment groups for 5 mcg BID. Nausea and vomiting were the most frequent adverse events and rates were significantly higher in the exenatide group than with insulin or with placebo. Nausea persisted in 8% of subjects after 2 years (1 study).

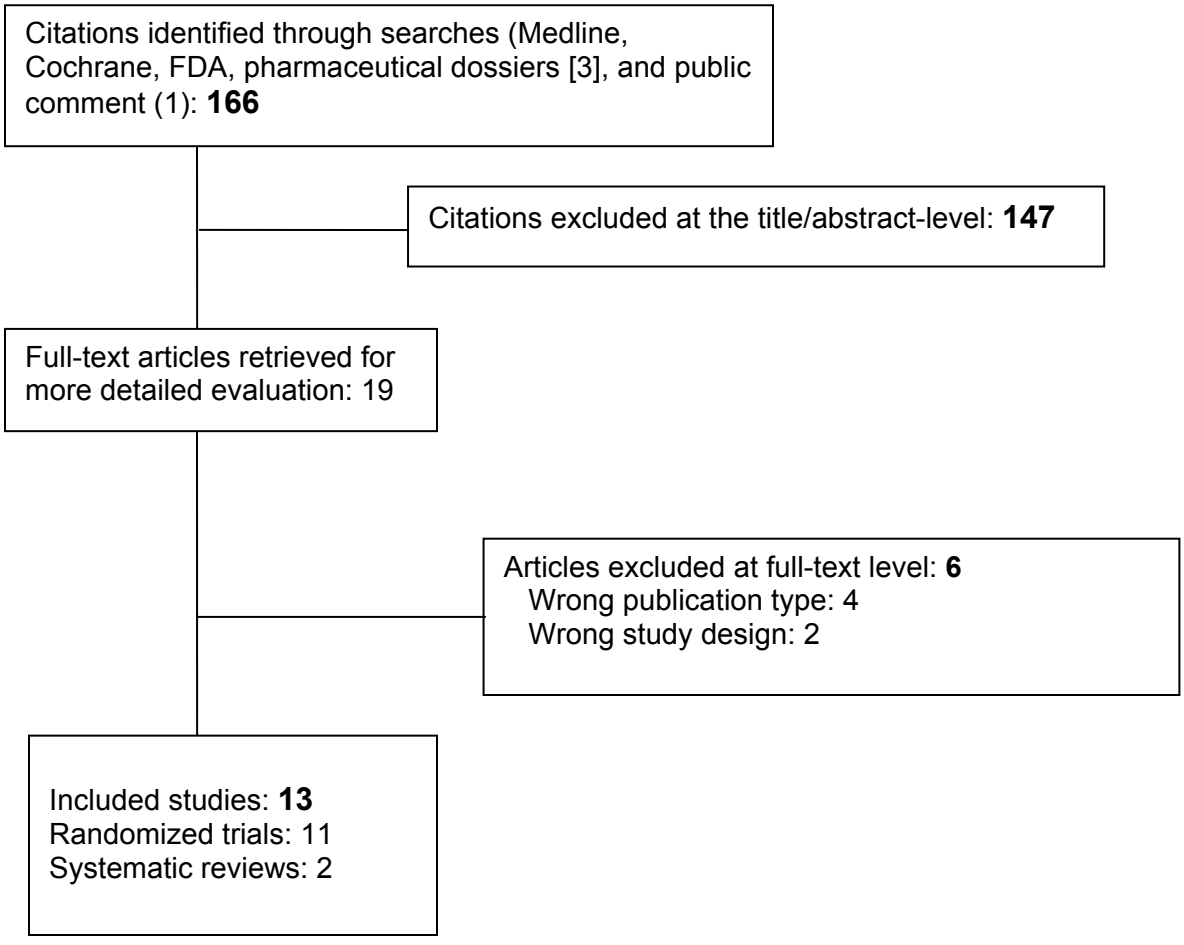
Type 2 Diabetes	Quality of evidence	Conclusion
		The incidence of hypoglycemia was elevated with exenatide 5 and 10 mcg BID compared with placebo (both groups received oral agents), but was significant only for the higher dosage. Hypoglycemia rates were similar between insulin-treated and exenatide groups. There was no evidence of cardiovascular, pulmonary, hepatic, or renal adverse effects across studies, and rates of serious events were similar between treatment groups.
Key Question 2. Are there subgroups of patients for which exenatide is more or less suitable than other hypoglycemic agents?	Poor quality, 1 subgroup analysis	One study showed exenatide improved A1c to a similar degree in persons over and under 65 years of age. There were no other data on subgroups of interest.

Abbreviations: BID, twice daily; RCT, randomized controlled trial.

Sitagliptin

We identified 166 citations by various methods of literature searching (Figure 5). Eleven randomized controlled trials and 2 systematic reviews fulfilled inclusion criteria. No comparative cohort or case-control studies were identified reporting either long-term benefits or adverse events. In the FDA Medical and Statistical Reviews we identified 10 relevant trials, of which 7 were published in peer-reviewed journals. One of the trials[46] identified from the FDA Reviews was not included because it did not meet inclusion criteria; the 3 remaining trials (study #P10X1, P014, and P014X1) could not be found in the medical literature. Details of included studies are found in Table 15 with their quality assessment in Evidence Tables 1-6. Trials excluded upon review of the full text are listed in Appendix D.

Figure 5. Literature search results for sitagliptin



Systematic Reviews

Amori and colleagues[41] published a high-quality systematic review of FDA approved and unapproved GLP-1 analogues (exenatide, linaclotide) and DPP-4 inhibitors (sitagliptin [8 studies] and vildagliptin [12 studies]). Sitagliptin and vildagliptin (examined together) lowered A1c, fasting plasma glucose, and postprandial glucose when used as either monotherapy or add-on therapy compared with placebo, with or without additional oral hypoglycemic agents. When sitagliptin and vildagliptin were compared with other active oral hypoglycemic agents, the DPP-4 inhibitors were slightly less effective in reducing A1c (pooled weighted mean difference in A1c: 0.21%, 95% CI 0.02 to 0.39; I^2= 66%). The results were pooled from 4 trials, 3 of which evaluated vildagliptin and included patients with baseline A1c of 8.7%. Small increases in weight were also observed with sitagliptin when compared with placebo. When compared with glipizide or pioglitazone, sitagliptin had a more favorable weight profile. Metformin was the only comparator medication that exhibited weight loss. Both DPP-4 inhibitors were generally well tolerated; severe hypoglycemia was reported in only two patients receiving DPP-4 inhibitors across the included studies. No differences in risk of mild-to-moderate hypoglycemia or gastrointestinal adverse events were reported when sitagliptin and vildagliptin were compared to placebo. Results for sitagliptin and vildagliptin were not examined individually; vildagliptin is also not yet approved in the United States.

Barnett and colleagues[42] reviewed the effects on weight of hypoglycemic agents, including GLP-1 analogs and DPP-4 inhibitors. This systematic review was considered low quality, as there was insufficient information about study selection criteria and individual study quality assessment. Thus, the study did not meet our inclusion criteria and we did not further evaluate its findings.

Summary of Evidence

Key Question 1 and 2. For children and adults with type 2 diabetes, does sitagliptin differ in effectiveness, efficacy, and in harms for achieving glycemic control when compared to other hypoglycemic agents as monotherapy, combined therapy, or when compared to placebo? or when added to other hypoglycemic agents as second-or third-line therapy?

Evidence in children

- Children and adolescents ≤ 18 years were not included in any of the published studies on effectiveness, efficacy, or harms.

Evidence on long-term health outcomes and harms

- No studies provided data on benefits or harms for follow-up periods longer than 52 weeks.

Evidence on efficacy

- When compared with placebo, sitagliptin 100 mg/d monotherapy significantly lowered A1c (pooled effect, between-group change -0.81%, 95% CI -0.94% to -0.67%) in patients inadequately controlled on diet and exercise over 12-24 weeks.

- Though formal statistical analyses were not conducted for glipizide-or metformin monotherapy compared with sitagliptin monotherapy, it appears that sitagliptin may be comparable to glipizide and metformin 1 g/d in lowering A1c based on estimated magnitude of difference between groups. Additional trials are needed to verify the findings.

- Overall, in patients inadequately managed on metformin, the addition of sitagliptin was as effective as the addition of glipizide or rosiglitazone in lowering A1c at the end of 18 and 52 weeks. Patients receiving glipizide or rosiglitazone gained weight compared with patients on sitagliptin who lost weight during the course of the trial.

- In patients inadequately managed on 2 oral hypoglycemic agents, the addition of sitagliptin lowered A1c by about 0.6% compared with an increase in A1c of 0.3% with placebo plus 2 oral hypoglycemic agents over 24 weeks.

- Using the initial combination of sitagliptin and metformin 1-2 g/d lowered A1c by about 1.4% to 1.9% from baseline compared with sitagliptin (-0.66%) or metformin 1-2 g/d (-0.82 to -1.13%) monotherapy in patients inadequately controlled on diet and exercise over 24 weeks.

- Sitagliptin's effects on fasting plasma glucose and postprandial glucose were moderate compared with placebo whether used as monotherapy (pooled estimates of fasting plasma glucose -24.4 mg/dL, 95% CI-1.6 to -1.1 mg/dL; postprandial glucose -54.5 mg/dL, 95% CI -3.6 to -2.4 mg/dL) or as adjunctive therapy (range of between-group difference for fasting plasma glucose -18 to -35 mg/dL; postprandial glucose -35 to -50 mg/dL).

Harms

- Weight generally decreased for both sitagliptin-treated and placebo-treated patients (range for change in weight from baseline: sitagliptin -0.1 to -0.6 kg vs. placebo -0.7 to -1.1 kg); however, subjects randomized to sitagliptin lost less weight than compared with placebo. Adjunctive therapy with sitagliptin also did not negatively affect weight, particularly in persons taking metformin; however, small increases in weight were seen when sitagliptin was added to sulfonylureas, pioglitazone, or rosiglitazone.

- Overall, sitagliptin appeared to be well-tolerated. There were 20 reports of severe hypoglycemia in 2 of 9 trials, mostly in patients taking glipizide (90%). The rates for total withdrawal were slightly lower with sitagliptin than compared with placebo (pooled RR 0.69, 95% CI 0.55-0.88) and withdrawal due to adverse events were not significantly different between the treatment groups (pooled RR 0.76, 95% CI 0.33-1.73).

- The more commonly reported adverse events across treatment groups were hypoglycemia, nausea, vomiting, diarrhea, and abdominal pain.

Detailed Assessment

Key Question 1 and 2. For children and adults with type 2 diabetes, does sitagliptin differ in efficacy, effectiveness, and in harms for achieving glycemic control when compared to placebo, when compared to other hypoglycemic agents as monotherapy or combined therapy, or when added to other hypoglycemic agents?

Eight randomized controlled trials were rated fair-quality and 1 fair-poor. This review is organized by how sitagliptin was used (mono- or combined therapy compared with placebo or active control).

Table 15. Characteristics of sitagliptin placebo-controlled trials in adults with type 2 diabetes

Author, year Country Quality	Sample size (N) Follow-up (weeks)	Age (years) (SD)[a] % Male[a] % White[a] % Hispanic[a] Diabetes duration (years)[a]	Baseline A1c (%) (SD)[a] FPG (mg/dL)[a] PPG (mg/dL)[a] Weight (kg)[a] BMI (kg/m^2)[a]	Intervention Dosages	Other Diet and exercise? % not on OHA Rescue medication?
Monotherapy					
Aschner, 2006[47] Multinational Fair	741 24	53.4-54.9 (9.5-10.1) 46.8-57.1 50.2-52.8 21.2-25.3 4.4	8.0[a] 173.7 257-270 83.7-85.0 (18.1-19.2) 30.3-30.8 (5.2-5.5)	Sitagliptin 100 mg daily Sitagliptin 200 mg daily Placebo	Yes 51 Metformin
Raz, 2006[48] Multinational Fair	521 18	54.5-55.5 (9.2-10.1) 50.5-62.7 61.8-70.9 18.0-20.0 4.5	8.1[a] 182.2 262.8-279 89.6-92.8 (18.8-19.4) 31.8-32.5 (5.2-5.5)	Sitagliptin 100 mg daily Sitagliptin 200 mg daily Placebo (randomized to 2:2:1 ratio)	Yes 36-42 Metformin
Nonaka, 2008[49] Japan Fair	152 12	55.0-55.6 (8.0-8.6) 60-66 NR/Asian NR/Japanese 4.0	7.6[a] 163.5 296.6-276.3 (58.7-74.8) NR 25.1-25.2 (3.2-3.5)	Sitagliptin 100 mg daily Placebo	Yes 43 NR
Add-on therapy					
Charbonnel, 2006 Multinational Fair	701 24	54.4-54.7 (9.7-10.4) 55.8-59.5 63.1-67.1 11.8-15.5 6.2	8.0[a] 171.5 271.8-273.6 86.7-89.6 (17.5-17.8) 30.9-31.5 (4.9-5.3)	Sitagliptin 100 mg or Placebo Added-on to metformin ≥ 1500 mg/day	NR 6 Pioglitazone
Rosenstock, 2006 Multinational Fair	353 24	55.6-56.9 (10.4-11.1) 53.1-57.9 72.5-72.6 12.0-12.4 6.1 (5.4-5.7)	8.0-8.1 (0.8)[b] 165.6-168.3 (39.5-39.9) NR 86.4-90.9 (17.0-17.4) 31.0-32.0 (5.0-5.2)	Sitagliptin 100 mg or Placebo Added-on to Pioglitazone 30-45 mg/day	Yes 8.0-11.3 Metformin
Hermansen, 2007[50] Denmark, USA Fair	441 24	55.6-56.5 (9.6) 52.7-53.4 61.3-63.9 14.6-17.6 8.8	8.34[c] 181.2 267-271.1 (58.4-62.6) 85.9-86.5 (21.1-21.8) 30.7-31.2 (6.3)	Sitagliptin 100 mg or Placebo Added on to glimepiride 4-8 mg/day or glimepiride+ metformin >1500 mg/day	NR 2.7-10.4 Pioglitazone

Author, year Country Quality	Sample size (N) Follow-up (weeks)	Age (years) (SD)[a] % Male[a] % White[a] % Hispanic[a] Diabetes duration (years)[a]	Baseline A1c (%) (SD)[a] FPG (mg/dL)[a] PPG (mg/dL)[a] Weight (kg)[a] BMI (kg/m^2)[a]	Intervention Dosages	Other Diet and exercise? % not on OHA Rescue medication?
Scott, 2008[51] Multinational Fair	273 18	54.8-55.3 (9.3-10.5) 59-61 NR 4.6-5.4 (3.5-4.0)	7.7-7.8 (0.8-1.0) 157-160 (31.4-37.4) 220.1-224.4 (48-63.2) 83.1-84.9 (16.5-18.5) 30-30.4 (4.5-5.5)	Sitagliptin 100 mg or Rosiglitazone 8 mg or Placebo Added to metformin monotherapy ≥ 1500 mg/day	Yes NR NR
Raz, 2008[52] Multinational Fair	190 30	53.6-56.1 (9.5) 41.5-51.0 42-47 25-32 7.3-8.4 (5.3-6.5)	9.2[d] 200 NR 81.2-81.5 30.1-30.4	Sitagliptin 100 mg or Placebo Added to metformin > 1500 mg/day	Yes 0% Glipizide

[a] Data presented are the range across treatment groups for mean and standard deviation.
[b] >50% had A1c <8% at baseline.
[c] > 30% had A1c <8% at baseline; means are reported as standard deviation unless otherwise specified.
[d] >50% had A1c >9% at baseline.
Abbreviation: NR, not reported.

Table 16. Characteristics of sitagliptin active-controlled trials with or without placebo study arms in adults with type 2 diabetes

Author, year Country Quality	Sample size (N) Follow-up (weeks)	Age (years) (SD)[a] % Male[a] % White[a] % Hispanic[a] Diabetes duration (years)[a]	Baseline A1c (%) (SD)[a] FPG (mg/dL)[a] PPG (mg/dL)[a] Weight (kg)[a] BMI (kg/m^2)[a]	Intervention Dosages	Other Diet and exercise? % not on OHA Rescue medication?
Scott, 2007[53] Multinational Fair	743 12	54.7-56.2 (9.0-10.7) 48.0-62.4 61.0-69.4 NR 4.2-5.0 (4.0-5.2)	7.8-7.9 (0.9-1.0) 169.2-172.8 (36.0-45.0) 257.4-278.5 (72.0-92.2) NR 30.4-31.6 (4.9-6.9)	Sitagliptin 5-, 12.5-, 25, 50 mg BID Glipizide 5-20 mg/day Placebo	Yes NR NR
Goldstein, 2007[54] Multinational Fair	1091 24	53.2-54.1 (9.6-10.2) 42.3-55.3 46.0-58.2 21.4-30.2 4.5	8.8[b] 200 276.8-292.7 (66.7-84.6) NR 31.2-32.5 (5.9-7.1)	Sitagliptin 50+MET 500 mg BID Sitagliptin 50+MET 1000 mg BID Sitagliptin 100 mg daily Metformin 500 mg BID Metformin 1000 mg BID Placebo	Yes 50 Glyburide
Nauck, 2007[55] Multinational Fair-Poor	1172 (per-protocol 793) 52	56.6-56.8 (9.3-9.8) 61.3-57.1 73.5-74.3 7.3-7.9 5.8	7.5[c] 158 NR 89.5-89.7 (17.4-17.5) 31.2-31.3 (5.0-5.2)	Sitagliptin 100 mg daily or Glipizide 5-20 mg/day Added-on to metformin >1500 mg/day	Yes 5 NR

[a] Data presented are the range across treatment groups for mean and standard deviation.
[b] >50% had A1c <9% at baseline.
[c] >70% had A1c <8% at baseline.
Abbreviations: NR, rot reported; BID, twice daily.

Sitagliptin monotherapy

Sitagliptin compared with placebo

Five fair-quality trials ranging from 12-24 weeks in duration compared sitagliptin 100 mg/d to placebo (Table 15).[47, 48, 53, 54, 56] Patients randomized to receive sitagliptin 100 mg/d showed significant reductions in A1c (placebo-corrected change 0.81%, 95% CI -0.94% to -0.67%) and fasting plasma glucose (placebo-corrected change 24.4 mg/dL, 95% CI -29.5 to -19.3 mg/dL), while placebo-treated patients generally showed worsening glycemic control (Table 17, Figures 6 and 7). For patients who volunteered to participate in a meal-tolerance test, sitagliptin lowered postprandial glucose relative to placebo (placebo-corrected change 54.5 mg/dL, 95% CI -65.5 to -43.5 mg/dL). A greater proportion of patients receiving sitagliptin than placebo reached the A1c goal of <7%, although 9%-21% of subjects on sitagliptin required the use of a second medication.

Weight generally decreased in both treatment arms (range for change from baseline: sitagliptin -0.1 to -0.6 kg compared with placebo -0.7 to -1.1 kg). Overall, however, subjects randomized to sitagliptin lost slightly less weight than subjects randomized to placebo (weighted mean difference: 0.62, 95% CI 0.36-0.89; see Figure 7).

Approximately 50% of subjects were on 1 or more oral hypoglycemic agents at screening. These agents were discontinued before diet and exercise run-in periods. Patients not responding to diet and exercise were eligible for study inclusion but were required to participate in a 2-week single-blind, placebo run-in period prior to randomization. Three trials allowed use of prespecified rescue medications based on certain glycemic criteria. Mean baseline A1c was 7.6%-8.9% and mean duration of diabetes was 4-5 years.

Sitagliptin compared with an active agent

In 2 fair-quality trials that evaluated sitagliptin 100 mg/d, active treatment arms of glipizide 5-20 mg/d or metformin 1000-2000 mg/d were included in the studies (Table 16).[53, 54] Patients had baseline A1c of 7.9%-8.9% with 4-5 years duration of diabetes. Overall, patients on glipizide and metformin 1-2g/d monotherapy showed numerically larger reductions in A1c, fasting plasma glucose, and postprandial glucose than compared with sitagliptin monotherapy (Table 18). However, based on the estimated magnitude of difference between groups, it appears that sitagliptin may be comparable to glipizide and metformin 1 g/day for lowering A1c (sitagliptin-glipizide difference: +0.22% and sitagliptin-metformin 1g difference: +0.16%; Table 18). The estimated magnitude of difference between sitagliptin and metformin 2 g/d was greater (+0.47%); it is unclear whether this larger difference between treatments would have statistical significance if analyses were conducted. Hence, these results should be considered with caution since neither trial performed statistical analyses for these comparisons and power may not have been adequate to detect the between-group differences in A1c, fasting plasma glucose, or postprandial glucose.

With regard to changes in weight, patients randomized to glipizide gained about 1 kg from baseline compared with a nominal increase in weight for those on sitagliptin (0.4 kg).[53] In another trial[54] patients on metformin observed slightly larger reductions in weight by about 1 kg from baseline than no change in weight experienced by those receiving sitagliptin.

Table 17. Sitagliptin monotherapy compared with placebo

Author, year	Change in A1c from baseline at (%)		Change in FPG from baseline at (mg/dL)		Change in PPG from baseline at (mg/dL)		Percent achieving A1c <7%		Change in weight from baseline at (kg)		Percent requiring rescue medication (%)	
	S100	PBO	S100	PBO	S100	PBO	S100	PBO	S100	PBO	S100	PBO
	12 weeks		12 weeks		12 weeks		12 weeks		12 weeks		12 weeks	
Nonaka, 2008[49]	-0.65	+0.41	-22.5	+9.4	-69.3	+12.0	58.1	14.5	-0.1	-0.7[a]	NR	NR
Scott, 2007[53]	-0.54	+0.23	-18	+8	-48[b]	+6	NR	NR	NR	NR	NR	NR
	18 weeks		18 weeks		18 weeks		18 weeks		18 weeks		18 weeks	
Raz, 2006[48]	-0.48	+0.12	-13	+7	-41	+5	35.8	15.5	-0.6	-0.7	9	17
	24 weeks		24 weeks		24 weeks		24 weeks		24 weeks		24 weeks	
Aschner, 2006[47]	-0.61*	+0.18	-12.6*	+5.4	-48.6*	-1.8	41**	17	-0.2	-1.1[a]	9	21
Goldstein, 2007[54]	-0.66	+0.17	-17.5	+5.8	-51.9	+0.3	20	9	0.0	-0.9[a]	21	32
Meta-analysis results, (95% CI)	-0.81 (-0.94 to -0.67)		-24.4 (-29.5 to -19.3)		-54.5 (-65.5 to -43.5)		---		+0.62 (+0.36 to +0.89)		---	

[a] $P<0.001$ compared with sitagliptin.
[b] $P<0.001$ compared with baseline.
Abbreviation: PBO, placebo; S100, sitagliptin 100 mg daily; NR, not reported.

Table 18. Sitagliptin compared with an active agent

Author, year	Change in A1c from baseline at (%)			Change in FPG from baseline at (mg/dL)			Change in PPG from baseline at (mg/dL)			Percent achieving A1c <7%			Change in weight from baseline at (kg)[a]			Percent requiring rescue medication (%)		
	S100	Glip		S100	Glip		S100	Glip		S100	Glip		S100	Glip		S100	Glip	
	12 weeks			12 weeks			12 weeks			12 weeks			12 weeks			12 weeks		
Scott, 2007[53]	-0.54	-0.76		-18.2	-24.8		-48.4[b]	-66.4[b]		NR	NR		+0.4	+0.9		NR	NR	
	S100	M1	M2	S100	M1	M2	S100	M1	M2	S100	M1	M2	S100	M1	M2	S100	M1	M2
	24 weeks			24 weeks			24 weeks			24 weeks			24 weeks			24 weeks		
Goldstein, 2007[54]	-0.66	-0.82	-1.13	-17.5	-27.3	-29.3	-51.9	-53.4	-78.0	20	23	38	0	-0.9	-1.1	21	17	12

[a] Data on weight not reported in the publication were provided by the manufacturer.
[b] *P*<0.01 compared with baseline.
Abbreviations: Glip, glipizide; M1, metformin 1000 mg/day; M2, metformin 2000 mg/day; S100, sitagliptin 100 mg daily; NR, not reported.

Figure 6. Meta-analysis of sitagliptin studies for A1c

Comparison: A1c (%)
Outcome: Difference from control

Study or sub-category	Sitagliptin N	Control N	Difference (SE)	Difference (random) 95% CI
100mg daily dose				
Aschner	229	244	-0.79 (0.09)	-0.79 [-0.96, -0.62]
Raz	193	103	-0.60 (0.11)	-0.60 [-0.81, -0.39]
Goldstein	175	165	-0.83 (0.12)	-0.83 [-1.06, -0.60]
Nonaka	75	75	-1.05 (0.11)	-1.05 [-1.26, -0.84]
Scott	121	121	-0.77 (0.10)	-0.77 [-0.96, -0.58]
Total (95% CI)	793	708		-0.81 [-0.94, -0.67]

Test for heterogeneity: Chi² = 8.81, df = 4 (P = 0.07), I² = 54.5%
Test for overall effect: Z = 11.83 (P < 0.00001)

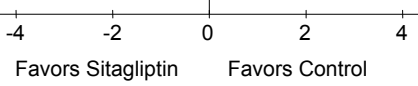
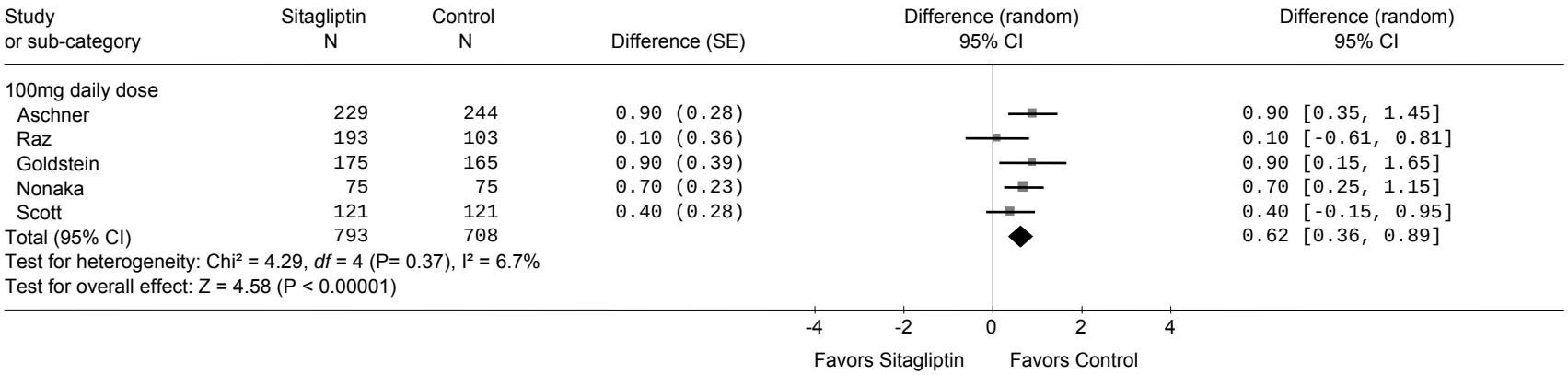


Figure 7. Meta-analysis of sitagliptin studies for weight loss

:
Comparison: Weight loss (kg)
Outcome: Difference from control



Add-on therapy

Sitagliptin or placebo added to one oral hypoglycemic agent

Three fair-quality randomized controlled trials[50, 57, 58] assessed the effects of sitagliptin added to background therapy of "failed" treatment with metformin, pioglitazone, or glimepiride. Mean baseline A1c ranged from 8.0% to 8.4% with 6.1-8.0 years' duration of diabetes. Approximately 60% of patients were on more than 1 oral hypoglycemic agent, while 30% were on more than 2 oral agents (Table 15). Patients were considered to have "failed" therapy with metformin, pioglitazone, or glimepiride at screening or after 10-19 weeks of dose stabilization and if A1c was between 7-10% or 7.5-10.5%. Patients also entered 2-week single-blind, placebo run-in periods prior to randomization.

The addition of sitagliptin to metformin, pioglitazone, or glimepiride appears to show larger reductions in A1c and fasting plasma glucose compared with the addition of placebo over 24 weeks (Table 19). A larger proportion of sitagliptin-treated patients also achieved the A1c goal of <7% than placebo-treated patients (approximately 11%-47.0% compared with 9%-23.0%). Subjects who received placebo plus glimepiride showed worsening glycemic control, while subjects on placebo plus metformin or placebo plus pioglitazone had slight improvements or no change in A1c from baseline. Weight gain was generally seen in patients taking pioglitazone or glimepiride, with or without the addition of sitagliptin. Patients randomized to metformin lost weight by 0.6 kg to 0.7 kg ($P<0.017$ and $P<0.0001$ compared with baseline) (Table 19).

Another fair quality randomized trial[52] studied the effects of sitagliptin or placebo added to ongoing metformin therapy. Unlike the other studies[50, 57, 58], this trial evaluated the effects of sitagliptin in patients with worse glycemic control (baseline A1c between 8-11%). Of the 544 patients screened, 190 patients were randomized to treatment. These patients were on metformin and diet and exercise for 6 weeks, had baseline A1c between 8-11%, and had ≥85% adherence to their regimens during a 2-week, placebo run-in period. No patients were naïve to oral hypoglycemic agents and approximately 50% were already taking metformin monotherapy or combination oral therapy at baseline.

The addition of sitagliptin to ongoing metformin therapy was more effective than placebo plus metformin at lowering A1c (placebo-corrected difference: -1.0%, 95% CI -1.4 to -0.6%) and fasting plasma glucose (placebo-corrected difference: -25.2 mg/dL, 95% CI -37.8 to -12.6 mg/dL) over 30 weeks. Further evaluation of the data showed that the largest magnitude of A1c lowering was present in patients with the highest baseline A1c between 10-11%. Postprandial glucose levels at 18 weeks were also lower with sitagliptin plus metformin than placebo plus metformin (placebo-corrected difference: -54 mg/dL, 95% CI -75.6 to -34.2 mg/dL)—measurements at 30 weeks however, were not determined by the investigators. Overall, a significantly larger proportion of sitagliptin-treated patients achieved A1c <7% than placebo-treated patients ($P<0.001$) and also needed less rescue therapy over the study duration ($P<0.001$). Both treatment groups exhibited weight loss of -0.5 kg over 30 weeks.

Sitagliptin or glipizide added to metformin

One fair-to-poor-quality trial compared the effects of adding either sitagliptin 100 mg/d or glipizide 5-20 mg/d in patients with inadequate glycemic control on metformin (Table 16).[55] Glycemic control was considered inadequate if the metformin dose was ≥ 1500 mg/d with

baseline A1c 6.5-10% at initial screening or after several weeks of stabilizing the metformin dose prior to a 2-week single-blind, placebo run-in period before randomization.

Over 52 weeks the 2 study groups showed no significant differences in treatment effects for A1c, fasting plasma glucose, or proportion of patients achieving A1c <7% from one another (Table 20). The only significant difference between treatment groups was in the change in weight. Sitagliptin-treated subjects experienced slightly more weight loss (-1.5 kg) compared with a small weight gain (+1.1 kg) seen in glipizide-treated subjects. Most patients had low baseline A1c (mean 7.5%) and an average of 5.8 years' duration of diabetes. More than 70% of patients were on oral monotherapy while approximately 30% were on two oral agents at baseline.

This trial was rated fair-poor mainly because the withdrawal rate exceeded 30%. Of the 374 patients who withdrew, more sitagliptin-treated patients withdrew due to lack of efficacy than glipizide-treated patients (86 patients vs. 58 patients). Main reason for withdrawal due to lack of efficacy was because of prespecified fasting plasma glucose and/or A1c criteria per study protocol. Also, patients who withdrew due to lack of efficacy had more severe hyperglycemia at baseline (A1c 8.6%) than those who completed the trial (7.5%). Analyses of per-protocol populations were used to show noninferiority and analyses of all-patients-treated population were also reported.

Sitagliptin, rosiglitazone, or placebo added to metformin monotherapy

Another fair quality trial[51] assessed the effects of sitagliptin, rosiglitazone, or placebo added to regimens of metformin monotherapy over 18 weeks. Prior to randomization patients had to have inadequate glycemic control (A1c 7-11%) and had to be taking metformin at stable doses ≥1500 mg/d for at least 10 weeks before entering a 2-week run-in period. The mean duration of diabetes for included patients was 4.9 years with mean baseline A1c of 7.7%.

In these patients, the addition of sitagliptin or rosiglitazone to metformin was significantly more effective than the addition of placebo to metformin at lowering A1c (P≤0.001). The placebo-corrected LS mean change from baseline was -0.51% (95% CI, -0.70 to -0.32%) for sitagliptin, and was -0.57% (95% CI, -0.76 to -0.37%) for rosiglitazone. Also, comparisons between sitagliptin and rosiglitazone were conducted and showed no statistically significant differences in lowering A1c (between-group difference: -0.06%, 95% CI -0.25 to 0.14). Similarly, there were no significant differences between sitagliptin-treated and rosiglitazone-treated patients in the proportion achieving A1c <7% (55% compared with 63%; between-group difference 8%, 95% CI, -6 to 22%). Slightly larger reductions in fasting plasma glucose (between-group difference: -12.8 mg/dL, 95% CI, -22.6 to -3.0 mg/dL) and 2-hour postprandial glucose measurements (between-group difference: -15.9 mg/dL, 95% CI, -31.6 to -0.3) were observed with those randomized to rosiglitazone than compared with those on sitagliptin. Patients randomized to sitagliptin or placebo exhibited slight weight loss from baseline (sitagliptin, -0.4 kg, 95% CI -0.8 to 0.0 vs. placebo, -0.8 kg, 95% CI -1.2 to -0.4) while patients on rosiglitazone gained weight (from baseline: +1.5 kg, 95% CI 1.0 to 1.9) over 18 weeks of therapy.

Sitagliptin or placebo added to two existing oral hypoglycemic agents

One fair-quality trial evaluated the addition of sitagliptin or placebo in patients whose glycemia was inadequately controlled on glimepiride 4-8 mg/d alone or glimepiride plus metformin 1500-3000 mg/d.[50] Results of sitagliptin or placebo added to glimepiride alone have already been

reviewed. In patients already on glimepiride plus metformin, the addition of sitagliptin improved A1c by 0.89% (95% CI -1.1 to -0.68%), fasting plasma glucose by 20.7 mg/dL (95% CI -31.7 to -9.7 mg/dL), and postprandial glucose by 37.1 mg/dL (95% CI -62.7 to -11.6 mg/dL) over 24 weeks of treatment. More sitagliptin-treated patients than placebo-treated patients also achieved the A1c goal of <7% (P<0.001). Weight, however, increased slightly (+0.4 kg, 95% CI -0.1 to 0.9 kg) with sitagliptin relative to placebo; whereas, placebo-treated patients showed more weight loss (-0.7 kg, 95% CI -1.4 to -0.1 kg) (Table 21).

In this trial, mean baseline A1c was 8.3%, average duration of diabetes was 8.8 years, and approximately 65% of subjects had an A1c >8%. More than 95% of patients were also taking combination oral hypoglycemic agents at baseline and were considered to have failed this regimen either at screening or after several weeks of dose-stabilization of glimepiride and metformin before participating in a 2-week placebo run-in phase prior to randomization.

Initial treatment with a combination of sitagliptin plus metformin compared with placebo

Unlike other trials, this study compared initial combination therapy of sitagliptin plus metformin to placebo, sitagliptin monotherapy, and metformin monotherapy in subjects who were inadequately controlled only on diet and exercise.[54] As in the placebo-controlled monotherapy trials, patients in this study were taken off prior oral hypoglycemic agents and put through a diet and exercise run-in phase in addition to a 2-week single-blind placebo run-in period before enrollment. Approximately 50% of patients were taking oral hypoglycemic agents at baseline, implying that the remainder was medication naive. Mean A1c was close to 9% and duration of diabetes was less than 5 years (Table 22). In all treatment arms metformin was titrated to increase tolerability.

The initial use of sitagliptin 100 mg/d plus metformin 2000 mg/d significantly improved A1c, fasting plasma glucose, postprandial glucose, weight, and proportion of patients achieving A1c <7% compared with sitagliptin plus metformin 1000 mg/d, placebo alone, sitagliptin monotherapy, or metformin monotherapy over 24 weeks (Table 22). In general, patients in all but 1 treatment arm showed weight loss (-0.6 kg to -1.3 kg, P=0.01 and P<0.001 from baseline). Weight was unchanged for patients on sitagliptin monotherapy (0 kg) (weight data obtained from manufacturer).

Table 19. Sitagliptin or placebo added to one oral hypoglycemic agent

Author, year	Change in A1c from baseline at (%)		Change in FPG from baseline at (mg/dL)		Change in PPG from baseline at (mg/dL)		Percent achieving A1c <7%		Change in weight from baseline at (kg)[a]		Percent requiring rescue medication (%)	
	24 weeks		24 weeks		24 weeks		24 weeks		24 weeks		24 weeks	
	S/Pioglit	**P/Pioglit**	**S/Pioglit**	**P/Pioglit**	**S/Pioglit**	**P/Pioglit**	**S/Pioglit**	**P/Pioglit**	**S/Pioglit**	**P/Pioglit**	**S/Pioglit**	**P/Pioglit**
Rosenstock, 2006[57]	-0.85	-0.15	-16.7	+1	NR	NR	45.4[b]	23.0	+1.8	+1.5	6.9**	14.0
	S/MET	**P/MET**	**S/MET**	**P/MET**	**S/MET**	**P/MET**	**S/MET**	**P/MET**	**S/MET**	**P/MET**	**S/MET**	**P/MET**
Charbonnel, 2006[58]	-0.7	-0.02	-16.2	+9	-61.2[c]	-10.8	47.0	18.3	-0.7	-0.6	4.5[c]	13.5
	S/Glime	**P/Glime**	**S/Glime**	**P/Glime**	**S/Glime**	**P/Glime**	**S/Glime**	**P/Glime**	**S/Glime**	**P/Glime**	**S/Glime**	**P/Glime**
Hermansen, 2007[50]	-0.3	+0.27	-0.88	+18.4	-24.4	+10.7	10.8[d]	8.7	+1.1	0.0	NR	NR

[a] weight data not reported in the publication were provided by the manufacturer.
[b] *P*<0.001 compared with placebo.
[c] *P*<0.05 compared with placebo.
[d] *P*=0.638 (no difference).
Abbreviations: S/Pioglit, sitagliptin added to pioglitazone; S/MET, sitagliptin added to metformin; S/Glime, sitagliptin added to glimepiride; P/-, placebo added to- P/= placebo; NR, not reported.

Table 20. Sitagliptin or glipizide added to metformin

Author, year	Change in A1c from baseline at (%)		Change in FPG from baseline at (mg/dL)		Change in PPG from baseline at (mg/dL)		Percent achieving A1c <7%		Change in weight from baseline at (kg)		Percent requiring rescue medication (%)	
	52 weeks		52 weeks		52 weeks		52 weeks		52 weeks		52 weeks	
	S/MET	**Glip/MET**	**S/MET**	**Glip/MET**	**S/MET**	**Glip/MET**	**S/MET**	**Glip/MET**	**S/MET**	**Glip/MET**	**S/MET**	**Glip/MET**
Nauck, 2007[55]	-0.67	-0.67	-10.1	-7.6	NR	NR	63	59	-1.5	+1.1	NA	NA

Abbreviations: S/MET, sitagliptin added-on to metformin; Glip/MET, glipizide added-on to metformin; NR, not reported.

Table 21. Sitagliptin or placebo added to two oral hypoglycemic agents

Author, year	Change in A1c from baseline at (%)		Change in FPG from baseline at (mg/dL)		Change in PPG from baseline at (mg/dL)		Percent achieving A1c <7%		Change in weight from baseline at (kg)		Percent requiring rescue medication (%)	
	24 weeks		24 weeks		24 weeks		24 weeks		24 weeks		24 weeks	
	S/G/M	**P/G/M**	**S/G/M**	**P/G/M**	**S/G/M**	**P/G/M**	**S/G/M**	**P/G/M**	**S/G/M**	**P/G/M**	**S/G/M**	**P/G/M**
Hermansen, 2006[a]	-0.59[b]	+0.3	-7.8[b]	+12.9	-21.3	+15.8	22.6	1.0	+0.4	-0.7	NR	NR

[a] Note: this trial also included 2 other treatment arms: glimepiride alone, glimepiride plus metformin.
[b] *P*<0.001 compared with P/G/M.
Abbreviations: S/G/M, sitagliptin added-on to glimepiride and metformin; P/G/M, placebo added-on to glimepiride and metformin.

Table 22. Initial combination of sitagliptin plus metformin compared with placebo and individual agents

Author, year	Change in A1c from baseline at (%)						Change in FPG from baseline at (mg/dL)						Change in PPG from baseline at (mg/dL)					
	24 weeks						24 weeks						24 weeks					
	S/M1	S/M2	M1	M2	S100	PBO	S/M1	S/M2	M1	M2	S100	PBO	S/M1	S/M2	M1	M2	S100	PBO
Goldstein, 2007[54]	-1.4	-1.9	-0.82	-1.13	-0.66	+0.17	-47.1	-63.9	-27.3	-29.3	-17.5	+5.8	-92.5	-116.6	-53.4	-78.0	-51.9	+0.3

Author, year	Percent achieving A1c <7%						Change in weight from baseline at (kg)				Percent requiring rescue medication (%)					
	24 weeks						24 weeks				24 weeks					
	S/M1	S/M2	M1	M2	S100	PBO	S/M1	S/M2	M1	M2	S/M1	S/M2	M1	M2	S100	PBO
Goldstein, 2007[54]	43	66	23	38	**20**	9	NR	NR	NR	NR	8	2	17	12	21	32

Abbreviations: S/M1, sitagliptin added to metformin 1000 mg/day; S/M2, sitagliptin added to metformin 2000 mg/day; M1, metformin 1000 mg/day; M2, metformin 2000 mg/day; PBO, placebo; NR, not reported.

Harms

In 5 trials with data suitable for meta-analysis, total withdrawals and withdrawals due to adverse events were lower among patients randomized to sitagliptin monotherapy than patients receiving only placebo (relative risk for total withdrawals 0.69, 95% CI 0.55-0.88; relative risk for withdrawal due to adverse events 0.76, 95% CI 0.33-1.73). Patients on sitagliptin monotherapy also had lower rates of total withdrawal relative to patients on glipizide, who experienced more hypoglycemic events. When compared with metformin, however, sitagliptin was associated with a greater attrition rate, mainly due to withdrawal of consent, violations of protocol, and abnormalities in laboratory. The rate of total withdrawals was also higher in patients whose add-on therapy was sitagliptin than in patients using monotherapy metformin, pioglitazone, or glimepiride.

The most commonly reported adverse events were hypoglycemia, abdominal pain, nausea, vomiting, and diarrhea.

A total of 5 deaths occurred in 3 trials over 24-52 weeks. None was considered to be related to study interventions; 3 were sudden cardiac deaths, 1 was secondary to trauma, and 1 was related to chronic obstructive pulmonary disease and interstitial lung disease.

Rare adverse events

Five of the 10 randomized controlled trials reported adverse events. In those 5 trials adverse events occurring in at least 4% of study subjects included: upper respiratory tract infections, headache, influenza, nasopharyngitis, and urinary tract infection. Four studies[47, 50, 55, 58] reported small increases (≤10% from baseline) in mean white blood cell count, mainly an increase in absolute neutrophil count, in regimens with sitagliptin compared to regimens without. These increases appeared early and remained stable throughout the duration of the studies. No other trials provided data on changes in white blood cell count with sitagliptin.

Hypoglycemia

Two studies[53, 55] documented 20 cases of severe hypoglycemia, mostly associated with glipizide (90%) rather than with sitagliptin. In 1 trial 3 patients on glipizide monotherapy discontinued treatment. In the other trial 8 patients receiving glipizide plus metformin required non-medical, third-party assistance compared with 1 patient taking sitagliptin added to metformin. Seven patients taking glipizide plus metformin experienced severe symptoms requiring medical assistance compared with 1 patient receiving sitagliptin plus metformin. The remaining six studies reported no cases of severe hypoglycemia.

There was no statistically significant difference in the overall risk of mild to moderate hypoglycemia between sitagliptin and placebo (pooled relative risk 1.21, 95% CI 0.42 to 3.5) (see Table 23). The rate of mild-to-moderate hypoglycemia increased slightly when sitagliptin was added to glimepiride (7.6% compared with 2.8%) or pioglitazone (1.1% compared with 0%).

Abdominal pain, nausea, vomiting, and diarrhea

There were no statistically significant differences between sitagliptin monotherapy and placebo in the risk of abdominal pain (pooled RR 1.17, 95% CI 0.54-2.52) [47, 48, 54], nausea (pooled RR 1.56, 95% CI 0.53-4.57) [47, 48, 54], diarrhea (pooled RR 1.26, 95% CI 0.64-2.25) [47, 48, 54], and vomiting (pooled RR 0.65, 95% CI 0.18-2.4). [47, 48, 54] However, based on the elevated relative risks, there appears to be a trend for greater risk of experiencing abdominal pain, and nausea with sitagliptin monotherapy compared with placebo.

Compared with metformin monotherapy, sitagliptin was associated with lower incidence of abdominal pain, nausea, vomiting, and diarrhea (Table 23). Combination therapy of sitagliptin plus glimepiride, metformin, or pioglitazone had <6% incidence of abdominal pain, nausea, vomiting, and diarrhea; these results were not significantly different from their comparisons (Table 23).

Table 23. Adverse events of sitagliptin compared with oral hypoglycemic agents

	Scott, 2007		Goldstein, 2006			Rosenstock, 2006		Charbonnel, 2006		Hermansen, 2007[a]		Nauck, 2007	
Adverse event	**S100**	**Glip**	**S100**	**M1**	**M2**	**S/Pioglit**	**Pioglit**	**S/MET**	**MET**	**S/Glime**	**Glime**	**S/MET**	**Glip/MET**
Treatment- emergent adverse events (%)													
Hypoglycemia	1.64[b]	17.1	0.6	0.6	1.1	1.1	0.0	1.3	2.1	7.6	2.8	4.9	32.0
Nausea	NR	NR	1.1	2.8	8.2	1.1	0.0	1.3	0.8	0.0	0.0	2.6	2.7
Vomiting	NR	NR	0.0	0.0	1.1	0.6	0.6	1.1	0.8	0.9	0.0	0.9	1.5
Diarrhea	NR	NR	2.8	5.0	10.4	1.7	1.1	2.6	2.5	1.9	1.9	5.8	5.5
Abdominal pain	NR	NR	3.4	2.8	5.0	3.4	0.0	2.2	3.8	2.8	0.0	2.7	2.1
Rarer adverse events occurring with ≥4% incidence													
Nasopharyngitis	---	---	---	---	---	4.0	3.9	4.1	3.4	---	---	10.5	7.5
Upper respiratory tract infection	---	---	---	---	---	6.3	3.4	7.3	9.3	---	---	---	---
Influenza	---	---	---	---	---	4.0	2.8	4.3	5.5	---	---	---	---
Headaches	---	---	---	---	---	5.7	3.9	---	---	---	---	---	---
Urinary tract infections	---	---	---	---	---	---	---	---	---	---	---	5.4	2.7

[a] Data are presented as percentages (%).
[b] Note: this trial also included treatment arms: glimepiride plus metformin, glimepiride plus metformin plus sitagliptin.
Abbreviations: Glime, glimepiride; Glip, glipizide 5-20 mg/d; Glip/MET, glipizide added to metformin; M1, metformin 1000 mg/d; M2, metformin 2000 mg/d; MET, metformin; NR, not reported; Pioglit, pioglitazone; S100, sitagliptin 100 mg daily; S/Glime, sitagliptin added to glimepiride; S/MET, sitagliptin added to metformin; S/Pioglit, sitagliptin added to pioglitazone.

Key Question 3. Are there subgroups of patients for which sitagliptin is more or less suitable than other hypoglycemic agents?

There was insufficient evidence to perform subgroup analyses based on age, sex, race, ethnicity, baseline A1c, or other characteristics at the study level. Subgroup data not available in publications were supplemented by data provided by the manufacturer. The results from this section should be considered with caution until larger prospective trials evaluating these populations verify the findings.

Age, sex, race, body mass index, and prior use of oral hypoglycemic agents

Four published trials[48, 49, 51, 52] reported no significant differences in changes in A1c based on subgroups defined by age, sex, race, and BMI. Data on file from 3 additional trials (Rosenstock 2006, Aschner 2006, Hermansen 2007)[59] also showed similar findings.

Data on file from one trial (Charbonnel 2006)[59] showed a significant interaction between treatment effect and race for those on sitagliptin monotherapy and placebo. Hispanic patients experienced the largest decline in A1c (placebo-corrected difference in A1c from baseline: -1.04%, 95% CI -1.38 to -0.70%) followed by White patients (placebo-corrected difference: in A1c from baseline: -0.69%, 95% CI -0.84 to 0.55%), and Other patients (placebo-corrected difference in A1c from baseline: -0.44%, 95% CI, -0.82 to -0.07%).

Of the 5 studies (Scott 2007, Hermansen 2007, Nonaka 2008, Charbonnel 2006, Goldstein 2007)[59] that stratified groups by prior oral hypoglycemic agent use, only 1 trial (Goldstein 2007)[59] showed a large numerical difference in treatment effect. Patients who were not taking an oral hypoglycemic agent prior to this trial experienced greater decline in A1c across all treatment arms compared with patients who were using oral agents before enrolling into the study. For instance, the change in A1c from baseline for "no prior oral agent use" for sitagliptin versus placebo was -1.11% vs. -0.13% compared with -0.26% vs. +0.52% for those "treated with prior oral agents." Between-group difference calculations were not conducted.

Baseline A1c

Subgroup information stratified by baseline A1c were found in 10 of 11 trials. Some data were available from the 9 published studies[47-52, 54, 55, 57] and additional information from 4 of these trials (Scott 2007, Charbonnel 2006, Nauck 2006, Scott 2008) were obtained from data on file.[59]

Four trials (Charbonnel 2006, Hermansen 2006, Nonaka 2008, Raz 2006) found no significant differences in the change in baseline A1c among those in the following subgroups: <7.5%, <8%, 8-8.9%, >7.5%, ≥8.5%, and ≥9%. One trial[47] showed significant interaction (P<0.001) in the change in A1c stratified by baseline A1c <8% and ≥9%. In patients with baseline A1c ≥9%, placebo-corrected reductions of -1.52% were observed for sitagliptin 100 mg/d compared with about -0.6% decrease in those with baseline A1c <8%. Data from Goldstein, et al.[59] also showed consistent findings for sitagliptin 100 mg/d compared with placebo. For this study, interaction analyses were not conducted (change in A1c from baseline for those with A1c <8%: sitagliptin, -0.37% vs. placebo, +0.15% compared with those with A1c ≥9%: sitagliptin, -0.88% vs. placebo, +0.08%).

Duration of diabetes

One trial[48] reported a potential interaction between median baseline duration of diabetes and A1c effects in patients randomized to sitagliptin 100 mg compared with placebo. Patients with

diabetes of ≤ 3 years' duration had significantly greater reductions in A1c than patients who had diabetes for > 3 years (placebo-corrected mean change A1c for ≤ 3years -0.90%, 95% CI -1.21% to -0.60% compared with mean change A1c for > 3years -0.28%, 95% CI -0.59 to +0.20).

Applicability to general diabetes populations

Patients enrolled in the 11 trials represented a highly selected population: primarily white, middle-aged, obese adults with moderately elevated baseline A1c (< 9%) and diabetes for less than 10 years. These populations were further selected during long dose-stabilization and run-in periods, where only persons with > 75% adherence to placebo went on to randomization. Moreover, these trials did not provide sufficient baseline information on comorbidities and other characteristics and laboratory values that would enable inference about the applicability of study findings to general diabetic populations. The available data appear to be limited to persons with diabetes without related comorbidities and who are highly motivated.

Table 24. Summary evidence table for sitagliptin

Type 2 Diabetes	Quality of evidence	Conclusion
Key Question 1. For children and adults with type 2 diabetes, does sitagliptin differ in efficacy, effectiveness, and in harms when compared to placebo, when compared to other hypoglycemic agents as monotherapy, or when added to other hypoglycemic agents?		Evidence in children is lacking.
Effectiveness	No available data	-No studies assessed long-term health outcomes and none were > 52 weeks in duration.
Efficacy	**Monotherapy compared with placebo** -Fair, 5 RCTs **Monotherapy compared with an oral hypoglycemic agent** -Fair, 2 RCTs **Combined therapy compared with placebo** -Fair, 4 RCTs **Combined therapy compared with oral hypoglycemic agents** -Fair-Poor, 1 RCT	-Evidence on time-to-treatment-failure is lacking. **Monotherapy compared with placebo** -Sitagliptin significantly improved A1c, FPG, and PPG relative to placebo. Pooled data for the above: A1c: -0.81% (95% CI, -0.94 to -0.67) FPG: -24.4 mg/dL (95% CI, -29.5 to -19.3) PPG: -54.5 mg/dL (95% CI, -65.5 to -43.5) -Sitagliptin-treated patients lost slightly less weight compared with placebo-treated patients (range: -0.1 to -0.6 kg compared with -0.7 to -1.1 kg; pooled: +0.62 kg (95% CI, +0.36 to +0.89) **Monotherapy compared with an oral hypoglycemic agent**-Though formal statistical analyses were not conducted for glipizide-or metformin monotherapy compared with sitagliptin monotherapy, it appears that sitagliptin may be comparable to glipizide and metformin 1 g/d in lowering A1c based on qualitative evaluation of the magnitude of difference between groups. Additional trials are needed to verify the findings. Ranges for sitagliptin monotherapy compared with glipizide and metformin monotherapies: A1c: -0.54% to -0.66% compared with -0.8% to -1.1% FPG: -18 mg/dL compared with -25 to -29 mg/dL PPG: -48 to -59 mg/dL compared with -53 to -78 mg/dL -Weight remained unchanged for sitagliptin while weight gain (+0.9 kg) occurred for those on glipizide. Weight loss occurred with metformin by about 1 kg. **Combined therapy compared with placebo**

Type 2 Diabetes	Quality of evidence	Conclusion
		-The addition of sitagliptin to one or two oral hypoglycemic agents was more effective for glycemic control than the addition of placebo. **Combined therapy compared with oral hypoglycemic agents** -There was no difference in A1c between regimens that included the addition of sitagliptin or glipizide to metformin. Sitagliptin-treated patients experienced slightly more weight loss (-1.5 kg) than compared with weight gain seen in glipizide-treated patients (+1.5 kg). -There were no significant differences in the reduction in A1c for those on sitagliptin or rosiglitazone added to metformin monotherapy (between-group difference: -0.06%, 95% CI -0.25 to +0.14%) at 18 weeks.
Harms	**Monotherapy compared with placebo** -Fair, 5 RCTs **Monotherapy compared with an oral hypoglycemic agent** -Fair, 2 RCTs **Combined therapy compared with placebo** -Fair, 4 RCTs **Combined therapy compared with oral hypoglycemic agents**	**-**Studies beyond 52 weeks in duration evaluating harms are lacking. **Monotherapy compared with placebo** -Fewer sitagliptin-treated patients than placebo-treated patients withdrew due to adverse events. -There was no statistically significant difference in the risk of hypoglycemia between sitagliptin and placebo groups (pooled relative risk 1.21, 95% CI 0.42 to 3.5). - There were no statistically significant differences between sitagliptin monotherapy and placebo in the risk of abdominal pain, nausea, vomiting, or diarrhea. Pooled relative risks: Abdominal pain: RR 1.17, 95% CI 0.54-2.52 Nausea: RR 1.56, 95% CI 0.53-4.57 Vomiting: pooled RR 0.65, 95% CI 0.18-2.4 Diarrhea: RR 1.26, 95% CI 0.64-2.25 **Monotherapy compared with an oral hypoglycemic agent** -Sitagliptin and metformin had a lower incidence of hypoglycemia than glipizide. -Sitagliptin had lower rates of abdominal pain, nausea, vomiting, and diarrhea than metformin. **Combined therapy compared with placebo** - Regimens that included sulfonylurea ± sitagliptin exhibited greater risk of hypoglycemia than therapies without sulfonylurea. -Combination therapies of sitagliptin with sulfonylurea, thiazolidinedione, and metformin

Type 2 Diabetes	Quality of evidence	Conclusion
	-Fair-Poor, 1 RCT	had slightly greater rates of abdominal pain, nausea, vomiting, and diarrhea than the individual oral hypoglycemic agents as monotherapy. **Combined therapy compared with oral hypoglycemic agents** -Sitagliptin added to metformin had lower rates of hypoglycemia than glipizide added to metformin. - Sitagliptin + metformin versus glipizide + metformin showed minimal difference in the incidence of abdominal pain, nausea, vomiting, and diarrhea.
Key Question 2. Are there subgroups of patients for which sitagliptin is more or less suitable than other hypoglycemic agents?	-Fair-Poor	-In general, it appears that there are no significant differences in treatment effect based on age, sex, BMI, race. Data on file from 1 trial showed that Hispanic patients showed slightly larger reductions in A1c than White or "Other" patients. - Patients with higher baseline A1c ≥9% tended to exhibit larger treatment effects than patients with baseline A1c <8%. -Patients with <3 years' duration of diabetes tended to exhibit larger treatment effects than those with > 3 years' duration of diabetes.

Abbreviations: CI, confidence interval; FPG, fasting plasma glucose; PPG, postprandial glucose; RCT, randomized controlled trial.

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59. Data on File. Supplemental dossier: Sitagliptin.Compiled October 2007.

Appendix A. Search strategies

Pramlintide

Database: Ovid MEDLINE(R) <1950 to September Week 1 2007> and updated on <1996 to April Week 3 2008>

Search Strategy:
---
1 196078-30-5.rn. (0)
2 pramlintide.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (167)
3 amylin agonist.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (4)
4 amylin analogue.mp. (35)
5 symlin.mp. (7)
6 amylin ag$.mp. (20)
7 amylin analogue$.mp. (40)
8 amylin agonist$.mp. (11)
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (186)
10 limit 9 to (humans and english language) (167)
11 from 10 keep 1-167 (167)

Database: Ovid MEDLINE(R) <1996 to April Week 3 2008>
Search Strategy:
---
1 196078-30-5.rn. (0)
2 pramlintide.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (172)
3 amylin agonist.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (4)
4 amylin analogue.mp. (34)
5 symlin.mp. (7)
6 amylin ag$.mp. (17)
7 amylin analogue$.mp. (39)
8 amylin agonist$.mp. (9)
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (187)
10 limit 9 to (humans and english language) (170)
11 2008$.ed. (210631)
12 10 and 11 (10)
13 from 12 keep 1-10 (10)
14 from 13 keep 1-10 (10)

****

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <3rd Quarter 2007>
Search Strategy:
---
1 [196078-30-5.rn.] (0)
2 pramlintide.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (31)
3 amylin agonist.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (0)
4 amylin analogue.mp. (11)
5 symlin.mp. (0)
6 amylin ag$.mp. (1)
7 1 or 2 or 3 or 4 or 5 or 6 (32)
8 from 7 keep 1-32 (32)

Exenatide

Database: Ovid MEDLINE(R) <1950 to September Week 1 2007> and updated on <1996 to April Week 3 2008>

Search Strategy:
---
1 141732-76-5.rn. (316)
2 exenatide.mp. (363)
3 byetta.mp. (17)
4 exendin-4.mp. (253)
5 glp-1 analog$.mp. (74)
6 (incretin adj mimetic).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (43)
7 1 or 2 or 3 or 4 or 5 or 6 (476)
8 limit 7 to (humans and english language) (275)
9 from 8 keep 1-275 (275)

Database: Ovid MEDLINE(R) <1996 to April Week 3 2008>
Search Strategy:
---
1 141732-76-5.rn. (354)
2 exenatide.mp. (409)
3 byetta.mp. (18)
4 exendin-4.mp. (258)
5 glp-1 analog$.mp. (91)
6 (incretin adj mimetic).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (49)
7 1 or 2 or 3 or 4 or 5 or 6 (534)

8 limit 7 to (humans and english language) (314)
9 2008$.ed. (210631)
10 8 and 9 (28)
11 from 10 keep 1-28 (28)
12 from 11 keep 1-28 (28)

****

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <3rd Quarter 2007>
Search Strategy:
---
1 exenatide.mp. (24)
2 byetta.mp. (0)
3 exendin-4.mp. (13)
4 glp-1 analog$.mp. (3)
5 (incretin adj mimetic).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (11)
6 1 or 2 or 3 or 4 or 5 (29)
7 from 6 keep 1-29 (29)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <3rd Quarter 2007>
Search Strategy:
---
1 exenatide.mp. (1)
2 byetta.mp. (1)
3 exendin-4.mp. (0)
4 glp-1 analog$.mp. (1)
5 (incretin adj mimetic).mp. (0)
6 1 or 2 or 3 or 4 or 5 (1)
7 from 6 keep 1 (1)

Sitagliptin

Database: Ovid MEDLINE(R) <1950 to September Week 1 2007> and updated on <1996 to April Week 3 2008>

Search Strategy:
---
1 sitagliptin.mp. (73)
2 januvia.mp. (5)
3 790712-60-6.rn. (0)
4 dipeptidyl peptidase inhibit$.mp. (14)
5 cd26 inhibit$.mp. (14)
6 gliptin$.mp. (5)

7 (incretin adj mimetic).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (43)
8 DPP-IV inhibit$.mp. (134)
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (264)
10 limit 9 to (humans and english language) (187)
11 from 10 keep 1-187 (187)

- -

Database: Ovid MEDLINE(R) <1996 to April Week 3 2008>
Search Strategy:
----
1 sitagliptin.mp. (111)
2 januvia.mp. (8)
3 790712-60-6.rn. (0)
4 dipeptidyl peptidase inhibit$.mp. (13)
5 cd26 inhibit$.mp. (14)
6 gliptin$.mp. (7)
7 (incretin adj mimetic).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (49)
8 DPP-IV inhibit$.mp. (145)
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (312)
10 limit 9 to (humans and english language) (225)
11 2008$.ed. (210631)
12 10 and 11 (26)
13 from 12 keep 1-26 (26)
14 from 13 keep 1-26 (26)

****

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <3rd Quarter 2007>
Search Strategy:
----
1 sitagliptin.mp. (11)
2 januvia.mp. (0)
3 [790712-60-6.rn.] (0)
4 dipeptidyl peptidase inhibit$.mp. (0)
5 DPP-IV inhibitor$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (2)
6 1 or 2 or 3 or 4 or 5 (12)
7 from 6 keep 1-12 (12)

- -

Database: EBM Reviews - Cochrane Database of Systematic Reviews <3rd Quarter 2007>
Search Strategy:
----
1 sitagliptin.mp. (1)

2 januvia.mp. (0)
3 [790712-60-6.rn.] (0)
4 dipeptidyl peptidase inhibit$.mp. (0)
5 gliptin$.mp. (1)
6 DPP-IV inhibitor$.mp. [mp=title, short title, abstract, full text, keywords, caption text] (0)
7 1 or 2 or 3 or 4 or 5 or 6 (1)
8 from 7 keep 1 (1)

Appendix B. Quality assessment methods for drug class reviews for the Drug Effectiveness Review Project

Study quality is objectively assessed using predetermined criteria for internal validity which are based on the US Preventive Services Task Force and the National Health Service Center for Reviews and Dissemination[1 2] criteria.

All included studies, regardless of design, are assessed for quality and assigned a rating of "good," "fair," or "poor." Studies that have a fatal flow are rated poor quality. A fatal flow is failure to meet combinations of criteria that together are consistent with absence of systematic bias. An example would be inadequate procedures for randomization and/or allocation concealment combined with important differences in prognostic factors at baseline. Studies that meet all criteria are rated good quality and the remainder is rated fair quality. As the "fair" category is broad, studies with this rating vary in their strengths and weaknesses: The results of some fair-quality studies are likely to be valid, while others are only probably valid. A poor-quality trial is not valid; the results are at least as likely to reflect flaws in the study design as to reflect true difference between the compared drugs.

Criteria for assessing scientific quality of systematic research reviews[3] (Oxman and Guyatt 1991)

The purpose of this index is to evaluate the scientific quality (i.e. adherence to scientific principles) of research overviews (review articles) published in the medical literature. It is not intended to measure literary quality, importance, relevance, originality, or other attributes of overviews.

The index is for assessing overviews of primary ("original") research on pragmatic questions regarding causation, diagnosis, prognosis, therapy, or prevention. A research overview is a survey of research. The same principles that apply to epidemiological surveys apply to overviews: a question must be clearly specified, a target population identified and accessed, appropriate information obtained from that population in an unbiased fashion, and conclusions derived, sometimes with the help of formal statistical analysis, as is done in "meta-analyses". The fundamental difference between overviews and epidemiological studies is the unit of analysis, not the scientific issues that the questions in this index address.

Since most published overviews do not include a methods section, it is difficult to answer some of the questions in the index. Base your answers, as much as possible, on information provided in the overview. If the methods that were used are reported incompletely relative to a specific question, score it as "can't tell", unless there is information in the overview to suggest either the criterion was or was not met.

Each Question is scored as Yes, Partially/Can't tell, or No.

Extensive Flaws		**Major Flaws**		**Minor Flaws**		**Minimal Flaws**
1	2	3	4	5	6	7

1. Were the search methods reported?
Were the search methods used to find evidence (original research) on the primary questions stated?

"Yes" if the review states the databases used, date of most recent searches, and some mention of search terms.

2. Was the search comprehensive?
Was the search for evidence reasonably comprehensive?
"Yes" if the review searches at least 2 databases and looks at other sources (such as reference lists, hand searches, queries experts).

Because EMBASE was launched in 1972 and Cochrane Database of Systematic Reviews was launched in 1994, papers prior to 1994 can be graded "Yes" if only one database is searched.

3. Were the inclusion criteria reported?

Were the criteria used for deciding which studies to include in the overview reported?

4. Was selection bias avoided?
Was bias in the selection of studies avoided?

"Yes" if the review reports how many studies were identified by searches, numbers excluded, and gives appropriate reasons for excluding them (usually because of pre-defined inclusion/exclusion criteria).

5. Were the validity criteria reported?

Were the criteria used for assessing the validity of the included studies reported?

6. Was validity assessed appropriately?
Was the validity of all the studies referred to in the text assessed using appropriate criteria (either in selecting studies for inclusion or in analyzing the studies that are cited)?

"Yes" if the review reports validity assessment and did some type of analysis with it (for example sensitivity analysis of results according to quality ratings, excluded low-quality studies, etc.)

7. Were the methods used to combine studies reported?
Were the methods used to combine the findings of the relevant studies (to reach a conclusion) reported?

"Yes" for studies that did qualitative analysis if there is some mention that quantitative analysis was not possible and reasons that it could not be done, or if 'best evidence' or some other grading of evidence scheme used.

8. Were the findings combined appropriately?
Were the findings of the relevant studies combined appropriately relative to the primary question the overview addresses?

"Yes" if the review performs a test for heterogeneity before pooling, does appropriate subgroup testing, appropriate sensitivity analysis, or other such analysis.

For Question 8, if not attempt has been made to combine findings, and no statement is made regarding the inappropriateness of combining findings, check "No". if a summary (general) estimate is given anywhere in the abstract, the discussion, or the summary section of the paper, and it is not reported how that estimate was derived, mark "No" even if there is a statement regarding the limitations of combining the findings of the studies reviewed. If in doubt, mark "Can't tell".

9. Were the conclusions supported by the reported data?

Were the conclusions made by the author(s) supported by the data and/or analysis reported in the overview?

For an overview to be scored as "Yes" in Question 9, data (not just citations) must be reported that support the main conclusions regarding the primary question(s) that the overview addresses.

10. What was the overall scientific quality of the overview?

How would you rate the scientific quality of this overview?

The score for Question 10, the overall scientific quality, should be based on your answers to the first nine questions. The following guidelines can be used to assist with deriving a summary score: If the "Can't tell" option is used one or more times on the preceding questions, a review is likely to have minor flaws at best and it is difficult to rule out major flaws (i.e. a score of 4 or lower). If the "No" option is used on Question 2, 4, 6 or 8, the review is likely to have major flaws (i.e. a score of 3 or less, depending on the number and degree of the flaws).

Controlled Trials

Assessment of Internal Validity

1. Was assignment to the treatment groups really random?
    - Adequate approaches to sequence generation:
        - Computer-generated random numbers
        - Random numbers tables
    - Inferior approaches to sequence generation:
        - Use of alternation, case record number, birth date, or day of the week
    - Not reported

2. Was the treatment allocation concealed?
    - Adequate approaches to concealment of randomization:
        - Centralized or pharmacy-controlled randomization
        - Serially-numbered identical containers
        - On-site computer-based system with a randomization sequence that is not readable until allocation
        - Other approaches that conceal the sequence to clinicians and patients until treatment allocation
    - Inferior approaches to concealment of randomization:
        - Use of alternation, case record number, birth date, or day of the week
        - Open random-numbers lists
        - Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
    - Not reported

3. Were the groups similar at baseline in terms of prognostic factors?

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to the treatment allocation?

6. Was the care provider blinded?

7. Was the patient kept unaware of the treatment received?

8. Did the article include an intention-to-treat analysis or provide the data needed to calculate it (that is, number assigned to each group, number of subjects who finished in each group, and results for those subjects)?

9. Did the study maintain comparable groups?

10. Did the article report attrition, crossovers, adherence, and contamination?

11. Is there important differential loss to follow-up or overall high loss to follow-up (report numbers in each group)?

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?

2. How many patients were recruited?

3. What were the exclusion criteria for recruitment? (report numbers excluded at each step.)

4. What was the funding source and role of the funder in the study?

5. Did the control group receive the standard of care?

6. What was the length of follow-up? (report numbers at each stage of attrition.)

Non-randomized studies

Assessment of Internal Validity

1. Was the selection of patients for inclusion non-biased? (e.g., was no group of patients systematically excluded?)

2. Is there important differential loss to follow-up or overall high loss to follow-up? (Give numbers in each group.)

3. Were the investigated events specified and defined?

4. Was there a clear description of the techniques used to identify the events?

5. Was there non-biased and accurate ascertainment of events (independent ascertainers, validation of ascertainment technique)?

6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?

7. Did the duration of follow-up correlate to reasonable timing for investigated events? (Does follow-up interval meet the stated threshold?)

Assessment of External Validity

1. Was the description of the population adequate?

2. How similar is the population to the population to whom the intervention would be applied?

3. How many patients were recruited?

4. What were the exclusion criteria for recruitment? (report numbers excluded at each step.)

5. What was the funding source and role of the funder in the study?

References

1. Anonymous. Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews CRD report number 4 (2nd edition. *CRD.* 2001.

2. Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. *American Journal of Preventive Medicine.* 2001;20(3 Suppl):21-35.

3. Oxman AD, Guyatt GH. Validation of an index of the quality of review articles. *Journal of Clinical Epidemiology.* 1991;44(11):1271-1278.

Appendix C. Excluded Studies

	Excluded studies	***Reasons for exclusion***
1	Pramlintide: (AC 137, AC 0137, Symlin, Tripro-Amylin). Biodrugs. 2003;17(1):73-79."	Wrong publication type (letter, editorial, non-systematic review, case-report, case series)
2	Ahren B. Dipeptidyl peptidase-4 inhibitors: clinical data and clinical implications. Diabetes Care. Jun 2007;30(6):1344-1350.	Study design not included
3	Barnett AH, Trautmann ME, Burger J, et al. A comparison of exenatide and insulin glargine in patients using a single oral antidiabetic agent. Diabetologia. 2006;49(Suppl 1):474.	Wrong publication type (letter, editorial, non-systematic review, case-report, case series)
4	Borm AK, Klevesath MS, Borcea V, et al. The effect of pramlintide (amylin analogue) treatment on bone metabolism and bone density in patients with type 1 diabetes mellitus. Hormone & Metabolic Research. Aug 1999;31(8):472-475.	Wrong publication type (letter, editorial, non-systematic review, case-report, case series)
5	Bronsky J, Prsa R, Nevoral J. The role of amylin and related peptides in osteoporosis. Clinica Chimica Acta. Nov 2006;373(1-2):9-16.	Wrong publication type (letter, editorial, non-systematic review, case-report, case series)
6	Cvetkovi RS, Plosker GL. Exenatide: a review of its use in patients with type 2 diabetes mellitus (as an adjunct to metformin and/or a sulfonylurea). Drugs. 2007;67(6):935-954.	Study design not included
7	Denker PS, Dimarco PE. Exenatide (exendin-4)-induced pancreatitis: a case report. Diabetes Care. Feb 2006;29(2):471.	Study design not included
8	Doggrell SA. Recent evidence of sustained benefit with exenatide in Type 2 diabetes. Expert Opinion on Pharmacotherapy. Oct 2006;7(14):2003-2006.	Study design not included
9	Hanefield M, Herman G, Mickel C, et al. Effect of MK-0431, a dipeptidyl peptidase IV (DPP-IV) inhibitor, on glycemic control after 12 weeks in patients with type 2 diabetes. Diabetologia. 2005;48:287-288.	Wrong publication type (letter, editorial, non-systematic review, case-report, case series)
10	Home PD. Comment on: Nauck MA, Duran S, Kim D et al (2007) A comparison of twice-daily exenatide and biphasic insulin aspart in patients with type 2 diabetes who were suboptimally controlled with sulfonylurea and metformin: a non-inferiority study. Diabetologia 50:259-267. Diabetologia. Jul 2007;50(7):1561-1562; author reply 1563-1564.	Wrong publication type (letter, editorial, non-systematic review, case-report, case series)
11	Hood R, Valentine V, CNS, et al. Use of exenatide in patients with type 2 diabetes. Diabetes Spectrum. 2006;19(3):181-186.	Wrong publication type (letter, editorial, non-systematic review, case-report, case series)
12	Iltz JL, Baker DE, Setter SM, Keith Campbell R. Exenatide: an incretin mimetic for the treatment of type 2 diabetes mellitus. Clinical Therapeutics. May 2006;28(5):652-665.	Study design not included

	Excluded studies	***Reasons for exclusion***
13	Jeha GS, Heptulla RA. Newer therapeutic options for children with diabetes mellitus: theoretical and practical considerations. Pediatric Diabetes. Apr 2006;7(2):122-138.	Study design not included
14	Joy SV, Rodgers PT, Scates AC. Incretin mimetics as emerging treatments for type 2 diabetes. Annals of Pharmacotherapy. Jan 2005;39(1):110-118.	Study design not included
15	Karasik A, Aschner P, Katzeff H, Davies MJ, Stein PP. Sitagliptin, a DPP-4 inhibitor for the treatment of patients with type 2 diabetes: a review of recent clinical trials. *Current Medical Research & Opinion.* Feb 2008;24(2):489-496	Study design not included
16	Kendall D, Bhole D, Guan X, et al. Exenatide treatment for 82 weeks reduced C-reactive protein, HbA1C, and body weight in patients with type 2 diabetes mellitus. Diabetologia. 2006;49(Suppl 1):475.	Wrong publication type (letter, editorial, non-systematic review, case-report, case series)
17	Kim D, Macconell L, Zhuang D, et al. Effects of once-weekly dosing of a long-acting release formulation of exenatide on glucose control and body weight in subjects with type 2 diabetes. Diabetes Care. 2007;30(6):1487- 1493.	Intervention not included
18	Kleppinger EL, Vivian EM. Pramlintide for the treatment of diabetes mellitus. Annals of Pharmacotherapy. Jul-Aug 2003;37(7-8):1082-1089.	Study design not included
19	Mack CM, Moore CX, Jodka CM, et al. Antiobesity action of peripheral exenatide (exendin-4) in rodents: effects on food intake, body weight, metabolic status and side-effect measures. International journal of obesity. 2006;30:1332-1340.	Study design not included
20	Mathieu C, Bollaerts K. Antihyperglycaemic therapy in elderly patients with type 2 diabetes: potential role of incretin mimetics and DPP-4 inhibitors. International Journal of Clinical Practice. Aug 2007;Supplement.(154):29-37.	Study design not included
21	Mikhail NE. Is exenatide a useful addition to diabetes therapy? Endocrine Practice. May-Jun 2006;12(3):307-314.	Wrong publication type (letter, editorial, non-systematic review, case-report, case series)
22	Miller S, St Onge EL. Sitagliptin: a dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes. Annals of Pharmacotherapy. Jul-Aug 2006;40(7-8):1336-1343.	Study design not included
23	Minshall ME, Oglesby AK, Wintle ME, Valentine WJ, Roze S, Palmer AJ. Estimating the long-term cost-effectiveness of exenatide in the United States: an adjunctive treatment for type 2 diabetes mellitus. Value in Health.	Study design not included
24	Nogid A, Pham DQ. Adjunctive therapy with pramlintide in patients with type 1 or type 2 diabetes	Study design not included

	Excluded studies	***Reasons for exclusion***
	mellitus. Pharmacotherapy. Nov 2006;26(11):1626-1640.	
25	Nonaka K KT, Sato A, Okuyama K, Fujimoto G, Hayashi N, Suzuki H, Hirayama Y, Stein P. Twelve-week efficacy and tolerability of sitagliptin, a dipeptidyl peptidase-IV (DPP-4) inhibitor, in Japanese patients with T2DM. Diabetes 2007;9:194-205.	Wrong publication type (letter, editorial, non-systematic review, case-report, case series)
26	Pratley RE, Salsali A. Inhibition of DPP-4: a new therapeutic approach for the treatment of type 2 diabetes. Current Medical Research & Opinion. Apr 2007;23(4):919-931.	Study design not included
27	Rosenstock J, Fonseca V. Missing the point: substituting exenatide for nonoptimized insulin: going from bad to worse! Diabetes Care. Nov 2007;30(11):2972-2973.	Wrong publication type (letter, editorial, non-systematic review, case-report, case series)
28	Rubin RR, Peyrot M. Assessing treatment satisfaction in patients treated with pramlintide as an adjunct to insulin therapy. Current Medical Research & Opinion. Aug 2007;23(8):1919-1929.	Study design not included
29	Ryan GJ, Jobe LJ, Martin R. Pramlintide in the treatment of type 1 and type 2 diabetes mellitus. Clinical Therapeutics. Oct 2005;27(10):1500-1512.	Study design not included
30	Salsali A, Pratley RE. Does addition of sitagliptin to metformin monotherapy improve glycemic control in patients with type 2 diabetes mellitus? Nature Clinical Practice Endocrinology & Metabolism. Jun 2007;3(6):450-451.	Wrong publication type (letter, editorial, non-systematic review, case-report, case series)
31	Sicat BL, Morgan LA. New therapeutic options for the management of diabetes. Consultant Pharmacist. Jan 2007;22(1):45-56.	Study design not included
32	Singh-Franco D, Robles G, Gazze D. Pramlintide acetate injection for the treatment of type 1 and type 2 diabetes mellitus. Clinical Therapeutics. Apr 2007;29(4):535-562.	Study design not included
33	Stephens JW, Bain SC. Safety and adverse effects associated with GLP-1 analogues. Expert Opinion on Drug Safety. Jul 2007;6(4):417-422.	Study design not included
34	Tang-Christensen M, Cowley MA. GLP-1 analogs: satiety without malaise? American Journal of Physiology - Regulatory Integrative & Comparative Physiology. Sep 2007;293(3):R981-982.	Population not included
35	Taylor K, Kim D, Nielsen LL, Aisporna M, Baron AD, Fineman MS. Day-long subcutaneous infusion of exenatide lowers glycemia in patients with type 2 diabetes. Hormone & Metabolic Research. Oct 2005;37(10):627-632.	Study design not included

	Excluded studies	***Reasons for exclusion***
36	Toft AD. American Diabetes Association - 67th Scientific Sessions: pros and cons of GLP-1 agonists and DPP-IV inhibitors. Idrugs. Sep 2007;10(9):606-609.	Wrong publication type (letter, editorial, non-systematic review, case-report, case series)
37	Triplitt C, Chiquette E. Exenatide: from the Gila monster to the pharmacy. Journal of the American Pharmacists Association: JAPhA. Jan-Feb 2006;46(1):44-52; quiz 53-45.	Wrong publication type (letter, editorial, non-systematic review, case-report, case series)
38	Viswanathan P, Chaudhuri A, Bhatia R, Al-Atrash F, Mohanty P, Dandona P. Exenatide therapy in obese patients with type 2 diabetes mellitus treated with insulin. Endocrine Practice. Sep-Oct 2007;13(5):444-450.	Study design not included
39	Webb DM, Wintle M, Malone JK. Exenatide effects on glucose metabolism and metabolic disorders common to overweight and obese patients with type 2 diabetes. Drug development Research. 2006;67:666-676.	Wrong publication type (letter, editorial, non-systematic review, case-report, case series)
40	Wysham C, Lush C, Zhang B, Maier H, Wilhelm K. Effect of pramlintide as an adjunct to basal insulin on markers of cardiovascular risk in patients with type 2 diabetes. *Current Medical Research & Opinion.* Jan 2008;24(1):79-85	Wrong outcome
41	Yoo BK, Triller DM, Yoo DJ. Exenatide: a new option for the treatment of type 2 diabetes. Annals of Pharmacotherapy. Oct 2006;40(10):1777-1784.	Study design not included

Appendix D. Abbreviations

A1c	hemoglobin A1c
AE	adverse event(s)
ANCOVA	analysis of covariance
ANOVA	analysis of variance
CI	confidence interval
CSII	continuous subcutaneous insulin infusion
d	day
dL	deciliter
g	gram
GIP	glucose-dependent insulinotropic peptide
GLP-1	glucagon-like peptide-1
ITT	intent-to-treat
L	liter
mcg	microgram
MDI	multiple dose injections
mg	milligram
mmol	millimole
N	total sample size
n	size of a subsample
SD	standard deviation
SE	standard error