# Drug Class Review

# Newer Drugs for the Treatment of Diabetes Mellitus

**Final Report**
**Evidence Tables**

**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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| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| **Aronne 2007**<br>US<br>placebo-controlled<br>Poor | 44 enrolled<br>25 weeks | Obese adults, 30-70 yrs with or without DM2; BMI 30-50 kg/m^2; lab values within normal limits; stable body weight 2 mos before screening; obese subjects with DM2 eligible if A1c ≤8% and not on OHA except for MET | Clinically significant cardiac disease, hepatic disease; BP > 160/95 mmHg; malignant disease requiring chemotherapy; psychiatric illness; eating disorders; gastrointestinal disorders; enrolled in or enrolling in a weight loss study; taking weight loss medications; any OHA except MET, steroids, or any drugs affecting GI motility | NR | Pramlintide (Symlin) | Type 2 Diabetes<br>Age, mean (SD): 48 (10)<br>% male: 19.71%<br>Race/ethnicity<br>White: 77%<br>Black: NR<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 23%<br>More than 1 race: NR<br>Hispanic: NR<br>Baseline A1c: NR<br>Baseline BMI: 37.9 | NR | |
| | | | | | Placebo | Type 2 Diabetes<br>Age, mean (SD): 49 (19)<br>% male: 19.4%<br>Race/ethnicity<br>White: 79%<br>Black: NR<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 21%<br>More than 1 race: NR<br>Hispanic: NR<br>Baseline A1c: NR<br>Baseline BMI: 37.6 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Total sample size<br>Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| **Aschner 2006**<br>Multinational<br>placebo-controlled<br>Fair | 741 enrolled<br>24 weeks | 18-75 years of age, on and not on an OHA were eligible. | DM1, unstable cardiac disease, significant renal impairment (CrCL<50ml/min), or elevated (more than 2-fold the upper limit of normal), alanine aminotransferase, or creatine phosphokinase. | NR | Sitagliptin 100 mg | Type 2 Diabetes<br>Age, mean (SD): 53.4 (9.5)<br>% male: 57.1%<br>Race/ethnicity<br>White: 51.3%<br>Black: 4.2%<br>Asian: 13.4%<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 6.7%<br>More than 1 race: NR<br>Hispanic: 24.4%<br>Baseline A1c: 8.0<br>Baseline BMI: 30.3 | Merck | Patients received counseling on exercise and a wt-maintenance diet consistent with ADA recommendations throughout the study. |
| | | | | | Sitagliptin 200 mg | Type 2 Diabetes<br>Age, mean (SD): 54.9 (10.1)<br>% male: 46.8%<br>Race/ethnicity<br>White: 52.8%<br>Black: 4.8%<br>Asian: 14.8%<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 6.4%<br>More than 1 race: NR<br>Hispanic: 21.2%<br>Baseline A1c: 8.1<br>Baseline BMI: 30.3 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | Placebo | Type 2 Diabetes<br>Age, mean (SD): 54.3 (10.1)<br>% male: 51.4%<br>Race/ethnicity<br>White: 50.2%<br>Black: 6.3%<br>Asian: 13.4%<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 4.7%<br>More than 1 race: NR<br>Hispanic: 25.3%<br>Baseline A1c: 8.0<br>Baseline BMI: 30.8 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| **Barnett 2007**<br>Europe, Mexico<br>active-control<br>Fair-poor | 141 enrolled<br>32 weeks | T2DM; > or = 30 yrs; receivingin stable doses of metformin > 1500mg/day or optimally effective dose of SU x 3 mos; A1c 7.1-11%; BMI 25-40 kg/m2; stable body weight (within 10%) >3 mos. | Not reported | NR | Exenatide + MET or SU | Type 2 Diabetes<br>Age, mean (SD): 54.5 ()<br>% male: 48.53%<br>Race/ethnicity<br>White: NR<br>Black: NR<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: NR<br>More than 1 race: NR<br>Hispanic: NR<br>Baseline A1c: 8.89<br>Baseline BMI: 31.3 | Eli Lilly | Crossover was at 16 weeks.<br><br>Despite significant improvements in A1c, the mean A1c at the study endpoint remained aboved the ADA target of <7%. |
| | | | | | Glargine+ MET or SU | Type 2 Diabetes<br>Age, mean (SD): 55.3 ()<br>% male: 45.71%<br>Race/ethnicity<br>White: NR<br>Black: NR<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: NR<br>More than 1 race: NR<br>Hispanic: NR<br>Baseline A1c: 9.0<br>Baseline BMI: 30.9 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Total sample size<br>Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| **Blonde 2006**<br>US<br>Open label extension<br>N/A | 974 enrolled<br>82 weeks | Patients who completed the 30-wk studies (Buse 2004, Kendall 2005, DeFronzo 2005) could participate in the open-label extension. All patients received exenatide 5 mcg Bid x4 wks then 10 mcg Bid. | Those randomized to placebo in the initial trials were not included | NR | Exenatide 10 mcg | Type 2 Diabetes<br>Age, mean (SD): 55 (10)<br>% male: 61%<br>Race/ethnicity<br>White: 74%<br>Black: 10%<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 4%<br>More than 1 race: NR<br>Hispanic: 12%<br>Baseline A1c: 8.4<br>Baseline BMI: 34 | Amylin Pharmaceuticals, Eli Lilly | Same study as Buse 2007 |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| **Buse 2004**<br>US<br>placebo-controlled<br>Fair | 377 enrolled<br>30 weeks | 22-76 yrs with DM2 on maximum SU-monotherapy ≥ 3 mos; FPG <240 mg/dL; BMI 27-45 kg/m^2; A1c 7.1-11.0%; stable wt x 3mos and no clinically relevant lab abnormality (>25% of normal values) | Used MET, TZDs, meglitinides, alpha-glucosidase inhibitors, insulin, or wt-loss drugs within the prior 3 mos; tx with corticosteroids, drugs known to affect GI motility, transplant meds, or any investigational drugs; evidence of clinically significant comorbidities | NR | Exenatide 10 mcg + SU | Type 2 Diabetes<br>Age, mean (SD): 56 (11)<br>% male: 57.4%<br>Race/ethnicity<br>White: 59.7%<br>Black: 16.3%<br>Asian: 1.6%<br>American Indian, Native Alaskan: 0.0%<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 0.8%<br>More than 1 race: NR<br>Hispanic: 21.7%<br>Baseline A1c: 8.6<br>Baseline BMI: NR | Eli Lilly & Amylin Pharmaceuticals | Included an acclimation period of 4 wks to minimize nausea for all arms including placebo (ie, started all meds at 5 mcg Bid dose); equivalent volumes of placebo were administered.<br><br>Randomization was stratified according to A1c values (< 9.0% and ≥9.0%).<br><br>All patients on max SU but dose of SU could be decreased by 50% increments based on hypoglycemic events.<br><br>Placebo 5 mcg and Placebo 10 mcg arms were combined for the analysis. |
| | | | | | Exenatide 5 mcg + SU | Type 2 Diabetes<br>Age, mean (SD): 55 (10)<br>% male: 59.2%<br>Race/ethnicity<br>White: 61.6%<br>Black: 16.8%<br>Asian: 1.6%<br>American Indian, Native Alaskan: 0.8%<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 0.8%<br>More than 1 race: NR<br>Hispanic: 18.4%<br>Baseline A1c: 8.5<br>Baseline BMI: NR | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | Placebo (combined) + SU | Type 2 Diabetes<br>Age, mean (SD): 55 (11)<br>% male: 62.6%<br>Race/ethnicity<br>White: 66.7%<br>Black: 9.8%<br>Asian: 1.6%<br>American Indian, Native Alaskan: 0.0%<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 0.8%<br>More than 1 race: NR<br>Hispanic: 21.1%<br>Baseline A1c: 8.7<br>Baseline BMI: NR | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| **Buse 2007**<br>U.S.<br>Open label extension<br>N/A | 974 enrolled<br>104 weeks | Patients who completed the 30-wk studies (Buse 2004, Kendall 2005, DeFronzo 2005) could participate in the open-label extension. All patients received exenatide 5 mcg Bid x4 wks then 10 mcg Bid. | NR | NR | Exenatide 10 mcg | Type 2 Diabetes<br>Age, mean (SD): 55 (10)<br>% male: 59%<br>Race/ethnicity<br>White: 74%<br>Black: 11%<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 3%<br>More than 1 race: NR<br>Hispanic: 12%<br>Baseline A1c: 8.4<br>Baseline BMI: 34 | Amylin Pharmaceuticals, Eli Lilly | Same population as Blonde 2007<br><br>Weight change at wk 104 was minimally correlated with baseline ALT (r= -0.09) or ALT change (r= 0.31) for the overall group.<br><br>The correlation between change in A1c and change in ALT were minimally correlated with those with elevated baseline ALT (r= 0.29)<br><br>When stratified by baseline ALT, those with elevated ALT at baseline lost more weight than those with normal ALT at baseline. Between-treatment difference: -1.4 kg (95% CI -2.7, -0.1), p=0.04<br><br>Exenatide was also associated with improved ALT and AST in those with elevated ALT and AST at baseline but had little to no effect in those with normal ALT and AST at baseline. Those with normal ALT and AST |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Total sample size<br>Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| **Charbonnel 2006**<br>multinational<br>placebo-controlled<br>Fair | 701 enrolled<br>24 weeks | 18-78 yrs with DM2; A1c 7%-10%; taking MET monotherapy of at least 1500 mg/day. Patients not currently on any OHA, were taking any OHA in monotherapy, or were taking MET in combination with another OHA were also eligible | DM1, insulin use within 8 wks of screening, renal function impairment inconsistent with the use of MET or a FPG >14.4 mmol/l (260mg/dl). | NR | Sitagliptin 100mg + MET ≥ 1.5 g | Type 2 Diabetes<br>Age, mean (SD): 54.4 (10.4)<br>% male: 55.8%<br>Race/ethnicity<br>White: 63.1%<br>Black: 6.7%<br>Asian: 10.6%<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 4.1%<br>More than 1 race: NR<br>Hispanic: 15.5%<br>Baseline A1c: 8.0<br>Baseline BMI: 30.9 | Merck | Randomized in a 1:2 ratio (placebo vs. sitagliptin) |
| | | | | | Placebo + MET ≥ 1.5 g | Type 2 Diabetes<br>Age, mean (SD): 54.7 (9.7)<br>% male: 59.5%<br>Race/ethnicity<br>White: 67.1%<br>Black: 5.9%<br>Asian: 11.0%<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 4.2%<br>More than 1 race: NR<br>Hispanic: 11.8%<br>Baseline A1c: 8.0<br>Baseline BMI: 31.5 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| **Davis 2007**<br>U.S.<br>active-control<br>Fair-poor | 51 enrolled<br>16 weeks | Between 30 - 75 yrs; DM2 > or = 2 yrs; treated with 1 of following > or =3 mos to 12 yrs: 1 or 2x daily NPH insulin, once daily insulin glargine, 1 or 2 x daily ultralente insulin or an insulin mixture; all pts on oral antidiabetes regimens of an immediate or extended release MET and/or a SU for at least 3 mos or a fixed-dose SU/MET combo therapy; HbA1c < or = 10.5%, BMI > 27 and < 40 kg/m2, history of stable wt | More than 3 episodes of severe hypoglycemia w/in 6 mos; prescription drug use for wt loss w/in 3 mos; previously received exenatide or GLP-1 analogues | Metformin: 43%<br>SU: 8%<br>Insulin: 100% | Exenatide (Byetta) 10 mcg BID + oral antidiabetes | Type 2 Diabetes<br>Age, mean (SD): 54 (8)<br>% male: 45.45%<br>Race/ethnicity<br>White: NR<br>Black: NR<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: NR<br>More than 1 race: NR<br>Hispanic: NR<br>Baseline A1c: 8.0<br>Baseline BMI: 33 | Eli Lilly & Amylin | This was a substitution study of exenatide for insulin.<br><br>Patients randomized 2:1 to exenatide or insulin reference therapy.<br><br>Patients continued oral antidiabetes meds, diet, and exercise regimens.<br><br>SU dose decreased by ~ 50%.<br><br>Exenatide acclimation period of 4 wks at 5 mcg BID before fixed dose of exenatide to 10 mcg BID for 12 wks. |
| | | | | | Insulin + oral diabetes meds | Type 2 Diabetes<br>Age, mean (SD): 52 (8)<br>% male: 50%<br>Race/ethnicity<br>White: NR<br>Black: NR<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: NR<br>More than 1 race: NR<br>Hispanic: NR<br>Baseline A1c: 8.3<br>Baseline BMI: 35 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| **DeFronzo 2005**<br>U.S.<br>placebo-controlled<br>Fair | 336 enrolled<br>30 weeks | DM2 treated with metformin monotherapy > or = 1,500 mg/day for 3 mos; FPG < 13.3 mmol/l; BMI 27 - 45 kg/m2; HbA1c 7.1 - 11.0%; weight stable (+/-10%) for 3 mos before screening w/no clinically significant (for DM2 population) abnormal lab test values (>25% outside normal) | Use of sulfonylureas, meglitinides, TZDs, alpha-glucosidase inhibitors, exogenous insulin, weight loss drugs, corticosteroids, drugs known to affect gastrointestinal motility, transplantation medications, or any investigational drug or evidence of clinically significant comorbid conditions for 3 mos before screening | Metformin: 100%<br>SU: 0%<br>Insulin: 0%<br>antihypertensives = ACEs only, hyperlipidemia drugs = hydroxymethylglutaryl-CoA reductase inhibitors only | Exenatide (Byetta) 10 mcg BID + metformin | Type 2 Diabetes<br>Age, mean (SD): 52 (11)<br>% male: 60.2%<br>Race/ethnicity<br>White: 79.6%<br>Black: 8.8%<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 3.5%<br>More than 1 race: NR<br>Hispanic: 8%<br>Baseline A1c: 8.2<br>Baseline BMI: NR | Pharmaceutical (Amylin & Eli Lilly) | Exenatide acclimation period of 4 wks at 5 mcg BID before fixed dose of exenatide to 10 mcg BID or kept at 5 mcg BID. |
| | | | | | Exenatide (Byetta) 5mcg BID + metformin | Type 2 Diabetes<br>Age, mean (SD): 53 (11)<br>% male: 51.8%<br>Race/ethnicity<br>White: 77.3%<br>Black: 10.9%<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 4.6%<br>More than 1 race: NR<br>Hispanic: 7.3%<br>Baseline A1c: 8.3<br>Baseline BMI: NR | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | Placebo + metformin | Type 2 Diabetes<br>Age, mean (SD): 54 (9)<br>% male: 59.3%<br>Race/ethnicity<br>White: 72.6%<br>Black: 13.3%<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 3.5%<br>More than 1 race: NR<br>Hispanic: 10.6%<br>Baseline A1c: 8.2<br>Baseline BMI: NR | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| **Edelman 2006**<br>US<br>placebo-controlled<br>Fair | 296 enrolled<br>29 weeks | > or = 18 yrs, insulin use > 1 yr, A1C 7.5-9%, and no severe hypoglycemia for 6 mos before screening. Most were on intensive insulin therapy. | Clinically significant comorbid conditions including gastroparesis; using medications affecting gastrointestinal motility, or using oral antidiabetic or antiobesity agents. | NR | Combined Pramlintide arms + insulin | Type 1 Diabetes<br>Age, mean (SD): 41 (14)<br>% male: 48.65%<br>Race/ethnicity<br>White: 90.5%<br>Black: NR<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 9.5%<br>More than 1 race: NR<br>Hispanic: NR<br>Baseline A1c: 8.1<br>Baseline BMI: 27.7 | NR; Amylin Pharmaceuticals? | |
| | | | | | Pramlintide 30mcg + insulin | Type 1 Diabetes<br>Age, mean (SD): 40 (11)<br>% male: 36.59%<br>Race/ethnicity<br>White: 85.4%<br>Black: NR<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 14.6%<br>More than 1 race: NR<br>Hispanic: NR<br>Baseline A1c: 8.2<br>Baseline BMI: 27 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Total sample size<br>Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | Pramlintide 60mcg + insulin | Type 1 Diabetes<br>Age, mean (SD): 41 (16)<br>% male: 53.47%<br>Race/ethnicity<br>White: 92%<br>Black: NR<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 8%<br>More than 1 race: NR<br>Hispanic: NR<br>Baseline A1c: 8.1<br>Baseline BMI: 28.1 | | |
| | | | | | Placebo+insulin | Type 1 Diabetes<br>Age, mean (SD): 41 (12)<br>% male: 40.82%<br>Race/ethnicity<br>White: 91%<br>Black: NR<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 9%<br>More than 1 race: NR<br>Hispanic: NR<br>Baseline A1c: 8.1<br>Baseline BMI: 27.8 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| **Goldstein 2007**<br>multinational<br>placebo-controlled<br>Fair | 1091 enrolled<br>24 weeks | 18-78 with DM2 either on or not on OHA | DM1, unstable cardiac disease, significant renal impairment (CrCL < 60 mL/min), > 2x upper limit of normal for ALT and AST; those who had A1c >11% or FG > 280 mg/dL after run-in were not eligible for randomization | NR | MET 1000 mg Bid | Type 2 Diabetes<br>Age, mean (SD): 53.2 (9.6)<br>% male: 45.05%<br>Race/ethnicity<br>White: 58.2%<br>Black: 4.9%<br>Asian: 5.5%<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 9.9%<br>More than 1 race: NR<br>Hispanic: 21.4%<br>Baseline A1c: 8.7<br>Baseline BMI: 32.2 | Merck | Patients with baseline A1c >11% were enrolled into a single-arm open-label study. This was not included in our review since it did not meet study inclusion criteria. |
| | | | | | MET 500 mg Bid | Type 2 Diabetes<br>Age, mean (SD): 53.4 (10.2)<br>% male: 48.9%<br>Race/ethnicity<br>White: 47.8%<br>Black: 6.6%<br>Asian: 7.7%<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 7.7%<br>More than 1 race: NR<br>Hispanic: 30.2%<br>Baseline A1c: 8.9<br>Baseline BMI: 32.1 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | Sitagliptin 100 mg | Type 2 Diabetes<br>Age, mean (SD): 53.3 (10.2)<br>% male: 51.96%<br>Race/ethnicity<br>White: 52%<br>Black: 6.1%<br>Asian: 3.4%<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 9.5%<br>More than 1 race: NR<br>Hispanic: 29.1%<br>Baseline A1c: 8.9<br>Baseline BMI: 31.2 | | |
| | | | | | Sitagliptin 50 mg + MET 1000 mg Bid | Type 2 Diabetes<br>Age, mean (SD): 53.3 (9.6)<br>% male: 42.31%<br>Race/ethnicity<br>White: 52.2%<br>Black: 7.7%<br>Asian: 6%<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 7.1%<br>More than 1 race: NR<br>Hispanic: 26.9%<br>Baseline A1c: 8.7<br>Baseline BMI: 32.4 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | Sitagliptin 50 mg + MET 500 mg Bid | Type 2 Diabetes<br>Age, mean (SD): 54.1 (10.0)<br>% male: 55.26%<br>Race/ethnicity<br>White: 53.7%<br>Black: 6.8%<br>Asian: 4.7%<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 5.8%<br>More than 1 race: NR<br>Hispanic: 28.9%<br>Baseline A1c: 8.8<br>Baseline BMI: 32.1 | | |
| | | | | | Placebo | Type 2 Diabetes<br>Age, mean (SD): 53.6 (10)<br>% male: 52.84%<br>Race/ethnicity<br>White: 46%<br>Black: 9.7%<br>Asian: 6.8%<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 10.8%<br>More than 1 race: NR<br>Hispanic: 26.7%<br>Baseline A1c: 8.7<br>Baseline BMI: 32.5 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Total sample size<br>Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| **Goldstein 2007**<br><br>Open-label cohort<br><br>Poor | 117 enrolled<br>weeks | Those who had A1c > 11% or fasting glucose > 280 mg/dL after run-in could participate | NR | NR | Sitagliptin 50 mg + MET 1000 mg Bid | Type 2 Diabetes<br>Age, mean (SD): 53 (NR)<br>% male: 57.26%<br>Race/ethnicity<br>White: 38%<br>Black: NR<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: NR<br>More than 1 race: NR<br>Hispanic: 46%<br>Baseline A1c: 11.2<br>Baseline BMI: 31 | NR | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Total sample size<br>Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| **Heine 2005**<br>Multinational<br>active-control<br>Fair | 551 enrolled<br>26 weeks | 30-75 yr with DM2 on max effective doses of MET and SU for at least 3-mos before screening; A1c 7.0%-10.0%; BMI 25-45 kg/m2; stable body wt for >3 mos before screening | Participation in any study within 30 days before screening; >3 severe hypoglycemia within 6 mos; undergoing treatment malignant disease other than basal-or squamous-cell skin cancer; cardiac disease that was NYHA class III or IV; Scr >1.5 mg/dL for men or >1.2 mg/dL for women; liver disease; receiving >2 wks of systemic glucocorticoid therapy or received such therapy within 2 wks before screening; used any prescription weight loss drug within 3 mos; tx with insulin within 3 mos; tx with TZDs within 4 mos; tx with alpha-glucosidase inhibitors or meglitinides within 3 mos | NR | Exenatide + MET/SU | Type 2 Diabetes<br>Age, mean (SD): 59.8 (8.8)<br>% male: 55%<br>Race/ethnicity<br>White: 79.8%<br>Black: 0.7%<br>Asian: 1.8%<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 2.1%<br>More than 1 race: NR<br>Hispanic: 15.6%<br>Baseline A1c: 8.2<br>Baseline BMI: 31.4 | Amylin & Eli Lilly | Exenatide arm received exenatide 5 mcg Bid x 4 weeks then increased to 10 mcg Bid for the remainder of the study.<br><br>Unknown what % achieved 10 mcg Bid by the end of the study period (NR). |
| | | | | | Glargine + MET/SU | Type 2 Diabetes<br>Age, mean (SD): 58 (9.5)<br>% male: 56.6%<br>Race/ethnicity<br>White: 80.5%<br>Black: 1.1%<br>Asian: 0.7%<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 2.6%<br>More than 1 race: NR<br>Hispanic: 15%<br>Baseline A1c: 8.3<br>Baseline BMI: 31.3 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Total sample size<br>Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| **Hermansen 2007**<br>Denmark, USA<br>placebo-controlled<br>Fair | 441 enrolled<br>24 weeks | 18-75 yrs with DM 2 (i) already taking glimepiride alone or in combo with MET (ii) taking another OHA in monotherapy or in dual- or triple-combination therapy or (iii) patients not taking any OHAs over the prior 8 wks | DM1; treated with insulin within 8 wks of the screening; had CrCL <45 ml/min or <60 ml/min if on MET; or hx of hypersensitivity, intolerance or a contraindication to the use of glimepiride, other SU agents, MET or pioglitazone | NR | Entire Placebo cohort | Type 2 Diabetes<br>Age, mean (SD): 56.5 (9.6)<br>% male: 53.42%<br>Race/ethnicity<br>White: 63.9%<br>Black: 5.5%<br>Asian: 11.4%<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 4.6%<br>More than 1 race: NR<br>Hispanic: 14.6%<br>Baseline A1c: 8.34<br>Baseline BMI: 30.7 | Merck | Patients could be given open-label rescue therapy (pioglitazone 30 mg/day) if FPG were not at prespecified goals. These patients were discontinued from the study if they were on rescue therapy for >4 wks and had an FPG consistently >200m/dL |
| | | | | | Entire Sitagliptin cohort | Type 2 Diabetes<br>Age, mean (SD): 55.6 (9.6)<br>% male: 52.7%<br>Race/ethnicity<br>White: 61.3%<br>Black: 4.5%<br>Asian: 9.9%<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 6.8%<br>More than 1 race: NR<br>Hispanic: 17.6%<br>Baseline A1c: 8.34<br>Baseline BMI: 31.2 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | Sitagliptin + Glimepiride | Type 2 Diabetes<br>Age, mean (SD): 54.4 (10.3)<br>% male: 52.83%<br>Race/ethnicity<br>White: 57.5%<br>Black: 6.6%<br>Asian: 5.7%<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 5.7%<br>More than 1 race: NR<br>Hispanic: 24.5%<br>Baseline A1c: 8.42<br>Baseline BMI: 31.0 | | |
| | | | | | Sitagliptin + Glimepiride + MET | Type 2 Diabetes<br>Age, mean (SD): 56.6 (8.8)<br>% male: 52.59%<br>Race/ethnicity<br>White: 64.7%<br>Black: 2.6%<br>Asian: 13.8%<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 7.8%<br>More than 1 race: NR<br>Hispanic: 11.2%<br>Baseline A1c: 8.27<br>Baseline BMI: 31.3 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | Placebo + Glimepiride | Type 2 Diabetes<br>Age, mean (SD): 55.2 (10.2)<br>% male: 54.72%<br>Race/ethnicity<br>White: 55.7%<br>Black: 2.8%<br>Asian: 11.3%<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 6.6%<br>More than 1 race: NR<br>Hispanic: 23.6%<br>Baseline A1c: 8.43<br>Baseline BMI: 30.7 | | |
| | | | | | Placebo + Glimepiride + MET | Type 2 Diabetes<br>Age, mean (SD): 57.7 (8.9)<br>% male: 52.21%<br>Race/ethnicity<br>White: 71.7%<br>Black: 8.0%<br>Asian: 11.5%<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 2.7%<br>More than 1 race: NR<br>Hispanic: 6.2%<br>Baseline A1c: 8.26<br>Baseline BMI: 30.7 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| **Hollander 2003**<br>US<br>placebo-controlled<br>Fair | 656 enrolled<br>52 weeks | > or = 18 yrs with DM2; A1c > or = 8%; no severe hypo- or hyperglycemic symptoms for > or = 2 wks before screening; stable body wt, stable daily insulin dose for > or = 2 mos. Patients using stable doses of MET or SU with their insulin for > or = 3 mos | Hx diabetic ketoacidosis consistent with DM1; hx clinically significant cardiovascular, pulmonary, central nervous system, gastrointestinal (including gastroparesis), renal or hematologic diseases; eating disorders; alcohol or drug abuse; acute illness within 2 wks, and chronic use of systemic corticosteroids, dexfenfluramine, drugs that affect gastrointestinal motility. | NR | Pramlintide 120 mcg + adjunct insulin | Type 2 Diabetes<br>Age, mean (SD): 56.9 (10.5)<br>% male: 48%<br>Race/ethnicity<br>White: 73%<br>Black: 13%<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 1%<br>More than 1 race: NR<br>Hispanic: 13%<br>Baseline A1c: 9.0<br>Baseline BMI: 34.1 | NR | Initially, subjects were randomized to 4-treatment arms but the pramlinitide 60 mcg Tid arm was later excluded from both efficacy and safety analyses as another study noted decreased effectiveness with this dose. |
| | | | | | Pramlintide 90 mcg + adjunct inuslin | Type 2 Diabetes<br>Age, mean (SD): 57.0 (10.2)<br>% male: 49%<br>Race/ethnicity<br>White: 77%<br>Black: 14%<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 1%<br>More than 1 race: NR<br>Hispanic: 8%<br>Baseline A1c: 9.1<br>Baseline BMI: 33.8 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | Placebo + adjunct insulin | Type 2 Diabetes<br>Age, mean (SD): 56.4 (10.2)<br>% male: 52%<br>Race/ethnicity<br>White: 75%<br>Black: 12%<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 1%<br>More than 1 race: NR<br>Hispanic: 12%<br>Baseline A1c: 9.3<br>Baseline BMI: 33.7 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Total sample size<br>Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| **Hollander 2003**<br>NR<br>Pooled analysis<br>N/A | 26 weeks | Included data from all subjects from Hollander 2003 and Gottlieb 1999-abstract) who had been randomized to either placebo or pramlintide 120 mg Bid with A1c 7-8.5%. | NR | NR | Pramlintide 120 mcg + insulin | Type 2 Diabetes<br>Age, mean (SD): 58 (9)<br>% male: 51%<br>Race/ethnicity<br>White: 90%<br>Black: 5%<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 2%<br>More than 1 race: NR<br>Hispanic: 3%<br>Baseline A1c: 8.0<br>Baseline BMI: 33.0 | NR | |
| | | | | | Placebo + insulin | Type 2 Diabetes<br>Age, mean (SD): 58 (10)<br>% male: 50%<br>Race/ethnicity<br>White: 86%<br>Black: 10%<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 3%<br>More than 1 race: NR<br>Hispanic: 1%<br>Baseline A1c: 8.0<br>Baseline BMI: 30.7 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| **Hollander 2004**<br>N/A<br>Pooled analysis<br>N/A | 26 weeks | Included data from patients (from Hollander 2003 and Gottlieb 1999-abstract) with BMI >25 kg/m2 and had been randomized to pramlintide 120 mcg Bid or placebo. | NR | NR | Pramlintide + insulin | Type 2 Diabetes<br>Age, mean (SD): 57 (10)<br>% male: 47%<br>Race/ethnicity<br>White: 83%<br>Black: 8%<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 10%<br>More than 1 race: NR<br>Hispanic: NR<br>Baseline A1c: 9.2<br>Baseline BMI: 34.1 | NR | |
| | | | | | Placebo + insulin | Type 2 Diabetes<br>Age, mean (SD): 56 (10)<br>% male: 49%<br>Race/ethnicity<br>White: 83%<br>Black: 8%<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 9%<br>More than 1 race: NR<br>Hispanic: NR<br>Baseline A1c: 9.4<br>Baseline BMI: 33.6 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Total sample size<br>Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| **Karl**<br>**2007**<br>US<br>Open-label cohort<br>N/A | 24 weeks | > or = 18 yrs with DM2 on insulin therapy with or without OHA for at least 6 months. A1c 7-11%; unable to achieve adequate glycemic control with insulin therapy. | Clinically significant thyroid, cardiac, hepatic or renal disease, malignancy or either current or expected use of antiobesity agents. | NR | Pramlintide 120mcg + insulin | Type 2 Diabetes<br>Age, mean (SD): 54 (11)<br>% male: 51%<br>Race/ethnicity<br>White: 82%<br>Black: NR<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 18%<br>More than 1 race: NR<br>Hispanic: NR<br>Baseline A1c: 8.3<br>Baseline BMI: 38.6 | NR | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| **Kendall 2005**<br>US<br>placebo-controlled<br>Fair | 733 enrolled<br>30 weeks | 22–77 yrs with DM 2 on MET and SU; FPG <13.3 mmol/L; BMI 27–45 kg/m2; A1C 7.5–11.0%; MET dose > or =1500 mg/day and SU dose at least at the maximally effective dose x 3 mos before screening; stable body wt x 3 mos before screening; no clinically relevant abnormal laboratory test | Clinically significant comorbidities; used TZDs, meglitinides, alpha-glucosidase inhibitors, insulin, or wt loss drugs within prior 3 mos; therapy with corticosteroids, drugs known to affect GI motility, transplant meds, or any investigational drug. | NR | Exenatide 10 mcg + MET/SU | Type 2 Diabetes<br>Age, mean (SD): 55 (10)<br>% male: 59.3%<br>Race/ethnicity<br>White: 66.4%<br>Black: 11.6%<br>Asian: 2.9%<br>American Indian, Native Alaskan: 0.8%<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 1.7%<br>More than 1 race: NR<br>Hispanic: 16.6%<br>Baseline A1c: 8.5<br>Baseline BMI: 34 | Eli Lilly & Amylin Pharmaceuticals | *Note: Typo in Figure-1 for the total number randomized. It states 734 but in the text it states 733 (this matches the other parts in Figure-1).<br><br>After randomization, there was a 4 -week acclimation period for all arms to minimize nausea that is associated with exenatide. All groups (including placebo) started at 5 mcg Bid dose then the appropriate arms increased to 10 mcg; Volumes of injectable placebo were equal to the active arms. |
| | | | | | Exenatide 5 mcg + MET/SU | Type 2 Diabetes<br>Age, mean (SD): 55 (9)<br>% male: 59.2%<br>Race/ethnicity<br>White: 69.0%<br>Black: 10.2%<br>Asian: 2.9%<br>American Indian, Native Alaskan: 0.0%<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 2.0%<br>More than 1 race: NR<br>Hispanic: 15.9%<br>Baseline A1c: 8.5<br>Baseline BMI: 33 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Total sample size<br>Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | Placebo (combined) + MET/SU | Type 2 Diabetes<br>Age, mean (SD): 56 (10)<br>% male: 55.9%<br>Race/ethnicity<br>White: 68.4%<br>Black: 12.1%<br>Asian: 1.6%<br>American Indian, Native Alaskan: 0.4%<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 1.6%<br>More than 1 race: NR<br>Hispanic: 15.8%<br>Baseline A1c: 8.5<br>Baseline BMI: 34 | | |
| **King 2006**<br>U.S.<br>retrospective uncontrolled<br>Poor | 200 enrolled<br>12 weeks | NR | NR | Metformin: 40.5%<br>SU: 28%<br>Insulin: 21%<br>Values are for those who continued treatment, n=130. Mean diabetic concurrent med dosages reduced significantly (p<0.05). | Exenatide (Byetta) | Diabetes type not reported<br>Age: NR<br>Gender: NR<br>Race/ethnicity<br>White: NR<br>Black: NR<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: NR<br>More than 1 race: NR<br>Hispanic: NR<br>Baseline A1c: NR<br>Baseline BMI: NR | NR | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Total sample size<br>Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| **Klonoff 2008**<br>NR<br>Pooled analysis<br>N/A | weeks | This is a post-hoc analysis of the open-lebel extension arms from 3 studies (Buse, DeFronzo, Kendall).<br><br>3 yr and 3.5 yr completer cohorts were defined as all patients who had th opportunity to achieve 3-or 3.5 yrs of exenatide exposure regardless of their treatment arm in the original placebo trials. | N/A--post hoc analysis (see primary literature) | NR | 3 year completers | Type 2 Diabetes<br>Age, mean (SD): 58 (10)<br>% male: 64%<br>Race/ethnicity<br>White: 83%<br>Black: 10%<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 1%<br>More than 1 race: NR<br>Hispanic: 6%<br>Baseline A1c: 8.2<br>Baseline BMI: 33.5 | NR | N/A--post hoc analysis (see primary literature) |
| | | | | | 3.5 year completers | Type 2 Diabetes<br>Age, mean (SD): 57 (9)<br>% male: 68%<br>Race/ethnicity<br>White: 84%<br>Black: 9%<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 1%<br>More than 1 race: NR<br>Hispanic: 7%<br>Baseline A1c: 8.2<br>Baseline BMI: 33.4 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| **Maggs 2003**<br>NR<br>Pooled analysis<br>N/A | 52 weeks | Included all patients categorized as Caucasian, African American, and Hispanic who were randomized to placebo or pramlintide 120 mcg Bid or 150 mcg Tid. | Other ethnic groups were not included because they comprised less than 1.5% of the study population. | NR | Pramlintide (African American) + insulin | Type 2 Diabetes<br>Age, mean (SD): 56 (9)<br>% male: 46%<br>Race/ethnicity<br>White: NA%<br>Black: NA%<br>Asian: NA%<br>American Indian, Native Alaskan: NA%<br>Native Hawaiian/Other Pacific Islander:NA%<br>Other: NA%<br>More than 1 race: NA%<br>Hispanic: NA%<br>Baseline A1c: 9.7<br>Baseline BMI: 33.5 | Amylin Pharmaceuticals | |
| | | | | | Pramlintide (Caucasian) + insulin | Type 2 Diabetes<br>Age, mean (SD): 57 (9)<br>% male: 58%<br>Race/ethnicity<br>White: NA%<br>Black: NA%<br>Asian: NA%<br>American Indian, Native Alaskan: NA%<br>Native Hawaiian/Other Pacific Islander:NA%<br>Other: NA%<br>More than 1 race: NA%<br>Hispanic: NA%<br>Baseline A1c: 8.9<br>Baseline BMI: 32.8 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Total sample size<br>Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | Pramlintide (Hispanic) + insulin | Type 2 Diabetes<br>Age, mean (SD): 54 (12)<br>% male: 32%<br>Race/ethnicity<br>White: NA%<br>Black: NA%<br>Asian: NA%<br>American Indian, Native Alaskan: NA%<br>Native Hawaiian/Other Pacific Islander:NA%<br>Other: NA%<br>More than 1 race: NA%<br>Hispanic: NA%<br>Baseline A1c: 9.3<br>Baseline BMI: 33.4 | | |
| | | | | | Placebo (African American) + insulin | Type 2 Diabetes<br>Age, mean (SD): 58 (9)<br>% male: 29%<br>Race/ethnicity<br>White: NA%<br>Black: NA%<br>Asian: NA%<br>American Indian, Native Alaskan: NA%<br>Native Hawaiian/Other Pacific Islander:NA%<br>Other: NA%<br>More than 1 race: NA%<br>Hispanic: NA%<br>Baseline A1c: 9.2<br>Baseline BMI: 31.6 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | Placebo (Caucasian) + insulin | Type 2 Diabetes<br>Age, mean (SD): 58 (10)<br>% male: 60%<br>Race/ethnicity<br>White: NA%<br>Black: NA%<br>Asian: NA%<br>American Indian, Native Alaskan: NA%<br>Native Hawaiian/Other Pacific Islander:NA%<br>Other: NA%<br>More than 1 race: NA%<br>Hispanic: NA%<br>Baseline A1c: 9.1<br>Baseline BMI: 31.5 | | |
| | | | | | Placebo (Hispanic) + insulin | Type 2 Diabetes<br>Age, mean (SD): 51 (10)<br>% male: 50%<br>Race/ethnicity<br>White: NA%<br>Black: NA%<br>Asian: NA%<br>American Indian, Native Alaskan: NA%<br>Native Hawaiian/Other Pacific Islander:NA%<br>Other: NA%<br>More than 1 race: NA%<br>Hispanic: NA%<br>Baseline A1c: 9.6<br>Baseline BMI: 33.7 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Total sample size<br>Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| **Nauck**<br>**2007**<br>Multinational<br>active-control<br>Fair-poor | 1172 enrolled<br>52 weeks | 18-78 yrs with DM2 not currently on OHA, taking any OHA in monotherapy or takling MET in combination with another OHA | DM1, insulin use within 8 wks of screening, renal function impairment inconsistent with the use of MET or a FPG >15.0 mmol/l (270 mg/dl) | NR | Glipizide + MET | Type 2 Diabetes<br>Age, mean (SD): 56.6 (9.8)<br>% male: 61.3%<br>Race/ethnicity<br>White: 74.3%<br>Black: 6.0%<br>Asian: 8.4%<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 3.4%<br>More than 1 race: NR<br>Hispanic: 7.9%<br>Baseline A1c: 7.6<br>Baseline BMI: 31.3 | Merck | Patients received counseling on exercise and a diet consistent with ADA recommendations throughout the study.<br><br>*The number 'analyzed' is based on the per-protocol-population. Per-protocol-cohort includes randomized patients who completed all 52 wks of treatment and did not have any reasons for exclusion. |
| | | | | | Sitagliptin +MET | Type 2 Diabetes<br>Age, mean (SD): 56.8 (9.3)<br>% male: 57.1%<br>Race/ethnicity<br>White: 73.5%<br>Black: 7.0%<br>Asian: 8.5%<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 3.7%<br>More than 1 race: NR<br>Hispanic: 7.3%<br>Baseline A1c: 7.7<br>Baseline BMI: 31.2 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Total sample size<br>Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| **Nauck 2007**<br>Multinational<br>active-control<br>Fair | 505 enrolled<br>52 weeks | 30-75 yrs with suboptimal glycemic control despite receiving optimally effective MET and SU for at least 3 mos; A1c7%-11.0%; BMI 25-40 kg/m2; hx stable body wt for ≥3 mos | >3 episodes of severe hypoglycaemia within 6 mos prior to screening; used any prescription drug to promote wt loss within 3 mos; treated with insulin, TZDs, alpha-glucosidase inhibitors or meglitinides for > 2 wks within 3 mos. | NR | Biphasic Aspart + MET/SU | Type 2 Diabetes<br>Age, mean (SD): 58 (9)<br>% male: 49%<br>Race/ethnicity<br>White: NR<br>Black: NR<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: NR<br>More than 1 race: NR<br>Hispanic: NR<br>Baseline A1c: 8.6<br>Baseline BMI: 30.2 | Eli Lilly & Amylin | Patients in biphasic aspart group: the decision to adjust insulin therapy was ultimately left up to each investigator's clinical judgement.<br><br>If frequent nausea developed in exenatide 10 mcg Bid group, patients had the option to decrease to 5 mcg Bid. |
| | | | | | Exenatide + MET/SU | Type 2 Diabetes<br>Age, mean (SD): 59 (9)<br>% male: 53%<br>Race/ethnicity<br>White: NR<br>Black: NR<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: NR<br>More than 1 race: NR<br>Hispanic: NR<br>Baseline A1c: 8.6<br>Baseline BMI: 30.6 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Total sample size<br>Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| **Nelson**<br>**2007**<br>US<br><br>open label extension<br><br>N/A | 127 enrolled<br>30 weeks | Patients who completed the 28 day prior dose-response study.<br><br>18-75 years with DM2 treated with diet and exercise or metformin; A1c 6.5-9.0%, BMI 25-45 kg/m2; FPG <200 mg/dL (<240 mg/dL for diet and exercise pts);stable wt | Use of meglitinides, SUs, TZDs, alpha-glucosidase inhibitors, wt loss drugs, exogenous insulin, drugs affecting gastrointestinal motility, corticosteroids, transplantation meds, investigational drugs, or co-morbid conditions of a clinically significant nature | Metformin: 76% | Exenatide (Byetta) | Type 2 Diabetes<br>Age, mean (SD): 52 (11)<br>% male: 44.09%<br>Race/ethnicity<br>White: 76%<br>Black: 8%<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 9%<br>More than 1 race: NR<br>Hispanic: 6%<br>Baseline A1c: 7.5<br>Baseline BMI: 35 | Amylin Pharmaceuticals, Eli Lilly | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| **Nonaka 2007**<br>Japan<br>placebo-controlled<br>Fair | 152 enrolled<br>12 weeks | 20-69 yrs with DM2; A1c 6.5%-10% for those not on OHA, and A1c 6%-9% for those on OHA monotherapy. | DM1; use of insulin or pioglitazone in the 8 wks prior to screening; unstable cardiac disease, elevated Scr, elevations more than 2-times the upper limit of normal for ALT, AST or CPK | NR | Sitagliptin (Januvia) | Type 2 Diabetes<br>Age, mean (SD): 55.6 (8.6)<br>% male: 60%<br>Race/ethnicity<br>White: NR<br>Black: NR<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: NR<br>More than 1 race: NR<br>Hispanic: NR<br>Baseline A1c: 7.5<br>Baseline BMI: 25.2 | Banyu Pharmaceutical and Merck | Patients received diet and exercise counseling through the study. |
| | | | | | Placebo | Type 2 Diabetes<br>Age, mean (SD): 55.0 (8.0)<br>% male: 66%<br>Race/ethnicity<br>White: NR<br>Black: NR<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: NR<br>More than 1 race: NR<br>Hispanic: NR<br>Baseline A1c: 7.7<br>Baseline BMI: 25.1 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| **Ratner 2002**<br>U.S.<br>placebo-controlled<br>Fair-Poor | 538 enrolled<br>52 weeks | 26-76 yrs with DM2 requiring insulin at least 6 mos; A1c 7.5-13%, body weight within 60% of desirable weight. Insulin doses stable prior to randomization; no symptoms of severe hypo-or hyperglycemia for at least 2 wks. | Clinically significant hx of ischemic heart disease, uncontrolled hypertension, gastrointestinal disease (including diabetic gastroparesis), renal disease, or unstable diabetic retinopathy; treatment with drugs known to affect gastrointestinal motility or glucose metabolism. | NR | Pramlintide (Symlin) 150 mcgTID+Insulin | Type 2 Diabetes<br>Age, mean (SD): 56.4 (8.9)<br>% male: 56%<br>Race/ethnicity<br>White: 78%<br>Black: 13%<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 1%<br>More than 1 race: NR<br>Hispanic: 8%<br>Baseline A1c: 9.2<br>Baseline BMI: 31.1 | NR (but 6 of 8 authors are from Amylin Pharma) | Although analyses are reported as ITT, it is unclear how missing data were handled LOCF?) |
| | | | | | Pramlintide (Symlin) 30mcg TID+Insulin | Type 2 Diabetes<br>Age, mean (SD): 57.5 (10.8)<br>% male: 56%<br>Race/ethnicity<br>White: 77%<br>Black: 11%<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 3%<br>More than 1 race: NR<br>Hispanic: 9%<br>Baseline A1c: 9<br>Baseline BMI: 31.1 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | Pramlintide (Symlin) 75mcgTID+Insulin | Type 2 Diabetes<br>Age, mean (SD): 56.5 (10.3)<br>% male: 57%<br>Race/ethnicity<br>White: 76%<br>Black: 15%<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 1%<br>More than 1 race: NR<br>Hispanic: 8%<br>Baseline A1c: 9.3<br>Baseline BMI: 30.4 | | |
| | | | | | Placebo+Insulin | Type 2 Diabetes<br>Age, mean (SD): 55.5 (10.6)<br>% male: 62%<br>Race/ethnicity<br>White: 81%<br>Black: 8%<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 1%<br>More than 1 race: NR<br>Hispanic: 10%<br>Baseline A1c: 9.2<br>Baseline BMI: 30.4 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| **Ratner 2004**<br>U.S., & Canada<br>placebo-controlled<br>Fair-poor | 651 enrolled<br>52 weeks | 16-76 yrs, requiring insulin for at least 1-year with an A1C > or = 8% at screening; stable body weight; stable daily insulin use for > 2 mos; no severe hypo-or hyperglycemic symptoms for at least 2 wks | Clinically significant cardiovascular, pulmonary or central nervous system, gastrointestinal (including diabetic gastroparesis), renal or hematological systems, as well as eating disorders; acute febrile illness; alcohol/drug abuse or use of medications that affect gastrointestinal motility. | NR | Pramlintide 60 mcg QID+insulin | Type 1 Diabetes<br>Age, mean (SD): 41.9 (13.1)<br>% male: 52%<br>Race/ethnicity<br>White: 91%<br>Black: NR<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 9%<br>More than 1 race: NR<br>Hispanic: NR<br>Baseline A1c: 8.9<br>Baseline BMI: 26.8 | NR | Pramlintide 90mcg Tid arm was excluded from the efficacy analyses due to increased rate of AE from another study, however, data for this arm was kept for safety analysis. |
| | | | | | Pramlintide 60 mcg TID+insulin | Type 1 Diabetes<br>Age, mean (SD): 39.2 (13.1)<br>% male: 52%<br>Race/ethnicity<br>White: 92%<br>Black: NR<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 8%<br>More than 1 race: NR<br>Hispanic: NR<br>Baseline A1c: 8.9<br>Baseline BMI: 26.4 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Total sample size<br>Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | Pramlintide 90 mcg Tid+Insulin | Type 1 Diabetes<br>Age, mean (SD): 41 (12.8)<br>% male: 47%<br>Race/ethnicity<br>White: 89%<br>Black: NR<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 11%<br>More than 1 race: NR<br>Hispanic: NR<br>Baseline A1c: 8.9<br>Baseline BMI: 26.3 | | |
| | | | | | Placebo+insulin | Type 1 Diabetes<br>Age, mean (SD): 41.3 (13.6)<br>% male: 53%<br>Race/ethnicity<br>White: 90%<br>Black: NR<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 10%<br>More than 1 race: NR<br>Hispanic: NR<br>Baseline A1c: 9<br>Baseline BMI: 26.5 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| **Ratner 2005**<br>USA<br>Pooled analysis<br>N/A | 477 enrolled<br>26 weeks | Included data from patients with A1c 7.0%-8.5% who were taking pramlintide 30 or 60 mcg Tid-Qid (from Fineman 1999-abstract, Ratner 2004, Whitehouse 2002). Included data up to wk 26. | NR | NR | Pramlintide (Symlin)+Insulin | Type 1 Diabetes<br>Age, mean (SD): 41 (12)<br>% male: 50%<br>Race/ethnicity<br>White: 97%<br>Black: NR<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 3%<br>More than 1 race: NR<br>Hispanic: NR<br>Baseline A1c: 7.9<br>Baseline BMI: 25.7 | NR | |
| | | | | | Placebo+Insulin | Type 1 Diabetes<br>Age, mean (SD): 42 (13)<br>% male: 55%<br>Race/ethnicity<br>White: 94%<br>Black: NR<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 6%<br>More than 1 race: NR<br>Hispanic: NR<br>Baseline A1c: 7.9<br>Baseline BMI: 25.8 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| **Ratner 2006**<br>US<br>Open label extension<br>N/A | 150 enrolled<br>82 weeks | Patients who completed the 30-wk DeFronzo 2005 study could participate in the open-label extension. All patients received exenatide 5 mcg Bid x4 wks then 10 mcg Bid. | Those who were randomized to the placebo arm in the primary trial. | NR | Exenatide 10 mcg | Type 2 Diabetes<br>Age, mean (SD): 54 (10)<br>% male: 69%<br>Race/ethnicity<br>White: 86%<br>Black: 9%<br>Asian: 4%<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: NR<br>More than 1 race: NR<br>Hispanic: 1%<br>Baseline A1c: 8.1<br>Baseline BMI: 34 | Amylin Pharmaceuticals, Eli Lilly and Company | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| **Raz 2006**<br>Multinational<br>placebo-controlled<br>Fair | 521 enrolled<br>18 weeks | 18-75 years of age with DM2 not currently on OHA therapy or patients on OHA monotherapy (or dual oral combination therapy in low doses) who could be taken off their OHAs during the run-in period | DM1, insulin therapy, significnt hepatic or renal disease, hepatic transaminase or creatine phosphokinase (CK) levels > or = to 2 times the upper limit of normal, FPG >15 mmol/l (270mg/dl) and BMI<20kg/m2 or >43kg/m2 | NR | Sitagliptin 100 mg | Type 2 Diabetes<br>Age, mean (SD): 54.5 (10.0)<br>% male: 53.7%<br>Race/ethnicity<br>White: 69.3%<br>Black: 7.8%<br>Asian: 3.9%<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 1.0%<br>More than 1 race: NR<br>Hispanic: 18.0%<br>Baseline A1c: 8.0<br>Baseline BMI: 31.8 | Merck | Patients received counseling on a diet consistent wtih ADA recommendations |
| | | | | | Sitagliptin 200 mg | Type 2 Diabetes<br>Age, mean (SD): 55.4 (9.2)<br>% male: 50.5%<br>Race/ethnicity<br>White: 70.9%<br>Black: 5.3%<br>Asian: 3.4%<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 1.5%<br>More than 1 race: NR<br>Hispanic: 18.9%<br>Baseline A1c: 8.1<br>Baseline BMI: 32.0 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | Placebo | Type 2 Diabetes<br>Age, mean (SD): 55.5 (10.1)<br>% male: 62.7%<br>Race/ethnicity<br>White: 61.8%<br>Black: 10.9%<br>Asian: 4.5%<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 2.7%<br>More than 1 race: NR<br>Hispanic: 20.0%<br>Baseline A1c: 8<br>Baseline BMI: 32.5 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| **Raz 2008**<br>Multinational<br>placebo-controlled<br>Fair | 190 enrolled<br>30 weeks | 18-78 yrs currently on metformin monotherapy or any other single oral agent, or being treated with metformin in combination with another oral agent; A1c of 8-11% after run-in periods. | Received insulin therapy within 8 weeks prior to screening; treatment with TZD or incretin mimetics (exenatide) within 12 weeks; T1DM; BMI <20 or > 40 kg/m2; FPG < 7.2 or > 15.6 mmol/L | NR | Sitagliptin + MET | Type 2 Diabetes<br>Age, mean (SD): 53.6 (9.5)<br>% male: 51.04%<br>Race/ethnicity<br>White: 42%<br>Black: 3%<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 1%<br>More than 1 race: 22%<br>Hispanic: 32%<br>Baseline A1c: 9.3<br>Baseline BMI: 30.1 | Merck | To avoid confounding influence of rescue therapy on efficacy, the last results prior to initiation were carried forward for efficacy analyses.<br><br>Patients were discontinued from the study if they were on rescue medications (ie, glipizde) for at least 2 weeks and had a FPG consistently >11.1 mmol/L.<br><br>Selective outcome reporting (primary efficacy analyses were based on results at week 18 rather than 30 weeks which was a secondary endpoint). |
| | | | | | Placebo + MET | Type 2 Diabetes<br>Age, mean (SD): 56.1 (9.5)<br>% male: 41.49%<br>Race/ethnicity<br>White: 47%<br>Black: 1%<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 2%<br>More than 1 race: 25%<br>Hispanic: 25%<br>Baseline A1c: 9.1<br>Baseline BMI: 30.4 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| **Riddle 2006**<br>US<br>Open label extension<br>N/A | 518 enrolled<br>82 weeks | Patients who completed the 30-wk studies (Buse 2004, Kendall 2005) could participate in the open-label extension. All patients received exenatide 5 mcg Bid x4 wks then 10 mcg Bid. | Those who had been randomized to placebo in the primary trials were excluded | NR | Exenatide 10 mcg | Type 2 Diabetes<br>Age, mean (SD): 57 (10)<br>% male: 61%<br>Race/ethnicity<br>White: 75%<br>Black: 11%<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 2%<br>More than 1 race: NR<br>Hispanic: 12%<br>Baseline A1c: 8.4<br>Baseline BMI: 34 | Amylin Pharmaceuticals, Eli Lilly | This is a subset from Buse 2007 and Blond 2006. |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| **Riddle 2007**<br>US<br>placebo-controlled<br>Fair | 212 enrolled<br>16 weeks | 25-75 yrs with DM2 not achieving glycemic control with glargine with or without OHA; A1c >7 and ≤ 10.5%; BMI 25-45; on glargine for ≥ 3 mos with a stable dose for ≥ 1 mo and stable dose of OHA for ≥ 2 mos | Hx of unaware hypoglycemia or severe hypoglycemia during preceeding 6 mos; participating in a wt loss program; using antiobesity agents; gastroparesis or any other significant medical condition | NR | Pramlintide > 8.5% + glargine (+/- OHA) | Type 2 Diabetes<br>Age, mean (SD): 53 (9)<br>% male: 38.1%<br>Race/ethnicity<br>White: 71.4%<br>Black: NR<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 28.6%<br>More than 1 race: NR<br>Hispanic: NR<br>Baseline A1c: 9.4<br>Baseline BMI: 36 | NR | Dose acclimation period: patients started pramlintide at 60 mcg and increased to 120 mcg over 3-7 day period if no significant nausea occurred. |
| | | | | | Pramlintide ≤ 8.5% + glargine (+/- OHA) | Type 2 Diabetes<br>Age, mean (SD): 56 (8)<br>% male: 50.79%<br>Race/ethnicity<br>White: 74.6%<br>Black: NR<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 25.4%<br>More than 1 race: NR<br>Hispanic: NR<br>Baseline A1c: 7.9<br>Baseline BMI: 35 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | Total Placebo + glargine (+/- OHA) | Type 2 Diabetes<br>Age, mean (SD): 55 (10)<br>% male: 51.89%<br>Race/ethnicity<br>White: 72.0%<br>Black: NR<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 28.0%<br>More than 1 race: NR<br>Hispanic: NR<br>Baseline A1c: 8.5<br>Baseline BMI: 35 | | |
| | | | | | Total Pramlintide + glargine (+/- OHA) | Type 2 Diabetes<br>Age, mean (SD): 55 (9)<br>% male: 45.71%<br>Race/ethnicity<br>White: 73.0%<br>Black: NR<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 27.0%<br>More than 1 race: NR<br>Hispanic: NR<br>Baseline A1c: 8.5<br>Baseline BMI: 35 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Total sample size<br>Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | Placebo >8.5% + glargine (+/- OHA) | Type 2 Diabetes<br>Age, mean (SD): 56 (9)<br>% male: 41.67%<br>Race/ethnicity<br>White: 77.1%<br>Black: NR<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 22.9%<br>More than 1 race: NR<br>Hispanic: NR<br>Baseline A1c: 9.3<br>Baseline BMI: 35 | | |
| | | | | | Placebo ≤ 8.5% + glargine (+/- OHA) | Type 2 Diabetes<br>Age, mean (SD): 55 (11)<br>% male: 60.34%<br>Race/ethnicity<br>White: 69%<br>Black: NR<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 31%<br>More than 1 race: NR<br>Hispanic: NR<br>Baseline A1c: 7.7<br>Baseline BMI: 35 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| **Rosenstock 2006**<br>multinational<br>placebo-controlled<br>Fair | 353 enrolled<br>24 weeks | > or = 18 years of age with DM2 eligible whether taking an OHA or not. | DM1 or ketoacidosis; treatment with insulin within 8 wks of screening; moderate renal dysfunction (CrCL <45 mL/min); history of hypersensitivity, intolerance, or a contraindication to TZDs. | NR | Sitagliptin + Pioglitazone | Type 2 Diabetes<br>Age, mean (SD): 55.6 (10.4)<br>% male: 53.1%<br>Race/ethnicity<br>White: 72.6%<br>Black: 6.3%<br>Asian: 5.7%<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 3.4%<br>More than 1 race: NR<br>Hispanic: 12.0%<br>Baseline A1c: 8.1<br>Baseline BMI: 90.9 | Merck | It was unclear if outcome assessors were masked for harms-related outcomes. |
| | | | | | Placebo + Pioglitazone | Type 2 Diabetes<br>Age, mean (SD): 56.9 (11.1)<br>% male: 57.9%<br>Race/ethnicity<br>White: 72.5%<br>Black: 6.7%<br>Asian: 2.8%<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 5.6%<br>More than 1 race: NR<br>Hispanic: 12.4%<br>Baseline A1c: 8.0<br>Baseline BMI: 86.4 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| **Scott 2007**<br>Multinational<br>active-control<br>Fair | 743 enrolled<br>12 weeks | 21-75 yrs with DM2, either on OHA monotherapy (except TZDs) with A1C 6%-9% or not currently on a OHA with A1C 6.5%-10% | DM1; unstable cardiac disease, active liver or gall bladder disease; CrCL <60ml/min, or elevated (>2 fold the upper limit of normal) ALT, AST or creatinine phosphokinase. | NR | Glipizide | Type 2 Diabetes<br>Age, mean (SD): 54.7 (10.7)<br>% male: 56.9%<br>Race/ethnicity<br>White: 61%<br>Black: 3.3%<br>Asian: 4.9%<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 24.4%<br>More than 1 race: 6.5%<br>Hispanic: NR<br>Baseline A1c: 7.9<br>Baseline BMI: 30.6 | Merck | This was a dose-range finding study.<br><br>Randomization was stratified by OHA status at baseline and HbA1c > 8.5% or ≤ 8.5%.<br><br>Patients received counseling on diet and exercise consistent with ADA recommendations throughout the study duration. 5-days prior to each study visit, patients were asked to collect 7-point home glucose measurements. |
| | | | | | Sitagliptin (Januvia) 12.5 mg | Type 2 Diabetes<br>Age, mean (SD): 56.2 (9)<br>% male: 48%<br>Race/ethnicity<br>White: 63.4%<br>Black: 4.9%<br>Asian: 4.9%<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 21.1%<br>More than 1 race: 5.7%<br>Hispanic: NR<br>Baseline A1c: 7.9<br>Baseline BMI: 30.5 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | Sitagliptin (Januvia) 25mg | Type 2 Diabetes<br>Age, mean (SD): 55.6 (9)<br>% male: 57.7%<br>Race/ethnicity<br>White: 61%<br>Black: 8.9%<br>Asian: 4.9%<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 18.7%<br>More than 1 race: 6.5%<br>Hispanic: NR<br>Baseline A1c: 7.9<br>Baseline BMI: 31.4 | | |
| | | | | | Sitagliptin (Januvia) 50 mg | Type 2 Diabetes<br>Age, mean (SD): 55.1 (9.8)<br>% male: 52.4%<br>Race/ethnicity<br>White: 69.4%<br>Black: 4.8%<br>Asian: 2.4%<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 16.1%<br>More than 1 race: 7.3%<br>Hispanic: NR<br>Baseline A1c: 7.8<br>Baseline BMI: 30.4 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | Sitagliptin (Januvia) 5mg | Type 2 Diabetes<br>Age, mean (SD): 55.1 (9.5)<br>% male: 49.6%<br>Race/ethnicity<br>White: 68.8%<br>Black: 6.4%<br>Asian: 5.6%<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 12.8%<br>More than 1 race: 6.4%<br>Hispanic: NR<br>Baseline A1c: 7.9<br>Baseline BMI: 30.8 | | |
| | | | | | Placebo | Type 2 Diabetes<br>Age, mean (SD): 55.3 (9.7)<br>% male: 62.4%<br>Race/ethnicity<br>White: 66.4%<br>Black: 8.0%<br>Asian: 2.4%<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 16.0%<br>More than 1 race: 7.2%<br>Hispanic: NR<br>Baseline A1c: 7.9<br>Baseline BMI: 31.6 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| **Scott 2008**<br>Multinational<br>active-control<br>Fair | 273 enrolled<br>18 weeks | 18–75 yrs; taking metformin monotherapy ≥1500 mg/day for at least 10 weeks prior; had inadequate glycaemic control defined by A1c 7-11% | Type 1 diabetes; insulin use within 8 wks; any contraindications for use of TZDs or metformin; impaired renal function (CrCl <60 ml/min), alanine aminotransferase (ALT) or aspartate aminotransferase levels more than 2x the upper limit of normal; or FPG >270 mg/dl prior to randomization. | NR | Rosiglitazone + MET monotherapy | Type 2 Diabetes<br>Age, mean (SD): 54.8 (10.5)<br>% male: 63.22%<br>Race/ethnicity<br>White: 59%<br>Black: NR<br>Asian: 38%<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 3%<br>More than 1 race: NR<br>Hispanic: NR<br>Baseline A1c: 7.7<br>Baseline BMI: 30.4 | Merck | Change in weight was not assessed in this trial.<br><br>For Patients with a baseline HbA1c ≤ 7.5% had placebo-subtracted HbA1c reductions of -0.46% (95% CI: -0.63 to -0.28) and -0.41% (95% CI -0.58 to -0.23) in the sitagliptin and rosiglitazone groups, respectively, compared with reductions of -0.63% (95% CI -1.02 to -0.24) and -0.78% (-1.17 to -0.39), respectively, in patients with a baseline HbA1c > 7.5%. |
| | | | | | Sitagliptin + MET monotherapy | Type 2 Diabetes<br>Age, mean (SD): 55.2 (9.8)<br>% male: 55.32%<br>Race/ethnicity<br>White: 61%<br>Black: NR<br>Asian: 38%<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 1%<br>More than 1 race: NR<br>Hispanic: NR<br>Baseline A1c: 7.8<br>Baseline BMI: 30.3 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | Placebo + MET monotherapy | Type 2 Diabetes<br>Age, mean (SD): 55.3 (9.3)<br>% male: 58.7%<br>Race/ethnicity<br>White: 61%<br>Black: NR<br>Asian: 39%<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 0%<br>More than 1 race: NR<br>Hispanic: NR<br>Baseline A1c: 7.7<br>Baseline BMI: 30.0 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| **Whitehouse 2002**<br>US<br>placebo-controlled<br>Fair-poor | 480 enrolled<br>52 weeks | 16-70 yrs of age; DM1 for > or = 1 year, had C-peptide concentration < or =1.0 nl/mL; A1c 7-13%; no symptoms of severe hypoglycemia and hyperglycemia for 2 wks and not adjusted their daily insulin dose by more than +/- 10% for 1 wk before the study. | Clinically significant hx of ischemic heart disease, hypertension, gastrointestinal disease (including diabetic gastroparesis), renal disease, and unstable diabetic retinopathy; treatment with drugs that affect gastrointestinal motility or glucose metabolism. | NR | Pramlintide 30 mcg + 60 mcg (combined) + insulin | Type 1 Diabetes<br>Age, mean (SD): 40.3 (11.6)<br>% male: 55%<br>Race/ethnicity<br>White: 96%<br>Black: NR<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 5%<br>More than 1 race: NR<br>Hispanic: NR<br>Baseline A1c: 8.7<br>Baseline BMI: 25.2 | NR; Amylin Pharmaceuticals? | At week 20, those in pramlintide arm whose A1c decreased by < 1% to week 13 were re-randomized to either 30mcg Qid or 60mcg Qid. Re-randomization performed by an unblinded 3rd party. |
| | | | | | Placebo + insulin | Type 1 Diabetes<br>Age, mean (SD): 40.4 (12.1)<br>% male: 55%<br>Race/ethnicity<br>White: 92%<br>Black: NR<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 8%<br>More than 1 race: NR<br>Hispanic: NR<br>Baseline A1c: 8.9<br>Baseline BMI: 25.8 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Total sample size<br>Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| **Whitehouse 2002**<br>US<br>Open label extension<br>N/A | 236 enrolled<br>104 weeks | same as DB, RCT | same as DB, RCT | NR | Original Pramlintide arm + insulin | Type 1 Diabetes<br>Age, mean (SD): 42.7 (10.8)<br>% male: 59%<br>Race/ethnicity<br>White: 97%<br>Black: NR<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 3%<br>More than 1 race: NR<br>Hispanic: NR<br>Baseline A1c: 8.3<br>Baseline BMI: 25.4 | NR; Amylin Pharmaceuticals? | |
| | | | | | Switched to pramlintide from placebo + insulin | Type 1 Diabetes<br>Age, mean (SD): 44.7 (11.7)<br>% male: 56%<br>Race/ethnicity<br>White: 95%<br>Black: NR<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 6%<br>More than 1 race: NR<br>Hispanic: NR<br>Baseline A1c: 8.7<br>Baseline BMI: 26.3 | | |

## Evidence Table 1. Baseline characteristics of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Total sample size Follow-up duration | Inclusion criteria | Exclusion criteria | Hypoglycemic medications | Intervention | Population | Funder | Comments |
|---|---|---|---|---|---|---|---|---|
| **Zinman 2007**<br>Canada, Spain, U.S.<br>placebo-controlled<br>Fair | 233 enrolled<br>16 weeks | 21-75 yrs with DM2 on stable dose of TZD for at least 4 mos before screening, TZD alone or in combo with a stable dosage of MET (no min required) for 30 days; A1c 7.1-10.0%; BMI 25-45 kg/m2; stable body wt for at least 3 mos | NR | NR | Exenatide 10 mcg | Type 2 Diabetes<br>Age, mean (SD): 55.6 (10.8)<br>% male: 53.7%<br>Race/ethnicity<br>White: 85.1%<br>Black: NR<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 14.9%<br>More than 1 race: NR<br>Hispanic: NR<br>Baseline A1c: 7.9<br>Baseline BMI: 64.0 | Eli Lilly & Amylin | Lifestyle interventions were not included in the study protocol.<br><br>Exenatide patients received fixed 5 mcg doses BID for 4 wks, followed by 10 mcg doses BID for 12 wks.<br><br>At baseline for exenatide: TZDs-alone: 28/121 (23.1%); TZD-MET: 93/121 (76.9%); mean MET- dose: 1804 mg |
| | | | | | Placebo | Type 2 Diabetes<br>Age, mean (SD): 56.6 (10.2)<br>% male: 57.1%<br>Race/ethnicity<br>White: 82.1%<br>Black: NR<br>Asian: NR<br>American Indian, Native Alaskan: NR<br>Native Hawaiian/Other Pacific Islander:NR<br>Other: 17.9%<br>More than 1 race: NR<br>Hispanic: NR<br>Baseline A1c: 7.9<br>Baseline BMI: 34.0 | | |

## Evidence Table 2. Outcomes of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Outcome | Intervention | N | Result |
|---|---|---|---|---|
| **Aronne 2007** US placebo-controlled Poor | Weight, Kg 16 weeks | Pramlintide (Symlin) | N=44 | ITT-LOCF population for DM2 subgroup<br>Change from baseline: -2.4 (SE 0.9), p<0.01 vs. placebo |
| | | Placebo | N=44 | ITT-LOCF population for DM2 subgroup<br>Estimated from graph<br>Change from baseline: 0.0 |
| **Aschner 2006** Multinational placebo-controlled Fair | FPG, mmol/l 24 weeks | Sitagliptin 100 mg | N=234 | Change from baseline: -0.7 (95% CI -1.0, -0.4); p<0.001 vs. placebo --> -12.6 mg/dL |
| | | Sitagliptin 200 mg | N=244 | Change from baseline: -0.9 (95% CI -1.2, -0.7); p<0.001 vs. placebo --> -16 mg/dL |
| | | Placebo | N=247 | Change from baseline: 0.3 (95% CI -0.0, 0.5) --> +5.4 mg/dL |
| | HbA1c, percent 24 weeks | Sitagliptin 100 mg | N=229 | Change from baseline: -0.61 (95% CI -0.74, -0.49); p <0.001 vs. placebo |
| | | Sitagliptin 200 mg | N=238 | Change from baseline: -0.76 (95% CI -0.88, -0.64); p<0.001 vs. placebo |
| | | Placebo | N=244 | Change from baseline: 0.18 (95% CI 0.06, 0.30) |
| | PPG or random glucose, mmol/l | Sitagliptin 100 mg | N=201 | For 2hr PPG from meal tolerance test<br>Change from baseline: -2.7 (95% CI -3.2, -2.2); p<0.001 vs. placebo --> -48.6 mg/dL |
| | | Sitagliptin 200 mg | N=205 | For 2-hr PPG from meal tolerance test<br>Change from baseline: -3.1 (95% CI -3.6, -2.6); p<0.001 vs. placebo --> -64.8 mg/dL |
| | | Placebo | N=204 | For 2hr PPG for meal tolerance test<br>Change from baseline: -0.1 (95% CI -0.6, 0.4) -->-1.8 mg/dL |

## Evidence Table 2. Outcomes of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Outcome | Intervention | N | Result |
|---|---|---|---|---|
| **Barnett 2007**<br>Europe, Mexico<br>active-control<br>Fair-poor | FPG, mmol/L<br>32 weeks | Exenatide + MET or SU | N=68 | Change from baseline: -2.9 (SE 0.2), p<0.001 vs. baseline<br>5.5% achieved a FPG <5.6 mmol/L at 32 weeks |
| | | Glargine+ MET or SU | N=70 | Change from baseline: -4.1 (SE 0.2), p<0.001 vs. baseline<br>18.5% achieved a FPG <5.6 mmol/L at 32 weeks vs. exenatide, p=0.032 |
| | HbA1c, percent<br>32 weeks | Exenatide + MET or SU | N=68 | Change from baseline: -1.36 (SE 0.09), p<0.001 vs. baseline |
| | | Glargine+ MET or SU | N=70 | Change from baseline: -1.36 (SE 0.09), p<0.001 |
| | Weight, Kg<br>32 weeks | Exenatide + MET or SU | N=68 | Change from baseline: -2.2 (SE 0.4), p<0.001 vs. glargine |
| | | Glargine+ MET or SU | N=70 | Change from baseline: +2.3 (SE 0.4)<br>Subgroup: weight was almost unchanged for those on glargine/MET compared with weight gain observed in those on glargine/SU. |

## Evidence Table 2. Outcomes of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Outcome | Intervention | N | Result |
|---|---|---|---|---|
| **Buse 2004**<br>US | FPG, mmol/L<br>30 weeks | Exenatide 10 mcg + SU | N=129 | Change from baseline: -0.6 (SE 0.3), p<0.05 vs placebo --> -11 mg/dL |
| | | Exenatide 5 mcg + SU | N=125 | Change from baseline: -0.3 (SE 0.2) -->-5 mg/dL |
| | | Placebo (combined) + SU | N=123 | Change from baseline: +0.4 (SE 0.3) --> +7 mg/dL |
| placebo-controlled | HbA1c, percent<br>30 weeks | Exenatide 10 mcg + SU | N=83 | Stratified by A1c < 9%<br>Change from baseline: -0.65 (SE 0.12), p< 0.01 vs placebo |
| Fair | | Exenatide 10 mcg + SU | N=46 | Stratified by A1c >9%<br>Change from baseline: -1.22 (SE 0.19), p<0.05 vs placebo |
| | | Exenatide 10 mcg + SU | N=129 | Change from baseline: -0.86% (SE 0.11), p< or = 0.0002 vs. placebo |
| | | Exenatide 5 mcg + SU | N=79 | Stratified by A1c < 9%<br>Change from baseline: -0.39 (SE 0.12), p< 0.01 vs placebo |
| | | Exenatide 5 mcg + SU | N=46 | Stratified by A1c >9%<br>Change from baseline: -0.58 (SE 0.24), p<0.05 vs placebo |
| | | Exenatide 5 mcg + SU | N=125 | Change from baseline: -0.46% (SE 0.12), p< or = 0.0002 vs. placebo |
| | | Placebo (combined) + SU | N=77 | Stratified by baseline A1c < 9%<br>Change from baseline: +0.11 (SE 0.12) |
| | | Placebo (combined) + SU | N=46 | Stratified by baseline A1c > 9%<br>Change from baseline: +0.13 (SE 0.17) |
| | | Placebo (combined) + SU | N=123 | Change from baseline: +0.12% (SE 0.09) |
| | Weight, Kg<br>30 weeks | Exenatide 10 mcg + SU | N=129 | Change from baseline: -1.6 (SE 0.3), p<0.05 vs placebo |
| | | Exenatide 5 mcg + SU | N=125 | Change from baseline: -0.9 (SE 0.3), p>0.05 (NSD) vs placebo |
| | | Placebo (combined) + SU | N=123 | Change from baseline: -0.6 (SE 0.3) |

## Evidence Table 2. Outcomes of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Outcome | Intervention | N | Result |
|---|---|---|---|---|
| **Charbonnel 2006** | FPG, mmol/L<br>24 weeks | Placebo + MET ≥ 1.5 g | N=226 | Change from baseline: 0.5 (95% CI 0.2, 0.8) --> 9 mg/dL |
| multinational | HbA1c, percent<br>24 weeks | Sitagliptin 100mg + MET ≥ 1.5 g | N=453 | Change from Baseline: -0.67 (95% CI -0.77, -0.57); p<0.001 vs. placebo |
| | | Placebo + MET ≥ 1.5 g | N=224 | Change from baseline: -0.02 (95% CI -0.15, 0.10) |
| placebo-controlled | PPG or random glucose, mmol/L | Sitagliptin 100mg + MET ≥ 1.5 g | N=387 | 2hr PPG<br>Change from Baseline: -3.4 (95% CI -3.9, -3.0) --> -61 mg/dL, p<0.001 vs. placebo |
| Fair | | Placebo + MET ≥ 1.5 g | N=182 | 2hr PPG<br>Change from baseline: -0.6 (95% CI -1.2, -0.1) --> -11 mg/dL |
| **Davis 2007** | HbA1c, percent<br>16 weeks | Exenatide (Byetta) 10 mcg BID + oral antidiabetes | N=29 | Mean change +0.3, SD 1.5; NS compared with baseline or between grps |
| U.S. | | Insulin + oral diabetes meds | N=16 | Mean change -0.1, SD 0.7; NS compared with baseline or between grps |
| active-control | Weight, Kg<br>16 weeks | Exenatide (Byetta) 10 mcg BID + oral antidiabetes | N=29 | Mean change -4.2, SE 3.0; p<0.001 compared with baseline; p<0.001 between groups at endpoint |
| Fair-poor | | Insulin + oral diabetes meds | N=16 | Mean change +0.5, SE 1.7; NS compared with baseline; p<0.001 between groups |

## Evidence Table 2. Outcomes of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Outcome | Intervention | N | Result |
|---|---|---|---|---|
| **DeFronzo 2005** U.S. placebo-controlled Fair | FPG, mmol/L (mg/dL) | Exenatide (Byetta) 10 mcg BID + metformin | N=113 | -0.6 +/- 0.2 mmol/L (-10.1 +/- 4.4 mg/dL), p=0.0001<br>End of study difference from placebo averaged -1.4 mmol/L (-25 mg/dL), p=0.0001 |
| | | Exenatide (Byetta) 5mcg BID + metformin | N=110 | -0.4 +/- 0.3 mmol/L (-7.2 +/- 4.6 mg/dL), p<0.005 |
| | FPG, mmol/L (mg/dL) | Placebo + metformin | N=113 | +0.8 +/- 0.2 mmol/L (+14.4 +/- 4.2 mg/dL) |
| | HbA1c, percent 30 weeks | Exenatide (Byetta) 10 mcg BID + metformin | N=103 | Subgroup analysis of baseline HbA1c > 7 %<br>40 % reached HbA1c < or = 7 %, greater than placebo arm p< 0.01 |
| | | Exenatide (Byetta) 5mcg BID + metformin | N=100 | Subgroup analysis w/baseline HbA1c > 7 %<br>27 % reached HbA1c < or = 7 %, greater than placebo arm p< 0.01 |
| | | Placebo + metformin | N=100 | Subgroup analysis baseline HbA1c > 7 %<br>11 % reached HbA1c < or = 7 % |
| | HbA1c, percent up to 30 weeks | Exenatide (Byetta) 10 mcg BID + metformin | N=113 | Dose-dependent reduction vs placebo (p<0.001)<br>Change from baseline -0.8 (SE 0.1%) |
| | | Exenatide (Byetta) 5mcg BID + metformin | N=110 | At wk 4 reductions from baseline compared with placebo (p<0.0005)<br>At wk 30 dose-dependent reduction compared with placebo (p<0.001)<br>At wk 30 change from baseline -0.4 +/-0.1% |
| | | Placebo + metformin | N=113 | Change from baseline +0.1 (SE 0.1%) |
| | PPG, mmol/L up to 30 weeks | Exenatide (Byetta) 10 mcg BID + metformin | N=16 | At wk 4 meal cohort values reduced compared with placebo, p = 0.006<br>Mean AUC averaged 34 % lower than baseline and pattern continued to wk 30, p = 0.004 |
| | | Exenatide (Byetta) 5mcg BID + metformin | N=7 | At wk 4 meal cohort values reduced compared with placebo, p = 0.006<br>Mean AUC averaged 34 % lower than baseline and pattern continued to wk 30, p = 0.03 |
| | | Placebo + metformin | N=13 | At wk 4 meal cohort values mean AUC averaged 9 % lower than baseline and pattern continued to wk 30 |

## Evidence Table 2. Outcomes of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Outcome | Intervention | N | Result |
|---|---|---|---|---|
| | Weight, Kg up to 30 weeks | Exenatide (Byetta) 10 mcg BID + metformin | N=113 | Change -2.8 (SE 0.5) vs placebo p < or = 0.001<br>also stratifed by baseline BMI < 30 and > or = 30 kg/m2, reductions still observed |
| | | Exenatide (Byetta) 5mcg BID + metformin | N=110 | Change -1.6 (SE 0.4), vs placebo p < or = 0.05<br>Stratifed by baseline BMI < 30 and > or = 30 kg/m2, reductions still observed |
| | | Placebo + metformin | N=113 | Change from baseline -0.3 (SE 0.3) |
| **Edelman 2006**<br>US<br><br>placebo-controlled<br>Fair | HbA1c, percent 29 weeks | Combined Pramlintide arms + insulin | N=148 | Change from baseline: -0.5% (95% CI -0.61,-0.33) |
| | | Pramlintide 30mcg + insulin | NR | NR for this arm |
| | | Pramlintide 60mcg + insulin | NR | NR for this arm |
| | | Placebo+insulin | N=147 | Change from baseline: -0.5% (95% CI -0.63,-0.35) |
| | PPG or random glucose, mmol/L | Combined Pramlintide arms + insulin | N=33 | For MTT group at 3hrs<br>Change from baseline: -1.0 |
| | | Placebo+insulin | N=44 | For MTT group at 3hrs<br>Change from baseline: -1.8 |
| | Weight, Kg 29 weeks | Combined Pramlintide arms + insulin | N=148 | Change from baseline: -1.3 (SE 0.30), p< 0.001 |
| | | Pramlintide 30mcg + insulin | NR | NR for this arm |
| | | Pramlintide 60mcg + insulin | NR | NR for this arm |
| | | Placebo+insulin | N=147 | Change from baseline: +1.2 (SE 0.24) |

## Evidence Table 2. Outcomes of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Outcome | Intervention | N | Result |
|---|---|---|---|---|
| **Goldstein 2007** multinational placebo-controlled Fair | FPG, mg/dL 24 weeks | MET 1000 mg Bid | N=179 | Change from baseline: -29.3 (95% CI -35.9, -22.6) Change from placebo: -35.1 (95% CI -44.6, -25.6), p≤ 0.001 for between-group difference |
| | | MET 500 mg Bid | N=179 | Change from baseline: -27.3 (95% CI -34.0, -20.7) Change from placebo: -33.1 (95% CI -42.7, -23.6), p≤0.001 for between-group difference |
| | | Sitagliptin 100 mg | N=178 | Change from baseline: -17.5 (95% CI -24.1, -10.8) Change from placebo: -23.3 (95% CI -32.8, -13.8), p ≤ 0.001for between-group difference |
| | | Sitagliptin 50 mg + MET 1000 mg Bid | N=180 | Change from baseline: -63.9 (95% CI -70.5, -57.3) Change from placebo: -69.7 (95% -79.2, -60.2), p ≤0.001 for between-group difference and between-group difference comparing coadministration and both respective components |
| | | Sitagliptin 50 mg + MET 500 mg Bid | N=183 | Change from baseline: -47.1 (95% CI -53.7, -40.6) Change from placebo: -52.9 (95% CI -62.4, -43.5), p ≤0.001 forbetween-group difference and for between-group difference comparing coadministration and both respective components |
| | | Placebo | N=169 | Change from baseline: 5.8 (95% CI -1.0, 12.7) |

## Evidence Table 2. Outcomes of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Outcome | Intervention | N | Result |
|---|---|---|---|---|
| | HbA1c, percent 24 weeks | MET 1000 mg Bid | N=177 | Change from baseline: -1.13 (95% CI -1.29, 0.97)<br>Change from placebo: -1.3 (95% CI -1.53, -1.06), p≤0.001 for between-group difference |
| | | MET 500 mg Bid | N=178 | Change from baseline: -0.82 (95% CI -0.98, -0.66)<br>Change from placebo: -0.99 (95% CI -1.22, -0.75), p≤0.001 for between-group difference |
| | | Sitagliptin 100 mg | N=175 | Change from baseline: -0.66 (95% CI -0.83, -0.50)<br>Change from placebo: -0.83 (95% CI -1.06, -0.60), p≤0.001 for between-group difference |
| | | Sitagliptin 50 mg + MET 1000 mg Bid | N=178 | Change from baseline: -1.90 (95% CI -2.06, -1.74)<br>Change from placebo: -2.07 (95% -2.30, -1.84), p≤ 0.001 for between-group difference and for between-group differnece comparing co-administration and both respective components |
| | | Sitagliptin 50 mg + MET 500 mg Bid | N=183 | Change from baseline: -1.40 (95% CI -1.56, -1.24)<br>Change from placebo: -1.57 (95% CI -1.80, -1.34), p≤0.001 for between-group difference and for between-group difference comparing co-admininstration and both respective components |
| | | Placebo | N=165 | Change from baseline: 0.17 (95% CI 0.00, 0.33) |

## Evidence Table 2. Outcomes of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Outcome | Intervention | N | Result |
|---|---|---|---|---|
| | PPG or random glucose, mg/dL | MET 1000 mg Bid | N=138 | 2 hr PPG<br>Change from baseline: -78.0 (95% CI -88.3, -67.6)<br>Change from placebo: -78.3 (95% CI -93.1, -63.4), p-value NR |
| | | MET 500 mg Bid | N=141 | 2 hr PPG<br>Change from baseline: -53.4 (95% CI -63.6, -43.2)<br>Change from placebo: -53.7 (95% CI -68.5, -38.9), p≤0.001 for between-group difference |
| | | Sitagliptin 100 mg | N=136 | 2 hr PPG<br>Change from baseline: -51.9 (95% CI -62.3, -41.5)<br>Change from placebo: -52.2 (95% CI -67.1, -37.3), p≤0.001 for between-group difference relative to placebo |
| | | Sitagliptin 50 mg + MET 1000 mg Bid | N=152 | 2 hr PPG<br>Change from baseline: -116.6 (95% CI -126.4, -106.7)<br>Change from placebo: -116.9 (95% CI -131.4, -102.3), p ≤0.001 for between-group difference and between-group difference comparing coadministration and both respective components |
| | | Sitagliptin 50 mg + MET 500 mg Bid | N=147 | 2 hr PPG<br>Change from baseline: -92.5 (95% CI -102.6, -82.5)<br>Change from placebo: -92.8 (95% CI -107.5, -78.1), p ≤0.001 for between-group difference and for between-group difference comparing coadministration and both respective components |
| | | Placebo | N=129 | 2hr PPG<br>Change from baseline: 0.3 (95% CI -10.4, 11.0) |

## Evidence Table 2. Outcomes of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Outcome | Intervention | N | Result |
|---|---|---|---|---|
| | Weight, Kg<br>24 weeks | MET 1000 mg Bid | NR | Result NR<br>Authors report that all other groups had a reduction in weight from -0.6 to -1.3 kg, p<0.05 |
| | | MET 500 mg Bid | NR | Result NR<br>Authors report that all other groups had a reduction in weight from -0.6 to -1.3 kg, p<0.05 |
| | | Sitagliptin 100 mg | NR | N= NR<br>Change from baseline: 0.0 kg |
| | | Sitagliptin 50 mg + MET 1000 mg Bid | NR | Result NR<br>Authors report that all other groups had a reduction in weight from -0.6 to -1.3 kg, p<0.05 |
| | | Sitagliptin 50 mg + MET 500 mg Bid | NR | Result NR<br>Authors report that all other groups had a reduction in weight from -0.6 to -1.3 kg, p<0.05 |
| | | Placebo | NR | N= NR<br>Change from baseline: -0.9, p<0.01 vs. Sitagliptin |
| **Goldstein 2007**<br><br>Open-label cohort<br><br>Poor | HbA1c, percent<br>24 weeks | Sitagliptin 50 mg + MET 1000 mg Bid | NR | All-patients treated population<br>N= NR<br>Within-group change from baseline: -2.9 |
| | Weight, Kg<br>24 weeks | Sitagliptin 50 mg + MET 1000 mg Bid | NR | N= NR<br>Change from baseline: 1.3 |

## Evidence Table 2. Outcomes of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Outcome | Intervention | N | Result |
|---|---|---|---|---|
| **Heine 2005**<br>Multinational<br>active-control<br>Fair | FPG, mmol/L<br>26 weeks | Exenatide + MET/SU | NR | Change from baseline: -1.4 mmol/L -->25 mg/dL<br>% achieving FPG< 5.6 (<101 mg/dL): 8.6%<br>N= NR |
| | | Glargine + MET/SU | NR | Change from baseline: -2.9 mmol/L -->52 mg/dL, p<0.001 vs. exenatide<br>Between-treatment difference: -1.5 (27 mg/dL) (95% CI 1.1, 1.9 mmol/L) vs. exenatide<br>% achieving FPG< 5.6 (<101 mg/dL): 21.6%, p<0.001 vs. exenatide<br>N=NR |
| | HbA1c, percent<br>26 weeks | Exenatide + MET/SU | N=275 | Change from baseline: -1.11<br>Between-treatment difference: +0.017 (95% CI -0.123, +0.157), p>0.05 (NSD) vs. glargine |
| | | Glargine + MET/SU | N=260 | Change from baseline: -1.11 |
| | Weight, Kg<br>26 weeks | Exenatide + MET/SU | N=231 | Change from baseline: -2.3 kg<br>Between-group difference, -4.1 (95% CI, -4.6 to -3.5), p<0.001 vs. glargine |
| | | Glargine + MET/SU | N=244 | Change from baseline: +1.8 kg (SE 0.2) |

## Evidence Table 2. Outcomes of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Outcome | Intervention | N | Result |
|---|---|---|---|---|
| **Hermansen 2007**<br>Denmark, USA<br><br>placebo-controlled<br>Fair | FPG, mg/dL<br>24 weeks | Entire Placebo cohort | N=213 | Change from baseline: 15.7 (95% 9.8, 21.6), p<0.001 for within-treatment difference |
| | | Entire Sitagliptin cohort | N=219 | Change from baseline: -4.4 (95% -10.21.4), p-value NR<br>Between-treatment difference from baseline: -20.1 (95% -28.4, -11.8), p<0.001 vs. placebo |
| | | Sitagliptin + Glimepiride | N=104 | Change from baseline: -0.88 (95% -9.8, 8.0), p-value NR<br>Between-treatment difference from baseline: -19.3 (95% -31.9, -6.7), p<0.05 vs. placebo |
| | | Sitagliptin + Glimepiride + MET | N=115 | Change from baseline: -7.8 (95% -15.5, -0.2), p<0.005 for within-treatment difference<br>Between-treatment difference from baseline: -20.7 (95% -31.7, -9.7), p<0.001 vs. placebo |
| | | Placebo + Glimepiride | N=104 | Change from baseline: 18.4 (95% 9.5, 27.3), p<0.001 for within-treatment difference |
| | | Placebo + Glimepiride + MET | N=109 | Change from baseline: 12.9 (95% 5.0, 20.8), p<0.001 for within-treatment difference |

## Evidence Table 2. Outcomes of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Outcome | Intervention | N | Result |
|---|---|---|---|---|
| | HbA1c, percent 24 weeks | Entire Placebo cohort | N=208 | Change from baseline: 0.28 (95% 0.17, 0.40), p<0.001 for within-treatment difference |
| | | Entire Sitagliptin cohort | N=217 | Change from baseline: -0.45 (95% -0.57,-0.34), p< 0.001 for within-treatment difference<br>Between-treatment difference from baseline: -0.74 (-0.9, -0.57), p<0.001 vs. placebo |
| | | Sitagliptin + Glimepiride | N=102 | Change from baseline: -0.3 (95% -0.48, -0.12), p<0.001 for within-treatment difference<br>Between-treatment difference from baseline: -0.57 (95% -0.82, -0.32), p<0.001 vs. placebo |
| | | Sitagliptin + Glimepiride + MET | N=115 | Change from baseline: -0.59 (95% -0.74, -0.44), p<0.001 for within-treatment difference<br>Between-treatment difference from baseline: -0.89 (95% -1.10, -0.68), p<0.001 vs. placebo |
| | | Placebo + Glimepiride | N=103 | Change from baseline: 0.27 (95% 0.09, 0.45), p<0.05 for within-treatment difference |
| | | Placebo + Glimepiride + MET | N=105 | Change from baseline: 0.30 (95% 0.14, 0.45), p<0.001 for within-treatment difference |

## Evidence Table 2. Outcomes of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Outcome | Intervention | N | Result |
|---|---|---|---|---|
| | PPG or random glucose, mg/dL | Entire Placebo cohort | N=65 | Change from baseline: 13.5 (95% 0.3, 26.7), p<0.05 for within-treatment difference |
| | | Entire Sitagliptin cohort | N=69 | Change from baseline: -22.7 (95% -35.5, -9.9), p<0.001 for within-treatment difference |
| | | Sitagliptin + Glimepiride | N=38 | Change from baseline: -24.4 (95% -42.3, -6.4), p<0.05 for within-treatment difference<br>Between-treatment difference from baseline: -35.1 (95% -62.6, -2.5), p<0.05 vs. placebo |
| | | Sitagliptin + Glimepiride + MET | N=31 | Change from baseline: -21.3 (95% -40.1, -2.5), p<0.05 for within-treatment difference<br>Between-treatment difference from baseline: -37.1 (95% -62.7, -11.6), p< 0.05 vs. placebo |
| | | Placebo + Glimepiride | N=28 | Change from baseline: 10.7 (95% -10.2, 31.6), p-value NR |
| | | Placebo + Glimepiride + MET | N=37 | Change from baseline: 15.8 (95% -1.4, 33.1), p-value NR |
| | Weight, Kg 24 weeks | Entire Placebo cohort | NR | Change from baseline: -0.4 (95% -0.8, 0.1) |
| | | Entire Sitagliptin cohort | NR | Change from baseline: 0.8 (95% 0.4, 1.2)<br>Difference between placebo from baseline: 1.1 (95% 0.5, 1.7) |
| | | Sitagliptin + Glimepiride | NR | Change from baseline: 1.1 (95% 0.5, 1.8) |
| | | Sitagliptin + Glimepiride + MET | NR | Change from baseline: 0.4 (95% -0.1, 0.9) |
| | | Placebo + Glimepiride | NR | Change from baseline: 0.0 (95% -0.6, 0.7) |
| | | Placebo + Glimepiride + MET | NR | Change from baseline: -0.7 (95% -1.4, -0.1)<br>Difference between placebo from baseline: 1.1 (no CI reported) |

## Evidence Table 2. Outcomes of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Outcome | Intervention | N | Result |
|---|---|---|---|---|
| **Hollander 2003**<br>US<br>placebo-controlled<br>Fair | HbA1c, percent<br>52 weeks | Pramlintide 120 mcg + adjunct insulin | N=166 | Change from baseline: -0.62 (unclear if SD or SE 0.9), p< 0.05 vs. placebo |
| | | Pramlintide 90 mcg + adjunct inuslin | N=171 | Change from baseline: -0.35, p > 0.05 (NSD)vs. placebo |
| | | Placebo + adjunct insulin | N=161 | Change from baseline: -0.22 (unclear if SD or SE 0.9) |
| | Weight, Kg<br>52 weeks | Pramlintide 120 mcg + adjunct insulin | N=166 | Change from baseline: -1.25 (unclear if SD or SE 0.5), p< 0.05 vs. placebo |
| | | Pramlintide 90 mcg + adjunct inuslin | N=171 | Change from baseline: -0.5, p >0.05 (NSD) vs. placebo |
| | | Placebo + adjunct insulin | N=161 | Change from baseline: +0.6 (unclear if SD or SE 0.4) |
| **Hollander 2003**<br>NR<br>Pooled analysis<br>N/A | HbA1c, percent<br>26 weeks | Pramlintide 120 mcg + insulin | N=86 | For those with A1c 7%-8.5%<br>Estimated from graph (Figure 1)<br>Change from baseline: -0.3 (estimated SE 0.07)<br>Between-treatment difference from placebo: -0.43, p<0.0009 vs. placebo |
| | | Placebo + insulin | N=80 | For those who had HbA1 between 7% and 8.5%<br>Estimated from graph (Figure 1)<br>Change from baseline to week 26: +0.15 (estimated SE 0.03) |
| | Weight, Kg<br>26 weeks | Pramlintide 120 mcg + insulin | N=86 | For those with A1c 7%-8.5%<br>Estimated from graph (Figure 1)<br>Change from baseline: -1.8 (estimated SE 0.2)<br>Between-treatment difference from placebo: -2.0, p<0.0003 vs. placebo |
| | | Placebo + insulin | N=80 | For those with A1c 7%-8.5%<br>Estimated from graph (Figure 1)<br>Change from baseline: +0.3 (estimated SE 0.3) |

## Evidence Table 2. Outcomes of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Outcome | Intervention | N | Result |
|---|---|---|---|---|
| **Hollander 2004** | HbA1c, percent<br>26 weeks | Pramlintide + insulin | N=254 | Change from baseline: -0.59<br>Between-treatment difference from placebo: -0.41, p<0.0001 vs. placebo |
| N/A | | Placebo + insulin | N=244 | Change from baseline: -0.18 |
| Pooled analysis | Weight, Kg<br>26 weeks | Pramlintide + insulin | N=254 | Estimated from graph (Figure 1)<br>Change from baseline: -1.5 (estimated SE 0.25) |
| N/A | | Placebo + insulin | N=244 | Estimated from graph (Figure 1)<br>Change from baseline: +0.3 (estimated SE 0.25) |
| **Karl 2007** | Weight, Kg<br>12 weeks | Pramlintide 120mcg + insulin | N=166 | Change from baseline: -2.3 (SE 0.23), p<0.05 |
| US | Weight, Kg<br>24 weeks | Pramlintide 120mcg + insulin | N=166 | Change from baseline: -2.8 (SE 0.34), p<0.05 |
| Open-label cohort | | | | |
| N/A | | | | |

## Evidence Table 2. Outcomes of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Outcome | Intervention | N | Result |
|---|---|---|---|---|
| **Kendall 2005** US placebo-controlled Fair | FPG, mmol/L 30 weeks | Exenatide 10 mcg + MET/SU | N=241 | Change from baseline: -0.6 mmol/L (SE 0.2) --> 11 mg/dL, p<0.0001 vs. placebo |
| | | Exenatide 5 mcg + MET/SU | N=245 | Change from baseline: -0.5 mmol/L (SE 0.2) --> 9 mg/dL, p<0.0001 vs. placebo |
| | | Placebo (combined) + MET/SU | N=247 | Change from baseline: +0.8 mmol/L (SE 0.2) -->+14 mg/dL |
| | HbA1c, percent 30 weeks | Exenatide 10 mcg + MET/SU | N=241 | Estimated from graph<br>Change from baseline: -0.8 |
| | | Exenatide 5 mcg + MET/SU | N=245 | Estimated from graph<br>Change from baseline: -0.6 |
| | | Placebo (combined) + MET/SU | N=247 | Estimated from graph<br>Change from baseline: 0.2 |
| | PPG or random glucose, | Exenatide 5 mcg + MET/SU | N=27 | PPG 2.6hrs after meal tolerance test (estimated from graph)<br>Change from baseline: 0.9 --> 16 mg/dL |
| | PPG or random glucose, mmol/L | Exenatide 10 mcg + MET/SU | N=27 | PPG 2.6hrs after meal tolerance test (estimated from graph)<br>Change from baseline: -0.3 mmol/L -->- 5mg/dL |
| | | Placebo (combined) + MET/SU | N=23 | PPG 2.6hrs after meal tolerance test (estimated from graph)<br>Change from baseline: 3 --> 54 mg/dL |
| | Weight, Kg 30 weeks | Exenatide 10 mcg + MET/SU | N=241 | Change from baseline: -1.6 (SE 0.2), p< or =0.01 vs. placebo |
| | | Exenatide 5 mcg + MET/SU | N=245 | Change from baseline: -1.6 (SE 0.2), p< or =0.01 vs. placebo |
| | | Placebo (combined) + MET/SU | N=247 | Change from Baseline: -0.9 (SE 0.2) |

## Evidence Table 2. Outcomes of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Outcome | Intervention | N | Result |
|---|---|---|---|---|
| **Klonoff 2008** | HbA1c, percent<br>3 years | 3 year completers | N=56 | Subgroup by baseline age > 65 years<br>Change: -1.2 (95% CI -1.5, -0.9) |
| NR | | 3 year completers | N=161 | Subgroup by baseline age < 65 years<br>Change: -0.9 (95% CI -1.1, -0.7) |
| Pooled analysis | | | | |
| N/A | | | | |

## Evidence Table 2. Outcomes of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Outcome | Intervention | N | Result |
|---|---|---|---|---|
| **Maggs 2003**<br>NR<br>Pooled analysis<br>N/A | HbA1c, percent<br>52 weeks | Pramlintide (African American) + insulin | N=26 | Estimated from graph (Figure 1)<br>Change in HbA1c from baseline to week 52: -0.8 (estimated SE 0.22) |
| | | Pramlintide (Caucasian) + insulin | N=151 | Estimated from graph (Figure 1)<br>Change in HbA1c from baseline to week 52: -0.65 (estimated SE 0.1) |
| | | Pramlintide (Hispanic) + insulin | N=22 | Estimated from graph (Figure 1)<br>Change in HbA1c from baseline to week 52: -0.5 (estimated SE 0.3) |
| | | Placebo (African American) + insulin | N=21 | Estimated from graph (Figure 1)<br>Change in HbA1c from baseline to week 52: -0.15 (estimated SE 0.35) |
| | | Placebo (Caucasian) + insulin | N=164 | Estimated from graph (Figure 1)<br>Change in HbA1c from baseline: -0.12 (estimated SE 0.1) |
| | | Placebo (Hispanic) + insulin | N=26 | Estimated from graph (Figure 1)<br>Change in HbA1c from baseline to week 52: -0.2 (estimated SE 0.25) |
| | Weight, Kg<br>52 weeks | Pramlintide (African American) + insulin | N=26 | Estimated from graph (Figure 1)<br>Change in weight from baseline to week 52: -2.3 (estimated SE 0.5) |
| | | Pramlintide (Caucasian) + insulin | N=151 | Estimated from graph (Figure 1)<br>Change in weight from baseline to week 52: -1.5 (estimated SE 0.4) |
| | | Pramlintide (Hispanic) + insulin | N=22 | Estimated from graph (Figure 1)<br>Change in weight from baseline to week 52: -0.5 (estimated SE 0.1.1) |
| | | Placebo (African American) + insulin | N=21 | Estimated from graph (Figure 1)<br>Change in weight from baseline to week 52: +1.8 (estimated SE 1.25) |
| | | Placebo (Caucasian) + insulin | N=164 | Estimated from graph (Figure 1)<br>Change in weight from baseline: +0.8 (estimated SE 0.3) |
| | | Placebo (Hispanic) + insulin | N=26 | Estimated from graph (Figure 1)<br>Change in weight from baseline to week 52: +2.0 (estimated SE 0.7) |

## Evidence Table 2. Outcomes of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Outcome | Intervention | N | Result |
|---|---|---|---|---|
| **Nauck 2007**<br>Multinational<br>active-control<br>Fair-poor | FPG, mmol/L<br>52 weeks | Glipizide + MET | N=407 | Per-protocol population<br>Change from baseline: -0.42 (95% CI -0.67, -0.17) --> -8 mg/dL |
| | | Sitagliptin +MET | N=382 | Per-protocol population<br>Change from baseline: -0.56 (95% CI -0.81, -0.31) --> -10.1 mg/dL |
| | HbA1c, percent<br>52 weeks | Glipizide + MET | N=411 | Per-protocol-population<br>Change from baseline: -0.67 (95% CI -0.75, -0.59) --> -12.1 mg/dL |
| | | Sitagliptin +MET | N=382 | Per-protocol population<br>Change from baseline: -0.67% (95% CI -0.75, -0.59) |
| | Weight, Kg<br>52 weeks | Glipizide + MET | N=559 | Per APT protocol<br>Change from baseline: 1.1 kg (95% CI 0.5, 1.6) |
| | | Sitagliptin +MET | N=576 | Per APT-protocol<br>Change from baseline: -1.5 kg (95% CI -2.0, -0.9)<br>Between-treatment difference of -2.5 kg (95% CI -3.1,-2.0), p<0.001 vs. glipizide arm |
| **Nauck 2007**<br>Multinational<br>active-control<br>Fair | HbA1c, percent<br>52 weeks | Biphasic Aspart + MET/SU | N=248 | Change from baseline: −0.89 (SEM 0.06) |
| | | Exenatide + MET/SU | N=253 | Change from baseline: −1.04 (SEM 0.07)<br>Between-treatment difference: −0.15 (95% CI −0.32, 0.01), p=0.067 (NSD) vs. biphasic aspart |
| | Weight, Kg<br>52 weeks | Biphasic Aspart + MET/SU | N=248 | Change from baseline: +2.9 (SEM 0.2) |
| | | Exenatide + MET/SU | N=253 | Change from baseline: −2.5 (SEM 0.2)<br>Between-treatment difference: −5.4 (95% CI −5.9, −5.0), p<0.001 vs. biphasic aspart |

## Evidence Table 2. Outcomes of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Outcome | Intervention | N | Result |
|---|---|---|---|---|
| **Nonaka 2007** Japan placebo-controlled Fair | FPG, mg/dL 12 weeks | Sitagliptin (Januvia) | N=75 | Change from baseline: -22.5 (95% CI -28.0, -17.0), p-value NR<br>Between-group differences in change from baseline: -31.9 (95% CI -39.7, -24.1), p<0.001 |
| | | Placebo | N=75 | Change from baseline: 9.4 (95% CI 3.9, 14.9) |
| | HbA1c, percent 12 weeks | Sitagliptin (Januvia) | N=75 | Change from baseline: -0.65 (95% CI -0.80, -0.50), p-value NR<br>Between-group difference in change from baseline: -1.05 (95% CI -1.27, -0.84) |
| | | Placebo | N=75 | Change from baseline: 0.41 (95% CI 0.26, 0.56) |
| | PPG or random glucose, mg/dL | Sitagliptin (Januvia) | N=43 | 2- hr PPG<br>Change from baseline: -69.3 (95% CI -85.3, -53.4)<br>Between-group differences in change from baseline: -81.3 (95% CI -105.8, -56.9), p<0.001 |
| | | Placebo | N=32 | 2- h PPG<br>Change from baseline: 12.0 (95% CI -6.5, 30.5) |
| | Weight, Kg 12 weeks | Sitagliptin (Januvia) | N=75 | Change from baseline: -0.1 kg (95% CI -0.4, 0.3)<br>Between-group difference from baseline: -0.7 kg (95% CI -0.2, 1.1), p<0.01 |
| | | Placebo | N=76 | Change from baseline: -0.7 kg (95% CI -1.0, -0.4) |

## Evidence Table 2. Outcomes of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Outcome | Intervention | N | Result |
|---|---|---|---|---|
| **Ratner 2002** | HbA1c, percent 13 weeks | Pramlintide (Symlin) 150 mcgTID+Insulin | N=144 | Changefrom baseline -1.0 % (SE 0.1), p <0.01 vs. placebo (estimated from graph) |
| U.S. | | Pramlintide (Symlin) 30mcg TID+Insulin | N=122 | Change from baseline - 0.65 % (SE 0.05), p>0.05 vs. placebo (estimated from graph) |
| placebo-controlled | | Pramlintide (Symlin) 75mcgTID+Insulin | N=136 | Change from baselline: -0.9% (SE 0.1), p-value <0.01 vs. placebo |
| Fair-Poor | | Placebo+Insulin | N=136 | Change from baseline: - 0.5% (SE 0.05), (estimated from graph) |
| | HbA1c, percent 52 weeks | Pramlintide (Symlin) 150 mcgTID+Insulin | N=144 | Change from baseline -0.65% (SE 0.12), p<0.01 vs. placebo (estimated from graph) |
| | | Pramlintide (Symlin) 30mcg TID+Insulin | N=122 | Change from baseline: -0.3% (SE 0.07), p>0.05 vs. placebo (estimated from graph) |
| | | Pramlintide (Symlin) 75mcgTID+Insulin | N=136 | Change from baseline: -0.5% (SE 0.12), p-value >0.05 vs. placebo |
| | | Placebo+Insulin | N=136 | Change from baseline : -0.2% (SE 0.12), (estimated from graph) |
| | Weight, Kg 52 weeks | Pramlintide (Symlin) 150 mcgTID+Insulin | N=144 | Changefrom baseline -1.4 kg, (SE 0.4), p-value<0.01 vs. placebo |
| | | Pramlintide (Symlin) 30mcg TID+Insulin | N=122 | Change from baseline - 0.5 kg, (SE 0.4), p <0.01 vs. placebo |
| | | Pramlintide (Symlin) 75mcgTID+Insulin | N=136 | Change from baseline -0.5 kg, (SE 0.4), p<0.01 vs. placebo |
| | | Placebo+Insulin | N=136 | Change from baseline 1.0 kg, (SE 0.5) |

## Evidence Table 2. Outcomes of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Outcome | Intervention | N | Result |
|---|---|---|---|---|
| **Ratner 2004** | HbA1c, percent | Pramlintide 60 mcg QID+insulin | N=161 | % of patients in the ITT who achieved an A1c<7% at any time during the study= 12.5% (data interpreted from graph) |
| U.S., & Canada | | Pramlintide 60 mcg TID+insulin | N=164 | % of pts in ITT population who achieved A1C< 7% at any time during the study: 11% (data interpreted from graph) |
| placebo-controlled | | Placebo+insulin | N=154 | % of pts in the ITT population who achieved an A1C< 7% at any time during the study: 3.5% (data interpreted from graph). |
| Fair-poor | HbA1c, percent 26 weeks | Pramlintide 60 mcg QID+insulin | N=161 | Change from baseline at 26 wks: -0.39%, p=0.013 |
| | | Pramlintide 60 mcg TID+insulin | N=164 | Change from baseline -0.41% , p= 0.012 |
| | | Placebo+insulin | N=154 | Change from baseline at 26 wks: -0.18% |
| | HbA1c, percent 52 weeks | Pramlintide 60 mcg QID+insulin | N=161 | Change from baseline - 0.34% (p-value 0.001), SE as interpreted from graph <0.1 |
| | | Pramlintide 60 mcg TID+insulin | N=164 | Change from baseline -0.29, p=0.011. |
| | | Placebo+insulin | N=154 | Change from baseline: -0.04% |
| | Weight, Kg 26 weeks | Pramlintide 60 mcg QID+insulin | N=161 | Change from baseline: -0.8 kg (p=0.000), (SE 0.5) |
| | | Pramlintide 60 mcg TID+insulin | N=164 | Change from baseline at 26 wks: -1.3 kg (p=0.000), SE 0.50 |
| | | Placebo+insulin | N=154 | Change from baseline at 26 wks: 0.7 kg, SE 0.5 |
| | Weight, Kg 52 weeks | Pramlintide 60 mcg QID+insulin | N=161 | Change from baseline: - 0.4 kg (SE 0.7), p=0.040 (data interpreted from graph) |
| | | Pramlintide 60 mcg TID+insulin | N=164 | Change from baseline -0.4 kg (SE 0.07) p=0.027 (data interpreted from graph) |
| | | Placebo+insulin | N=154 | Change from baseline: 0.8 (SE 0.4), (data interpreted from graph) |

## Evidence Table 2. Outcomes of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Outcome | Intervention | N | Result |
|---|---|---|---|---|
| **Ratner 2005**<br>USA<br>Pooled analysis | HbA1c, percent<br>26 weeks | Pramlintide (Symlin)+Insulin | N=281 | % achieving A1c<7.0% : 9.6%, p-value NR |
| | | Pramlintide (Symlin)+Insulin | N=281 | Change from baseline -0.16%<br>Between-treatment difference from placebo: -0.3, p=0.0009 vs. placebo |
| | | Placebo+Insulin | N=196 | % achieving A1c<7% 7.1% |
| | | Placebo+Insulin | N=196 | Change from baseline -0.1%, (SE 0.05), p<0.05 (data from graph) |
| N/A | Weight, Kg<br>26 weeks | Pramlintide (Symlin)+Insulin | N=281 | Change from baseline: -1.35kg (SE 0.2), p-value <0.005 (data interpreted from graph)<br>Between-treatment difference from placebo: -1.8, p< or =0.0001 vs. placebo |
| | Weight, percent<br>26 weeks | Placebo+Insulin | N=196 | Change from baseline: 0.5kg, SE 0.2, p-value <0.005, |

## Evidence Table 2. Outcomes of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Outcome | Intervention | N | Result |
|---|---|---|---|---|
| **Raz 2006**<br>Multinational<br><br>placebo-controlled | FPG, mmol/L<br>18 weeks | Sitagliptin 100 mg | N=201 | Change from baseline: -0.7 (95% CI -1.1, -0.4) --> -12.6 mg/dL<br>Between-treatment difference with placebo in change from baseline:: -1.1 (95% CI -1.7, -0.5), p< or = 0.001 --> -19.8 mg/dL |
| | | Sitagliptin 200 mg | N=202 | Change from baseline: -0.6 (95% CI -0.9, -0.2) --> -10.8 mg/dL<br>Between-treatment difference with placebo in change from baseline:: -0.9 (95% CI -1.5, -0.3), p<=0.01 --> -16.2 mg/dL |
| Fair | HbA1c, percent<br>18 weeks | Sitagliptin 100 mg | N=193 | Change from baseline: -0.48 (95% CI -0.61, -0.35)<br>Between-treatment difference with placebo in change from baseline:: -0.60 (95% CI -0.82, -0.39), p< or = 0.001 |
| | | Sitagliptin 200 mg | N=199 | Change from baseline: -0.36 (95% CI -0.48, -0.23)<br>Between-treatment difference with placebo in change from baseline:: -0.48 (95% CI -0.70, -0.26), p<or=0.001 |
| | | Placebo | N=103 | Change from baseline: 0.12 (95% CI -0.05, 0.30) |
| | PPG or random glucose, mmol/L | Sitagliptin 100 mg | N=62 | For 2-hr PPG (meal tolerance test for subset of pts total n= 150)<br>Change from baseline: -2.3 (95% CI -3.2, -1.4) --> -41.4 mg/dL<br>Between-treatment difference with placebo in change from baseline:: -2.6 (95% CI -4.2, -1.0), p<=0.01 |
| | | Sitagliptin 200 mg | N=61 | For 2-hr PPG (meal tolerance test for subset of pts total n= 150)<br>Change from baseline: -2.7 (95% CI -3.6, -1.8) --> -48.6 mg/dL<br>Between-treatment difference with placebo in change from baseline:: -2.9 (95% CI -4.6, -1.3), p<=0.001 --> -52.2 mg/dL |
| | | Placebo | N=27 | For 2-hr PPG (meal tolerance test for subset of pts total n= 150)<br>Change from baseline: 0.3 (95% CI -1.1, 1.6) -->+5.4 mg/dL |

## Evidence Table 2. Outcomes of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Outcome | Intervention | N | Result |
|---|---|---|---|---|
| | Weight, Kg<br>18 weeks | Sitagliptin 100 mg | NR | Change from baseline: -0.6 kg (95% CI -1.0, -0.2)<br>(N, NR) |
| | | Sitagliptin 200 mg | NR | Body weight information found under 'safety' paragraph<br>Change from baseline: -0.2 kg (95% CI -0.7, 0.2)<br>N= NR |
| | | Placebo | NR | Body weight information found under 'safety' paragraph<br>Change from baseline: -0.7 kg (95% CI -1.3, -0.1)<br>N= NR |
| **Raz 2008**<br>Multinational<br><br>placebo-controlled<br><br>Fair | FPG, mmol/L<br>18 weeks | Sitagliptin + MET | N=96 | Change from baseline: -1.8 (95% CI -2.3 to -1.3), p<0.001 |
| | | Placebo + MET | N=92 | Change from baseline: -0.4 (95% CI -0.8 to 0.1) |
| | FPG, mmol/L<br>30 weeks | Sitagliptin + MET | N=96 | Change from baseline: -1.6 (95% CI -2.1 to -1.1), p<0.001 |
| | | Placebo + MET | N=92 | Change from baseline: -0.2 (95% CI -0.7 to 0.3) |
| | HbA1c, percent<br>18 weeks | Sitagliptin + MET | N=95 | Change from baseline: -1.0 (95% CI -1.2 to -0.8), p<0.001 |
| | | Placebo + MET | N=92 | Change from baseline: 0.0 (95% CI -0.2 to 0.3) |
| | HbA1c, percent<br>30 weeks | Sitagliptin + MET | NR | Subgroup with highest baseline A1c >10%<br>Change from baseline: -1.4 |
| | | Sitagliptin + MET | N=95 | Change from baseline: -1.0 (95% CI -1.3 to -0.7), p<0.001 |
| | | Placebo + MET | N=92 | Change from baseline: 0.0 (-0.2 to 0.3) |
| | PPG or random glucose, mmol/L | Sitagliptin + MET | N=79 | Change from baseline: -3.8 (95% CI -4.6 to -3.0), p<0.001<br>No data for 30 weeks |
| | | Placebo + MET | N=74 | Change from baseline: -0.8 (95% CI -1.6 to 0.1)<br>No data for 30 weeks |

## Evidence Table 2. Outcomes of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Outcome | Intervention | N | Result |
|---|---|---|---|---|
| **Riddle 2007**<br>US<br>placebo-controlled<br>Fair | FPG, mg/dL<br>16 weeks | Pramlintide > 8.5% + glargine (+/- OHA) | N=42 | Change from baseline: -44.4 (SE 12.7) |
| | | Pramlintide ≤ 8.5% + glargine (+/- OHA) | N=63 | Change from baseline: -17.3 (SE 7.1) |
| | | Total Placebo + glargine (+/- OHA) | N=106 | Change from baseline: -12.0 (SE 5.6)<br>31% achieved FPG <100 |
| | | Total Pramlintide + glargine (+/- OHA) | N=105 | Change from baseline: -28.3 (SE 6.8)<br>23% achieved FPG <100 |
| | | Placebo >8.5% + glargine (+/- OHA) | N=48 | Change from baseline: -18.4 (SE 9.4) |
| | | Placebo ≤ 8.5% + glargine (+/- OHA) | N=58 | Change from baseline: -7.5 (SE 6.8) |
| | HbA1c, percent<br>16 weeks | Pramlintide > 8.5% + glargine (+/- OHA) | N=42 | Change from baseline: -1.19 (SE 0.14) |
| | | Pramlintide ≤ 8.5% + glargine (+/- OHA) | N=63 | Change from baseline: -0.36 (SE 0.13) |
| | | Total Placebo + glargine (+/- OHA) | N=106 | Change from baseline: -0.36 (SE 0.08) |
| | | Total Pramlintide + glargine (+/- OHA) | N=105 | Change from baseline: -0.70 (SE 0.11), p<0.05 vs. placebo |
| | | Placebo >8.5% + glargine (+/- OHA) | N=48 | Change from baseline: -0.69 (SE 0.13) |
| | | Placebo ≤ 8.5% + glargine (+/- OHA) | N=58 | Change from baseline: -0.08 (SE 0.09) |

## Evidence Table 2. Outcomes of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Outcome | Intervention | N | Result |
|---|---|---|---|---|
| | PPG or random glucose, mg/dL | Pramlintide > 8.5% + glargine (+/- OHA) | N=42 | Change from baseline: -23.7 (SE 5.9) |
| | | Pramlintide ≤ 8.5% + glargine (+/- OHA) | N=63 | Change from baseline: -24.9 (SE 4.4) |
| | | Total Placebo + glargine (+/- OHA) | N=106 | Change from baseline: -0.4 (SE 3.0) |
| | | Total Pramlintide + glargine (+/- OHA) | N=105 | Change from baseline: -24.4 (SE 3.6), p <0.0001 vs. placebo |
| | | Placebo >8.5% + glargine (+/- OHA) | N=48 | Change from baseline: 3.2 (SE 4.6) |
| | | Placebo ≤ 8.5% + glargine (+/- OHA) | N=58 | Change from baseline: -3.6 (SE 3.8) |
| | Weight, Kg 16 weeks | Pramlintide > 8.5% + glargine (+/- OHA) | N=42 | Change from baseline: -1.0 (SE 0.3) |
| | | Pramlintide ≤ 8.5% + glargine (+/- OHA) | N=63 | Change from baseline: -2.0 (SE 0.4) |
| | | Total Placebo + glargine (+/- OHA) | N=106 | Change from baseline: 0.7 (SE 0.3) |
| | | Total Pramlintide + glargine (+/- OHA) | N=105 | Change from baseline: -1.6 (SE 0.3), p<0.0001 vs. placebo |
| | | Placebo >8.5% + glargine (+/- OHA) | N=48 | Change from baseline: 1.1 (SE 0.4) |
| | | Placebo ≤ 8.5% + glargine (+/- OHA) | N=58 | Change from baseline: -0.4 (SE 0.4) |

## Evidence Table 2. Outcomes of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Outcome | Intervention | N | Result |
|---|---|---|---|---|
| **Rosenstock 2006**<br>multinational<br>placebo-controlled<br>Fair | FPG, mg/dL<br>24 weeks | Sitagliptin + Pioglitazone | N=163 | Change from baseline: -16.7 (95% CI -22.4, -11.0)<br>Between-treatment difference in change from baseline:: -17.7 (95% CI -24.3, -11.0) |
| | | Placebo + Pioglitazone | N=174 | Change from baseline: 1.0 (95% CI -4.3, +6.3) |
| | HbA1c, percent<br>24 weeks | Sitagliptin + Pioglitazone | N=163 | Change from baseline: -0.85 (95%CI -0.98, -0.72)<br>Between-treatment difference in change from baseline: -0.70 (95% CI -0.85, -0.54), p< 001 vs. placebo |
| | | Placebo + Pioglitazone | N=174 | Change from baseline: -0.15 (95% CI -0.28, -0.03) |
| | Weight, Kg<br>24 weeks | Sitagliptin + Pioglitazone | NR | Change from baseline: 1.8 (95% 1.1, 2.4)<br>Between-treatment difference in change from baseline:: 0.2 (95% -0.5, 1.0), p>0.05 (NSD)<br>(N, NR) |
| | | Placebo + Pioglitazone | NR | Change from baseline: 1.5 (95% 0.9, 2.2), p>0.05 (NSD) |

## Evidence Table 2. Outcomes of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Outcome | Intervention | N | Result |
|---|---|---|---|---|
| **Scott 2007**<br>Multinational<br>active-control<br>Fair | FPG, mmol/L<br>12 weeks | Glipizide | N=121 | Change from baseline: -1.38 (95% CI -1.73, -1.03)<br>Change from placebo: -1.82 (95% CI -2.31, -1.32) |
| | | Sitagliptin (Januvia) 50 mg | N=122 | Change from baseline: -1.01 (95% CI -1.36, -0.66) --> -18 mg/dL<br>Change from placebo: -1.45 (-1.94, -0.96) -->-26 mg/dL, p<0.001 vs. placebo |
| | | Placebo | N=123 | Change from baseline: 0.44 (95% CI 0.09, 0.79) --> +8 mg/dL |
| | HbA1c, percent<br>12 weeks | Glipizide | N=119 | Change from baseline: -0.76 (95% CI -0.90, -0.62)<br>Change from placebo: -1.00 (95% CI -1.19, -0.80) |
| | | Sitagliptin (Januvia) 50 mg | N=121 | Change from baseline: -0.54 (95% CI -0.68, -0.40)<br>Change from placebo: -0.77 (95% CI -0.96, -0.58), p<0.001 vs. placebo |
| | | Placebo | N=121 | Change from baseline: +0.23 (95% CI 0.10, 0.37) |
| | PPG or random glucose, mmol/L | Glipizide | N=32 | 2hr PPG in a subset of patients who underwent meal tolerance test<br>Change from baseline: -3.69 (95% CI -4.80, -2.58) -->66 mg/dL, p<0.01 |
| | | Sitagliptin (Januvia) 50 mg | N=40 | 2hr PPG from meal tolerance test<br>Change from baseline: -2.69 (95% CI -3.69, -1.71) --> -48 mg/dL, p<0.01 vs. baseline |
| | | Placebo | N=38 | Change from baseline: +0.31 (95% CI -0.71, 1.33) --> 6 mg/dL |
| | Weight, Kg<br>12 weeks | Sitagliptin (Januvia) 50 mg | NR | Change from baseline relative to placebo: 0.4 kg (95% CI -0.2, 0.9), p>0.05<br>(N, NR) |

## Evidence Table 2. Outcomes of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Outcome | Intervention | N | Result |
|---|---|---|---|---|
| **Scott 2008** Multinational active-control Fair | FPG, mg/dL 18 weeks | Rosiglitazone + MET monotherapy | N=87 | Change from baseline: -24.5 mg/dL (95% CI -31.6 to -17.5)<br>Placebo-subtracted difference: -30.6 (95% CI -40.6 to -20.7)<br>Difference from sitagliptin: -12.8 (95% CI -22.6 to -3.0) |
| | | Sitagliptin + MET monotherapy | N=92 | Change from baseline: -11.7 mg/dL (95% CI -18.6 to -4.9)<br>Placebo-subtracted difference: -17.8 (95% CI -18.6 to -4.9), P≤0.001 |
| | | Placebo + MET monotherapy | N=89 | Change from baseline: +6.1 mg/dL (95% CI -0.8 to 13.1) |
| | HbA1c, percent 18 weeks | Rosiglitazone + MET monotherapy | N=87 | Change from baseline: -0.79 (95% CI -0.92 to -0.65)<br>Placebo-subtracted difference: -0.57 (95% CI -0.76 to -0.37)<br>Difference from sitagliptin: -0.06 (95% CI -0.25 to 0.14) |
| | | Sitagliptin + MET monotherapy | N=91 | Change from baseline: -0.73 (95% CI -0.87 to -0.60)<br>Placebo-subtracted difference: -0.51% (95% CI -0.70 to -0.32), P≤0.001 |
| | | Placebo + MET monotherapy | N=88 | Change from baseline: -0.22% (95% CI -0.36 to -0.08) |
| | PPG or random glucose, mg/dL | Rosiglitazone + MET monotherapy | N=76 | Change from baseline: -25.4 mg/dL (95% CI -33.2 to -17.5)<br>Placebo-subtracted difference: -46.4 (95% CI -62.1 to -30.7)<br>Difference from sitagliptin: -15.9 (95% CI -31.6 to -0.3) |
| | | Sitagliptin + MET monotherapy | N=80 | Change from baseline: -35.4 (95% CI -46.3 to -24.5)<br>Placebo-subtracted difference: -30.5 (95% CI -46.0 to -15.0), P≤0.001 |
| | | Placebo + MET monotherapy | N=78 | Change from baseline: -4.9 (95% CI -16.0 to 6.1) |
| | Weight, Kg 18 weeks | Rosiglitazone + MET monotherapy | N=87 | Change from baseline: +1.5 kg (estimated from graph) |
| | | Sitagliptin + MET monotherapy | N=91 | Change from baseline: -0.5 kg (estimated from graph) |
| | | Placebo + MET monotherapy | N=88 | Change from baseline: -1.0 kg (estimated from graph) |

## Evidence Table 2. Outcomes of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Outcome | Intervention | N | Result |
|---|---|---|---|---|
| **Whitehouse 2002**<br>US<br>placebo-controlled<br>Fair-poor | HbA1c, percent<br>52 weeks | Pramlintide 30 mcg + 60 mcg (combined) + insulin | N=174 | Placebo corrected difference: -0.39 %, p=0.0071 |
| | | Placebo + insulin | N=168 | Estimated from Figure 1A<br>Change in HbA1c from baselone: -0.12 % |
| | Weight, Kg<br>52 weeks | Pramlintide 30 mcg + 60 mcg (combined) + insulin | N=174 | Estimated from Figure 1B<br>Change in weight from baselone: -0.5 kg |
| | | Placebo + insulin | N=168 | Estimated from Figure 1B<br>Change in weight from baselone: 1.0 kg |
| **Whitehouse 2002**<br>US<br>Open label extension<br>N/A | HbA1c, percent<br>104 weeks | Original Pramlintide arm + insulin | N=125 | Estimated from graph<br>Change from baseline: -0.4 % (unable to determine SEM) |
| | | Switched to pramlintide from placebo + insulin | N=111 | Estimated from graph<br>Change from baseline: -0.4 % (unable to determine SEM from graph) |
| | Weight, Kg<br>104 weeks | Original Pramlintide arm + insulin | N=125 | Estimated from graph<br>Change from baseline: +0.5 kg (SEM 0.5) |
| | | Switched to pramlintide from placebo + insulin | N=111 | Change from baseline: -0.8 kg (SEM 0.5) |

## Evidence Table 2. Outcomes of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Outcome | Intervention | N | Result |
|---|---|---|---|---|
| **Zinman 2007** Canada, Spain, U.S. placebo-controlled Fair | FPG, mmol/L 16 weeks | Exenatide 10 mcg | N=114 | Change from baseline: -1.59 (SE 0.22) -->29 mg/dL<br>Between-treatment difference: -1.69 (95% CI -2.22, -1.17), p<0.001 vs. placebo -->-30 mg/dL |
| | | Placebo | N=105 | Change from baseline: 0.10 (SE 0.21) |
| | HbA1c, percent 16 weeks | Exenatide 10 mcg | N=117 | Change from baseline: -0.89 (SE 0.09), p<0.001 vs. placebo<br>Between-treatment dfference: -0.98 (95% CI -1.21, -0.74), p<0.001 vs. placebo |
| | | Placebo | N=105 | Change from baseline: 0.09 (SE 0.10) |
| | PPG or random glucose, mmol/L | Exenatide 10 mcg | N=106 | From self-monitored blood glucose readings<br>Change from baseline: -1.58<br>Between-treatment difference: -1.27 (95% CI -1.64, -0.91) |
| | | Placebo | N=108 | From self-monitored blood glucose readings<br>Change from baseline: -0.31 |
| | Weight, Kg 16 weeks | Exenatide 10 mcg | N=121 | Change from baseline: -1.75<br>Between-treatment difference: -1.51 (95% CI -2.15, -0.88), p< 0.001 vs. placebo |
| | | Placebo | N=110 | Change from baseline: -0.24 |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| **Aronne 2007**<br>US<br>placebo-controlled<br>Poor | Pramlintide (Symlin) | Total sample size: 137<br>Withdrawals, total: 40 (29.2%)<br>Withdrawals for AEs: 5 (3.65%) | Diarrhea: 12 (8.76%)<br>Nausea: 52 (37.96%)<br>MIld/moderate hypoglycemia: 11 (8.03%)<br>Dizziness: 9 (6.57%)<br>Injection site reaction: 59 (43.07%) | Total withdrawal for the entire cohort: 28%<br>Withdrawals for DM2 subgroup were NR.<br><br>No severe hypoglycemic events.<br><br>Most common AE: injection site reaction, nausea (which was higher during first few months of therapy)<br><br>No CNS AE<br><br>Injection site reactions included: bruising, burning, discomfort, erythema, hemorrhage, nodule, pain, pruritus, rash, scar, stinging, swelling, urticaria, and vesicles |
| | Placebo | Total sample size: 67<br>Withdrawals, total: 17 (25.37%)<br>Withdrawals for AEs: 2 (2.99%) | Diarrhea: 5 (7.46%)<br>Nausea: 15 (22.39%)<br>MIld/moderate hypoglycemia: 1 (1.49%)<br>Dizziness: 4 (5.97%)<br>Injection site reaction: 28 (41.79%) | |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| **Aschner 2006**<br>Multinational<br>placebo-controlled<br>Fair | Sitagliptin 100 mg | Total sample size: 238<br>Withdrawals, total: 29 (12.18%)<br>Withdrawals for AEs: 9 (3.78%) | Hypertension: 6 (2.52%)<br>Abdominal pain: 5 (2.1%)<br>Constipation: 9 (3.78%)<br>Diarrhea: 11 (4.62%)<br>Nausea: 5 (2.1%)<br>Vomiting: 3 (1.26%)<br>Influenza: 11 (4.62%)<br>Nasopharyngitis: 17 (7.14%)<br>Pharyngitis: 5 (2.1%)<br>Sinusitis: 2 (0.84%)<br>Upper Respiratory Tract Infection: 21 (8.82%)<br>Urinary Tract Infection: 5 (2.1%)<br>Viral infection: 2 (0.84%)<br>Blood glucose increase: 3 (1.26%)<br>Hyperglycemia: 5 (2.1%)<br>Hypoglycemia (unspecified): 3 (1.26%)<br>Arthralgia: 3 (1.26%)<br>Back pain: 4 (1.68%)<br>Myalgia: 5 (2.1%)<br>Neck pain: 0 (0%)<br>Pain in extremities: 3 (1.26%)<br>Dizziness: 3 (1.26%)<br>Fatigue: 3 (1.26%)<br>Headache: 11 (4.62%)<br>Pharyngolaryngeal Pain: 3 (1.26%)<br>Cough: 6 (2.52%) | There were no severe hypoglycemic events<br>Three patients had serious drug-related AE.<br><br>Table 2 in Online Appendix |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| | Sitagliptin 200 mg | Total sample size: 250<br>Withdrawals, total: 36 (14.4%)<br>Withdrawals for AEs: 7 (2.8%) | Hypertension: 8 (3.2%)<br>Abdominal pain: 3 (1.2%)<br>Constipation: 7 (2.8%)<br>Diarrhea: 10 (4%)<br>Nausea: 10 (4%)<br>Vomiting: 2 (0.8%)<br>Influenza: 10 (4%)<br>Nasopharyngitis: 15 (6%)<br>Pharyngitis: 5 (2%)<br>Sinusitis: 7 (2.8%)<br>Upper Respiratory Tract Infection: 22 (8.8%)<br>Urinary Tract Infection: 8 (3.2%)<br>Viral infection: 2 (0.8%)<br>Blood Gluc Increase: 6 (2.4%)<br>Hyperglycemia: 1 (0.4%)<br>Hypoglycemia (unspecified): 2 (0.8%)<br>Arthralgia: 10 (4%)<br>Back pain: 5 (2%)<br>Myalgia: 5 (2%)<br>Neck pain: 1 (0.4%)<br>Pain in extremities: 6 (2.4%)<br>Dizziness: 12 (4.8%)<br>Fatigue: 3 (1.2%)<br>Headache: 11 (4.4%)<br>Pharyngolaryngeal Pain: 7 (2.8%)<br>Cough: 5 (2%) | |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| | Placebo | Total sample size: 253<br>Withdrawals, total: 37 (14.62%)<br>Withdrawals for AEs: 10 (3.95%) | Hypertension: 5 (1.98%)<br>Abdominal pain: 4 (1.58%)<br>Constipation: 3 (1.19%)<br>Diarrhea: 6 (2.37%)<br>Nausea: 3 (1.19%)<br>Vomiting: 3 (1.19%)<br>Influenza: 12 (4.74%)<br>Nasopharyngitis: 12 (4.74%)<br>Pharyngitis: 1 (0.4%)<br>Sinusitis: 6 (2.37%)<br>Upper Respiratory Tract Infection: 22 (8.7%)<br>Urinary Tract Infection: 7 (2.77%)<br>Viral infection: 5 (1.98%)<br>Blood Gluc Increase: 8 (3.16%)<br>Hyperglycemia: 5 (1.98%)<br>Hypoglycemia (unspecified): 2 (0.79%)<br>Arthralgia: 7 (2.77%)<br>Back pain: 11 (4.35%)<br>Myalgia: 3 (1.19%)<br>Neck pain: 5 (1.98%)<br>Pain in extremities: 6 (2.37%)<br>Dizziness: 4 (1.58%)<br>Fatigue: 5 (1.98%)<br>Headache: 12 (4.74%)<br>Pharyngolaryngeal Pain: 2 (0.79%)<br>Cough: 8 (3.16%) | |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| **Barnett 2007**<br>Europe, Mexico<br>active-control<br><br>Fair-poor | Exenatide + MET or SU<br><br>Glargine+ MET or SU | Total sample size: 68<br>Withdrawals, total: 20 (29.41%)<br>Withdrawals for AEs: 11 (16.18%)<br><br>Total sample size: 70<br>Withdrawals, total: 2 (2.86%)<br>Withdrawals for AEs: 1 (1.43%) | Nausea: 29 (42.65%)<br>Vomiting: 7 (10.29%)<br>Hypoglycemia (unspecified): 10 (14.71%)<br>Severe hypoglycemia: 0 (0%)<br>Headache: 9 (13.24%)<br><br>Influenza: 8 (11.43%)<br>Pharyngitis: 6 (8.57%)<br>Hypoglycemia (unspecified): 18 (25.71%)<br>Severe hypoglycemia: 3 (4.29%)<br>Headache: 7 (10%)<br>Cough: 6 (8.57%) | AE leading to withdrawal were nausea (5), vomiting (3), and constipation, hypoesthesia, and urticaria (1 each) during exenatide treatment period. Adenocarcinoma of the pancreas (1) during glargine treatment period.<br><br>Total AE were reported by 65.4% of exenatide-treated subjects compared with 52.8% of glargine-treated subjects.<br><br>Nausea was generally mild-moderate and tended to occur during initiation of exenatide.<br><br>No exenatide-treated subjects reported severe hypoglycemia compared with 3 glargine-treated subjects who reported a total of 8 hypoglycemic episodes.<br><br>In patients on SU, there were no significant differences in rates of overall hypoglycemia or nocturnal hypoglycemia between the treatment arms. |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| **Blonde 2006**<br>US<br>Open label extension<br>N/A | Exenatide 10 mcg | Total sample size: 551<br>Withdrawals, total: 237 (43.01%)<br>Withdrawals for AEs: 39 (7.08%) | Nausea: 160 (29.04%)<br>Nausea: 83 (15.06%)<br>MIld/moderate hypoglycemia: 61 (11.07%)<br>MIld/moderate hypoglycemia: 55 (9.98%)<br>Severe hypoglycemia: 4 (0.73%) | Total withdrawals based on ITT population= 237 (43%)<br>Withdrawals due to AE based on ITT population= 39 (7%)<br><br>Table 3 has subgroup information on the effects of nausea on HbA1c and weight. Pearson correlation analysis that examined the nausea-by-weight correlations in the 82-week completer cohort found that the reduction in body weight was unlikely to be driven by the direct effect of nausea (r= -0.11).<br><br>Safety endpoints included AEs occuring upon or after receiving the 1st exenatide dose during the primary trials through the 82-wk period. All safety analyses were performed per ITT population. |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| **Buse 2004**<br>US<br>placebo-controlled<br>Fair | Exenatide 10 mcg + SU | Total sample size: 129<br>Withdrawals, total: 38 (29.5%)<br>Withdrawals for AEs: 13 (10.1%) | Constipation: 12 (9.3%)<br>Diarrhea: 11 (8.53%)<br>Nausea: 66 (51.16%)<br>Vomiting: 17 (13.18%)<br>Hypoglycemia (unspecified): 46 (35.66%)<br>Weakness: 2 (1.55%)<br>Dizziness: 19 (14.73%)<br>Headache: 10 (7.75%)<br>Feeling jittery: 19 (14.73%)<br>Increased sweating: 10 (7.75%) | No AE for vital signs, HR, BP, PE. 12 subjects had transient increases in creatine phosphokinase.<br><br>1-subject in the exenatide 10 mcg arm and 1-sibject in the placebo arm had an MI; 1-subject in the placebo arm experienced clinical manifestations of CAD.<br><br>No severe hypoglycemia, however, 1-subject in the exenatide 5 mcg arm withdrew due to hypoglycemia. |
| | Exenatide 5 mcg + SU | Total sample size: 125<br>Withdrawals, total: 30 (24.0%)<br>Withdrawals for AEs: 9 (7.2%) | Constipation: 2 (1.6%)<br>Diarrhea: 14 (11.2%)<br>Nausea: 49 (39.2%)<br>Vomiting: 12 (9.6%)<br>Hypoglycemia (unspecified): 18 (14.4%)<br>Weakness: 7 (5.6%)<br>Dizziness: 19 (15.2%)<br>Headache: 11 (8.8%)<br>Feeling jittery: 15 (12%)<br>Increased sweating: 3 (2.4%) | |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| | Placebo (combined) + SU | Total sample size: 123<br>Withdrawals, total: 49 (39.8%)<br>Withdrawals for AEs: 4 (3.3%) | Constipation: 4 (3.25%)<br>Diarrhea: 5 (4.07%)<br>Nausea: 9 (7.32%)<br>Vomiting: 3 (2.44%)<br>Hypoglycemia (unspecified): 4 (3.25%)<br>Weakness: 4 (3.25%)<br>Dizziness: 8 (6.5%)<br>Headache: 8 (6.5%)<br>Feeling jittery: 2 (1.63%)<br>Increased sweating: 1 (0.81%) | |
| **Buse 2007**<br>U.S.<br>Open label extension<br>N/A | Exenatide 10 mcg | Total sample size: 521<br>Withdrawals, total: 238 (45.68%)<br>Withdrawals for AEs: 45 (8.64%) | Nausea: 203 (39.04%)<br>Nausea: 23 (7.85%)<br>Nausea: 139 (29.08%)<br>Upper Respiratory Tract Infection: 6 (2.05%)<br>Upper Respiratory Tract Infection: 48 (10.04%)<br>Upper Respiratory Tract Infection: 36 (6.92%)<br>Hypoglycemia (unspecified): 62 (12.97%)<br>Hypoglycemia (unspecified): 67 (12.88%) | All safety analyses were performed by using the ITT population defined as all patients who received at least 1-dose of exenatide from the beginning of the OLE and who enrolled with timing such that they would achieve 2 years of exenatide tx prior to analysis cut-off date.<br><br>No evidence of exenatide-related cardiovascular, pulmonary, hepatic, or renal toxicity or of idiosnycratic AE associated with its use.<br><br>1-severe hypoglycemic event in 1010 subject-yrs of exenatide exposure in the ITT (n= 521) population. Prevalence of hypoglycemia was no different among those >65 yrs of age compared to younger subjects. |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| **Charbonnel 2006**<br>multinational<br>placebo-controlled<br>Fair | Sitagliptin 100mg + MET ≥ 1.5 g | Total sample size: 464<br>Withdrawals, total: 48 (10.34%)<br>Withdrawals for AEs: 11 (2.37%) | Hypertension: 7 (1.51%)<br>Abdominal pain: 10 (2.16%)<br>Diarrhea: 12 (2.59%)<br>Gastroenteritis: 4 (0.86%)<br>Nausea: 6 (1.29%)<br>Vomiting: 5 (1.08%)<br>Influenza: 20 (4.31%)<br>Nasopharyngitis: 19 (4.09%)<br>Upper Respiratory Tract Infection: 34 (7.33%)<br>Urinary Tract Infection: 11 (2.37%)<br>Blood Gluc Increase: 3 (0.65%)<br>Hyperglycemia: 2 (0.43%)<br>Hypoglycemia (unspecified): 6 (1.29%)<br>Arthralgia: 14 (3.02%)<br>Back pain: 15 (3.23%)<br>Headache: 13 (2.8%)<br>Bronchitis: 13 (2.8%)<br>Cough: 14 (3.02%) | Most common reasons for discontinuation were lack of efficacy, withdrawal of consent, clinical adverse experiences, and lost to follow-up.<br><br>There was no statistically significant differences in the incidence of hypoglycemia (did not report if there were reports of severe hypoglycemic events).<br><br>There was a small man increase (<10%) in WBC related to increase in ANC in the sitagliptin 100mg arm compared to placebo.<br><br>Prespecified AEs included hypoglycemia, change in wt, and gastrointestinal AE (abdominal pain, diarrhea, nausea, vomiting). |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| | Placebo + MET ≥ 1.5 g | Total sample size: 237<br>Withdrawals, total: 45 (18.99%)<br>Withdrawals for AEs: 7 (2.95%) | Hypertension: 6 (2.53%)<br>Abdominal pain: 9 (3.8%)<br>Diarrhea: 6 (2.53%)<br>Gastroenteritis: 5 (2.11%)<br>Nausea: 2 (0.84%)<br>Vomiting: 2 (0.84%)<br>Influenza: 13 (5.49%)<br>Nasopharyngitis: 8 (3.38%)<br>Upper Respiratory Tract Infection: 22 (9.28%)<br>Urinary Tract Infection: 3 (1.27%)<br>Blood Gluc Increase: 6 (2.53%)<br>Hyperglycemia: 7 (2.95%)<br>Hypoglycemia (unspecified): 5 (2.11%)<br>Arthralgia: 1 (0.42%)<br>Back pain: 6 (2.53%)<br>Headache: 7 (2.95%)<br>Bronchitis: 6 (2.53%)<br>Cough: 4 (1.69%) | |
| **Davis 2007**<br>U.S.<br>active-control<br><br>Fair-poor | Exenatide (Byetta) 10 mcg BID + oral antidiabetes | Total sample size: 33<br>Withdrawals, total: 14 (42.42%)<br>Withdrawals for AEs: 5 (15.15%) | Chest pain: 1 (%)<br>Hyperglycemia: 1 (%)<br>Severe hypoglycemia: 1 (%) | Five exenetide patients discontinued (bronchitis (1) , hyperglycemia (1) and nausea (3)) |
| | Insulin + oral diabetes meds | Total sample size: 16<br>Withdrawals, total: 1 (6.25%)<br>Withdrawals for AEs: 0 (0%) | Chest pain: 0 (%)<br>Hyperglycemia: 0 (%)<br>Severe hypoglycemia: 0 (0%) | |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| **DeFronzo 2005**<br>U.S.<br>placebo-controlled<br>Fair | Exenatide (Byetta) 10 mcg BID + metformin | Total sample size: 113<br>Withdrawals, total: 20 (17.7%)<br>Withdrawals for AEs: 8 (7.08%) | Diarrhea: 18 (15.93%)<br>Nausea: 51 (45.13%)<br>Vomiting: 13 (11.5%)<br>Sinusitis: 7 (6.19%)<br>Upper Respiratory Tract Infection: 11 (9.73%)<br>MIld/moderate hypoglycemia: 6 (5.31%)<br>Back pain: 7 (6.19%)<br>Dizziness: 5 (4.42%) | Withdrawals from loss of glucose control as defined in protocol: 9 (8.0%) for placebo, 5 (4.5%) for 5 mcg BID exenatide, and 1 (0.9%) for 10 mcg BID exenatide<br><br>No cases of severe hypoglycemia.<br>Exenatide not associated with an increased incidence of cardiovascular, hepatic, or renal adverse events.<br>No changes in plasma lipids, lab safety parameters, heart rate, blood pressure, or electrocardiogram variables observed w/ treatment arms. |
| | Exenatide (Byetta) 5mcg BID + metformin | Total sample size: 110<br>Withdrawals, total: 20 (18.18%)<br>Withdrawals for AEs: 4 (3.64%) | Diarrhea: 13 (11.82%)<br>Nausea: 40 (36.36%)<br>Vomiting: 12 (10.91%)<br>Sinusitis: 5 (4.55%)<br>Upper Respiratory Tract Infection: 15 (13.64%)<br>MIld/moderate hypoglycemia: 5 (4.55%)<br>Back pain: 3 (2.73%)<br>Dizziness: 10 (9.09%) | |
| | Placebo + metformin | Total sample size: 113<br>Withdrawals, total: 24 (21.24%)<br>Withdrawals for AEs: 1 (0.88%) | Diarrhea: 9 (7.96%)<br>Nausea: 26 (23.01%)<br>Vomiting: 4 (3.54%)<br>Sinusitis: 6 (5.31%)<br>Upper Respiratory Tract Infection: 12 (10.62%)<br>MIld/moderate hypoglycemia: 6 (5.31%)<br>Back pain: 3 (2.65%)<br>Dizziness: 7 (6.19%) | |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| **Edelman 2006**<br>US<br>placebo-controlled<br>Fair | Combined Pramlintide arms + insulin | Total sample size: 148<br>Withdrawals, total: 32 (21.62%)<br>Withdrawals for AEs: 8 (5.41%) | | High differential in total withdrawal between placebo (9.5%) and combined pramlintide arm (21.6%).<br><br>Patients were instructed to self-monitor BG at least 6x/day. |
| | Pramlintide 30mcg + insulin | Total sample size: 41<br>Withdrawals, total: 17 (41.46%)<br>Withdrawals for AEs: 6 (14.63%) | Nausea: 39 (95.12%)<br>Vomiting: 7 (17.07%)<br>Sinusitis: 9 (21.95%)<br>Decreased appetite: 6 (14.63%)<br>Depression: 1 (2.44%) | |
| | Pramlintide 60mcg + insulin | Total sample size: 101<br>Withdrawals, total: 10 (9.9%)<br>Withdrawals for AEs: 1 (0.99%) | Nausea: 49 (48.51%)<br>Vomiting: 12 (11.88%)<br>Sinusitis: 13 (12.87%)<br>Decreased appetite: 7 (6.93%) | |
| | Placebo+insulin | Total sample size: 147<br>Withdrawals, total: 14 (9.52%)<br>Withdrawals for AEs: 3 (2.04%) | Nausea: 53 (36.05%)<br>Vomiting: 9 (6.12%)<br>Sinusitis: 13 (8.84%)<br>Decreased appetite: 3 (2.04%) | |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| **Goldstein 2007**<br>multinational<br>placebo-controlled<br>Fair | MET 1000 mg Bid | Total sample size: 182<br>Withdrawals, total: 26 (14.29%)<br>Withdrawals for AEs: 5 (2.75%) | Abdominal pain: 9 (4.95%)<br>Diarrhea: 19 (10.44%)<br>Gastrointestinal disorders (unspecified): 46 (25.27%)<br>Nausea: 15 (8.24%)<br>Vomiting: 2 (1.1%)<br>Hypoglycemia (unspecified): 2 (1.1%) | Total withdrawn: 185/1091 (17%)<br>For AE: 27 (2.5%)<br><br>No severe hypoglycemic events; GI AE higher in high-dose MET arms<br>1 drug-related SAE (a patient in the placebo arm with ketoacidosis)<br>1 patient in the placebo arm died during the study due to sudden cardiac death |
| | MET 500 mg Bid | Total sample size: 182<br>Withdrawals, total: 29 (15.93%)<br>Withdrawals for AEs: 4 (2.2%) | Abdominal pain: 5 (2.75%)<br>Diarrhea: 9 (4.95%)<br>Gastrointestinal disorders (unspecified): 29 (15.93%)<br>Nausea: 5 (2.75%)<br>Vomiting: 0 (0%)<br>Hypoglycemia (unspecified): 1 (0.55%) | |
| | Sitagliptin 100 mg | Total sample size: 179<br>Withdrawals, total: 37 (20.67%)<br>Withdrawals for AEs: 6 (3.35%) | Abdominal pain: 6 (3.35%)<br>Diarrhea: 5 (2.79%)<br>Gastrointestinal disorders (unspecified): 27 (15.08%)<br>Nausea: 2 (1.12%)<br>Vomiting: 0 (0%)<br>Hypoglycemia (unspecified): 1 (0.56%) | |
| | Sitagliptin 50 mg + MET 1000 mg Bid | Total sample size: 182<br>Withdrawals, total: 18 (9.89%)<br>Withdrawals for AEs: 1 (0.55%) | Abdominal pain: 6 (3.3%)<br>Diarrhea: 16 (8.79%)<br>Gastrointestinal disorders (unspecified): 45 (24.73%)<br>Nausea: 10 (5.49%)<br>Vomiting: 6 (3.3%)<br>Hypoglycemia (unspecified): 4 (2.2%) | |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| | Sitagliptin 50 mg + MET 500 mg Bid | Total sample size: 190<br>Withdrawals, total: 26 (13.68%)<br>Withdrawals for AEs: 4 (2.11%) | Abdominal pain: 5 (2.63%)<br>Diarrhea: 12 (6.32%)<br>Gastrointestinal disorders (unspecified): 34 (17.89%)<br>Nausea: 8 (4.21%)<br>Vomiting: 2 (1.05%)<br>Hypoglycemia (unspecified): 2 (1.05%) | |
| | Placebo | Total sample size: 176<br>Withdrawals, total: 49 (27.84%)<br>Withdrawals for AEs: 7 (3.98%) | Abdominal pain: 4 (2.27%)<br>Diarrhea: 7 (3.98%)<br>Gastrointestinal disorders (unspecified): 19 (10.8%)<br>Nausea: 2 (1.14%)<br>Vomiting: 1 (0.57%)<br>Hypoglycemia (unspecified): 1 (0.57%) | |
| **Goldstein 2007**<br><br>Open-label cohort<br><br>Poor | Sitagliptin 50 mg + MET 1000 mg Bid | Total sample size: 117<br>Withdrawals, total: 38 (32.48%)<br>Withdrawals for AEs: (NR%) | Abdominal pain: 6 (5.13%)<br>Diarrhea: 10 (8.55%)<br>Gastrointestinal disorders (unspecified): 32 (27.35%)<br>Nausea: 7 (5.98%)<br>Vomiting: 4 (3.42%)<br>Hypoglycemia (unspecified): 2 (1.71%) | 32.5% withdrew from the open-label cohort and 16.2% withdrew due to lack of efficacy<br><br>"generally well tolerated, with a profile similar to that observed in patients in the randomized cohort" |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| **Heine 2005**<br>Multinational<br>active-control<br><br>Fair | Exenatide + MET/SU | Total sample size: 282<br>Withdrawals, total: 55 (19.5%)<br>Withdrawals for AEs: 27 (9.57%) | Chest pain: 6 (2.13%)<br>Rash: 3 (1.06%)<br>Constipation: 10 (3.55%)<br>Diarrhea: 24 (8.51%)<br>Dyspepsia: 10 (3.55%)<br>Nausea: 161 (57.09%)<br>Upper abdominal pain: 12 (4.26%)<br>Vomiting: 49 (17.38%)<br>Influenza: 7 (2.48%)<br>Nasopharyngitis: 22 (7.8%)<br>Sinusitis: 7 (2.48%)<br>Upper Respiratory Tract Infection: 15 (5.32%)<br>Urinary Tract Infection: 7 (2.48%)<br>Anorexia: 10 (3.55%)<br>Decreased appetite: 9 (3.19%)<br>Severe hypoglycemia: 4 (1.42%)<br>Arthralgia: 9 (3.19%)<br>Asthenia: 6 (2.13%)<br>Back pain: 17 (6.03%)<br>Pain in extremities: 11 (3.9%)<br>Anxiety: 6 (2.13%)<br>Dizziness: 15 (5.32%)<br>Headache: 25 (8.87%)<br>Pharyngolaryngeal Pain: 12 (4.26%)<br>Bronchitis: 5 (1.77%)<br>Cough: 11 (3.9%) | One patient from the insulin glargine group and 18 patients from the exenatide group withdrew from the trial because of nausea or other gastrointestinal symptoms.<br><br>Safety analysis according to those who were randomized to treatment; exenatide, n= 282; glargine, n= 267<br><br>Most common AE among exentaide patients was nausea 57.1% and vomiting 17.4%, p< 0.001 vs. glargline<br><br>1 patient in glargine and 18 from exenatide withdrew due to nausea or other gastrointestinal-related AE<br><br>4 patients in each arm had severe hypoglycemic events but none withdrew |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| | Glargine + MET/SU | Total sample size: 267<br>Withdrawals, total: 26 (9.74%)<br>Withdrawals for AEs: 2 (0.75%) | Chest pain: 3 (1.12%)<br>Rash: 6 (2.25%)<br>Constipation: 1 (0.37%)<br>Diarrhea: 8 (3%)<br>Dyspepsia: 1 (0.37%)<br>Nausea: 23 (8.61%)<br>Upper abdominal pain: 2 (0.75%)<br>Vomiting: 10 (3.75%)<br>Influenza: 15 (5.62%)<br>Nasopharyngitis: 24 (8.99%)<br>Sinusitis: 4 (1.5%)<br>Upper Respiratory Tract Infection: 13 (4.87%)<br>Urinary Tract Infection: 3 (1.12%)<br>Anorexia: 0 (0%)<br>Decreased appetite: 1 (0.37%)<br>Severe hypoglycemia: 4 (1.5%)<br>Arthralgia: 10 (3.75%)<br>Asthenia: 7 (2.62%)<br>Back pain: 8 (3%)<br>Pain in extremities: 8 (3%)<br>Anxiety: 2 (0.75%)<br>Dizziness: 6 (2.25%)<br>Headache: 23 (8.61%)<br>Pharyngolaryngeal Pain: 11 (4.12%)<br>Bronchitis: 7 (2.62%)<br>Cough: 8 (3%) | |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| **Hermansen 2007**<br>Denmark, USA<br>placebo-controlled<br>Fair | Entire Placebo cohort | Total sample size: 219<br>Withdrawals, total: 40 (18.26%)<br>Withdrawals for AEs: 2 (0.91%) | Abdominal pain: 2 (0.91%)<br>Diarrhea: 6 (2.74%)<br>Nausea: 1 (0.46%)<br>Vomiting: 1 (0.46%)<br>Hypoglycemia (unspecified): 4 (1.83%) | There was a numerically larger proportion of subjects in the sitagliptin+glimepiride arm that withdrew and withdrew due to AE<br><br>No severe hypoglycemic events. |
| | Entire Sitagliptin cohort | Total sample size: 222<br>Withdrawals, total: 37 (16.67%)<br>Withdrawals for AEs: 6 (2.7%) | Abdominal pain: 5 (2.25%)<br>Diarrhea: 3 (1.35%)<br>Nausea: 1 (0.45%)<br>Vomiting: 3 (1.35%)<br>Hypoglycemia (unspecified): 27 (12.16%) | The overall incidence of clinical adverse event and drug-related clinical AEs was higher in the sitagliptin+glimepiride+MET arm compared to the placebo+glimepiride+MET arm. |
| | Sitagliptin + Glimepiride | Total sample size: 106<br>Withdrawals, total: 23 (21.7%)<br>Withdrawals for AEs: 4 (3.77%) | Abdominal pain: 3 (2.83%)<br>Diarrhea: 2 (1.89%)<br>Nausea: 0 (0%)<br>Vomiting: 1 (0.94%)<br>Hypoglycemia (unspecified): 8 (7.55%) | 1 death in sitagliptin arm which was considered not to be study medication related by the investigator<br><br>There were small decreases in Alk Phos and Bilirubib for those in the sitagliptin arm vs. placebo.<br><br>There were small increases in WBC and ANC in those in the sitagliptin arm.<br><br>No differences in liver function test |
| | Sitagliptin + Glimepiride + MET | Total sample size: 116<br>Withdrawals, total: 14 (12.07%)<br>Withdrawals for AEs: 2 (1.72%) | Abdominal pain: 2 (1.72%)<br>Diarrhea: 1 (0.86%)<br>Nausea: 1 (0.86%)<br>Vomiting: 2 (1.72%)<br>Hypoglycemia (unspecified): 19 (16.38%) | |
| | Placebo + Glimepiride | Total sample size: 106<br>Withdrawals, total: 19 (17.92%)<br>Withdrawals for AEs: 0 (0%) | Abdominal pain: 0 (0%)<br>Diarrhea: 2 (1.89%)<br>Nausea: 0 (0%)<br>Vomiting: 0 (0%)<br>Hypoglycemia (unspecified): 3 (2.83%) | |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| | Placebo + Glimepiride + MET | Total sample size: 113<br>Withdrawals, total: 21 (18.58%)<br>Withdrawals for AEs: 2 (1.77%) | Abdominal pain: 2 (1.77%)<br>Diarrhea: 4 (3.54%)<br>Nausea: 1 (0.88%)<br>Vomiting: 1 (0.88%)<br>Hypoglycemia (unspecified): 1 (0.88%) | |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| **Hollander 2003**<br>US<br>placebo-controlled<br>Fair | Pramlintide 120 mcg + adjunct insulin | Total sample size: 166<br>Withdrawals, total: 53 (32%)<br>Withdrawals for AEs: (NR%) | Nausea: 50 (30.12%)<br>Severe nausea: 3 (1.81%)<br>Headache: 28 (16.87%) | 113 (70%) in placebo arm; 122 (71%) pramlintide 90 mcg Bid; 113 (68%) pramlintide 120 mcg Bid completed 52 weeks of treatment.<br><br>The most common reasons with withdrawal were withdrawal of consent and AE--NR.<br><br>All patients received a SMBG machine and were instructed to record BG readings and insulin doses into diaries. Patients were also to self-minitor for sx of hypoglycemia and if possible obtain BG readings.<br><br>Did not report any other AE; severe hypoglycemia was reported as an event rate per patient year (total number of events/total number of patients yrs of observation for all patients in that treatment regimen).<br><br>No evidence of CV, pulm, hepatic, or renal tox or of drug-related idiosyncratic SE as assoc'd with Pram; no abNL changes in lab values, EKG, VS<br><br>Incidence of nausea in those taking MET was no different than other groups |
| | Pramlintide 90 mcg + adjunct inuslin | Total sample size: 171<br>Withdrawals, total: 50 (29%)<br>Withdrawals for AEs: (NR%) | Nausea: 53 (30.99%)<br>Severe nausea: 7 (4.09%)<br>Headache: 26 (15.2%) | |
| | Placebo + adjunct insulin | Total sample size: 161<br>Withdrawals, total: 48 (30%)<br>Withdrawals for AEs: (NR%) | Nausea: 23 (14.29%)<br>Severe nausea: 2 (1.24%)<br>Headache: 13 (8.07%) | |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| **Hollander 2003**<br>NR<br>Pooled analysis<br>N/A | Pramlintide 120 mcg + insulin | Total sample size: 86<br>Withdrawals, total: (NR%)<br>Withdrawals for AEs: (NR%) | Nausea: 16 (18.6%)<br>Anorexia: 10 (11.63%)<br>Injection site reaction: 12 (13.95%) | Event rate for severe hypoglycemia at the beginning of the study (0-4wks) was the same in the 2 treatment groups, for 4-26 weeks, pramlinitide treated patients had fewer severe hypoglycemic events.<br><br>There was no evidence of cardiovascular, hepatic, or renal toxicity, etc. |
| | Placebo + insulin | Total sample size: 80<br>Withdrawals, total: (NR%)<br>Withdrawals for AEs: (NR%) | Nausea: 7 (8.75%)<br>Anorexia: 3 (3.75%)<br>Injection site reaction: 5 (6.25%) | |
| **Hollander 2004**<br>N/A<br>Pooled analysis<br>N/A | Pramlintide + insulin | Total sample size: 254<br>Withdrawals, total: (NR%)<br>Withdrawals for AEs: (NR%) | Nausea: 60 (23.62%) | There was no evidence of cardiovascular, hepatic, or renal toxicity, and no changes in lipid profile, etc.<br><br>The only treatment-emergent adverse event, with an incidence >10% and a 2-fold greater incidence among pramlintide-treated compared with placebo-treated patients, was nausea (23.6%-pram vs. 9.4%-placebo, for weeks 0 to 26). |
| | Placebo + insulin | Total sample size: 244<br>Withdrawals, total: (NR%)<br>Withdrawals for AEs: (NR%) | Nausea: 23 (9.43%) | |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| **Karl 2007**<br>US<br>Open-label cohort<br>N/A | Pramlintide 120mcg + insulin | Total sample size: 166<br>Withdrawals, total: 52 (31.33%)<br>Withdrawals for AEs: 15 (9.04%) | Diarrhea: 9 (5.42%)<br>Nausea: 49 (29.52%)<br>Severe nausea: 4 (2.41%)<br>Vomiting: 12 (7.23%)<br>MIld/moderate hypoglycemia: 19 (11.45%)<br>Severe hypoglycemia: 1 (0.6%)<br>Severe hypoglycemia: 2 (1.2%)<br>Severe hypoglycemia: 1 (0.6%) | Safety was assessed based on reports of adverse events, responses to nondirected questioning, etc.<br><br>Severe hypoglycemia is also reported as event rate/patient year= total number of events for all patients/total number of patient-years observed for all patients in that treatment group<br><br>No evidence of CV, pulmonary, hepatic, or renal tox, or of drug-related idiosyncratic effects. |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| **Kendall 2005**<br>US<br>placebo-controlled<br>Fair | Exenatide 10 mcg + MET/SU | Total sample size: 241<br>Withdrawals, total: 43 (17.84%)<br>Withdrawals for AEs: 22 (9.13%) | Diarrhea: 42 (17.43%)<br>Nausea: 117 (48.55%)<br>Vomiting: 33 (13.69%)<br>Upper Respiratory Tract Infection: 42 (17.43%)<br>Hypoglycemia (unspecified): 67 (27.8%)<br>Headache: 18 (7.47%)<br>Feeling jittery: 28 (11.62%) | More subjects in the placebo arm withdrew but more subjects in the exenatide 10 mcg arm withdrew due to AEs<br><br>Any subject with either an A1C change of +1.5% from baseline at any clinic visit or an A1C > or =11.5% at wk 18 or 24 could be withdrawn from the study.<br><br>*Base on ITT-population<br><br>Overall incidence of hypoglycemia was higher in each exenatide arm than those in the placebo arm.<br><br>No evidence of cardiovascular, pulmonary, hepatic, or renal toxicity or drug-related idiosyncratic side effects.<br><br>1-severe hypoglycemic event in the exenatide 5 mcg arm. |
| | Exenatide 5 mcg + MET/SU | Total sample size: 245<br>Withdrawals, total: 39 (15.92%)<br>Withdrawals for AEs: 14 (5.71%) | Diarrhea: 25 (10.2%)<br>Nausea: 96 (39.18%)<br>Vomiting: 36 (14.69%)<br>Upper Respiratory Tract Infection: 28 (11.43%)<br>Hypoglycemia (unspecified): 47 (19.18%)<br>Severe hypoglycemia: 1 (0.41%)<br>Headache: 27 (11.02%)<br>Feeling jittery: 21 (8.57%) | |
| | Placebo (combined) + MET/SU | Total sample size: 247<br>Withdrawals, total: 59 (23.89%)<br>Withdrawals for AEs: 11 (4.45%) | Diarrhea: 16 (6.48%)<br>Nausea: 51 (20.65%)<br>Vomiting: 11 (4.45%)<br>Upper Respiratory Tract Infection: 48 (19.43%)<br>Hypoglycemia (unspecified): 31 (12.55%)<br>Headache: 12 (4.86%)<br>Feeling jittery: 17 (6.88%) | |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| **King 2006**<br>U.S.<br>retrospective uncontrolled<br>Poor | Exenatide (Byetta) | Total sample size: 200<br>Withdrawals, total: 70 (35%)<br>Withdrawals for AEs: 26 (13%) | Urticaria: 4 (2%)<br>Abdominal pain: 2 (1%)<br>Nausea: 16 (8%)<br>Hypoglycemia (unspecified): 1 (0.5%)<br>Feeling jittery: 3 (1.5%) | Urticaria became generalized in one patient continuing exenatide. |
| **Klonoff 2008**<br>NR<br>Pooled analysis<br>N/A | 3 year completers<br><br>3.5 year completers | Total sample size: 217<br>Withdrawals, total: (%)<br>Withdrawals for AEs: (%)<br><br>Total sample size: 151<br>Withdrawals, total: (%)<br>Withdrawals for AEs: (%) | | There was no evidence of exenatide-related cardiovascular, pulmonary, hepatic or renal toxicity, or of drug-related idiosyncratic effects associated with its use. The 3 most commonly reported AE: nausea 59%, hypoglycemia 40%, upper respiratory tract infection 36%.<br><br>There was 1-severe hypoglycemic event in a patient who was treated with MET and SU.<br><br>The incidence of hypoglycemia were no different for those >65 yrs and those <65 yrs. |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| **Maggs 2003**<br>NR<br>Pooled analysis<br><br>N/A | Pramlintide (African American) + insulin | Total sample size: 26<br>Withdrawals, total: (%)<br>Withdrawals for AEs: (%) | | Overall withdrawal rates in the placebo-treated group were 28% compared with 35% in the pramlintide-treated group with the percent withdrawal evenly represented across the 3 ethnic groups: 29% versus 35% in Caucasians, 30% versus 35% in African Americans, and 24% versus 31% in Hispanics.<br><br>The main reasons for withdrawal in the placebo and pramlintide groups were withdrawal of consent (9% v 8%) and adverse events (9% v 15%).<br><br>No evidence of cardiovascular, pulmonary, hepatic, or renal toxicity or of drug-related idiosyncratic side effects associated with its use.<br><br>The incidence of nausea in the overall study population was 25% for pramlintide versus 16% for placebo, with comparable patterns in the 3 ethnic groups: 26% versus 17% in Caucasians, 23% versus 14% in African Americans, and 23% versus 12% in Hispanics.<br><br>The incidence rates of hypoglycemia were similar between pramlintide and placebo: 43% versus 40% in the overall study population, 48% versus 43% in Caucasians, 31% versus 33% in African Americans, and 23% versus 27% in Hispanics. |
| | Pramlintide (Caucasian) + insulin | Total sample size: 151<br>Withdrawals, total: (%)<br>Withdrawals for AEs: (%) | | |
| | Pramlintide (Hispanic) + insulin | Total sample size: 22<br>Withdrawals, total: (%)<br>Withdrawals for AEs: (%) | | |
| | Placebo (African American) + insulin | Total sample size: 21<br>Withdrawals, total: (%)<br>Withdrawals for AEs: (%) | | |
| | Placebo (Caucasian) + insulin | Total sample size: 164<br>Withdrawals, total: (%)<br>Withdrawals for AEs: (%) | | |
| | Placebo (Hispanic) + insulin | Total sample size: 26<br>Withdrawals, total: (%)<br>Withdrawals for AEs: (%) | | |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| **Nauck 2007**<br>Multinational<br>active-control<br><br>Fair | Biphasic Aspart + MET/SU | Total sample size: 248<br>Withdrawals, total: 25 (10.08%)<br>Withdrawals for AEs: 0 (0%) | Cardiac disorders (unspecified): 5 (2.02%)<br>Hypertension: 7 (2.82%)<br>Diarrhea: 5 (2.02%)<br>Dyspepsia: 1 (0.4%)<br>Nausea: 1 (0.4%)<br>Vomiting: 8 (3.23%)<br>Influenza: 16 (6.45%)<br>Nasopharyngitis: 24 (9.68%)<br>Anorexia: 0 (0%)<br>Decreased appetite: 0 (0%)<br>Arthralgia: 4 (1.61%)<br>Back pain: 10 (4.03%)<br>Pain in extremities: 8 (3.23%)<br>Depression: 1 (0.4%)<br>Headache: 13 (5.24%)<br>Accidental falls: 1 (0.4%)<br>Cancer/neoplasm: 2 (0.81%)<br>Deaths: 1 (0.4%)<br>Injection site reaction: 1 (0.4%)<br>Bronchitis: 6 (2.42%) | The incidence of GI AE was higher with exenatide than insulin.<br><br>No severe hypoglycemia reported |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| | Exenatide + MET/SU | Total sample size: 253<br>Withdrawals, total: 54 (21.34%)<br>Withdrawals for AEs: 20 (7.91%) | Cardiac disorders (unspecified): 10 (3.95%)<br>Hypertension: 5 (1.98%)<br>Diarrhea: 24 (9.49%)<br>Dyspepsia: 7 (2.77%)<br>Nausea: 84 (33.2%)<br>Vomiting: 38 (15.02%)<br>Influenza: 18 (7.11%)<br>Nasopharyngitis: 28 (11.07%)<br>Anorexia: 7 (2.77%)<br>Decreased appetite: 11 (4.35%)<br>Arthralgia: 6 (2.37%)<br>Back pain: 11 (4.35%)<br>Pain in extremities: 6 (2.37%)<br>Depression: 6 (2.37%)<br>Headache: 12 (4.74%)<br>Accidental falls: 3 (1.19%)<br>Cancer/neoplasm: 1 (0.4%)<br>Deaths: 2 (0.79%)<br>Injection site reaction: 4 (1.58%)<br>Bronchitis: 6 (2.37%) | |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| **Nauck 2007** Multinational active-control Fair-poor | Glipizide + MET | Total sample size: 584<br>Withdrawals, total: 172 (29.45%)<br>Withdrawals for AEs: 26 (4.45%) | Abdominal pain: 12 (2.05%)<br>Diarrhea: 32 (5.48%)<br>Nausea: 16 (2.74%)<br>Vomiting: 9 (1.54%)<br>Nasopharyngitis: 44 (7.53%)<br>Sinusitis: 11 (1.88%)<br>Urinary Tract Infection: 16 (2.74%)<br>Hypoglycemia (unspecified): 187 (32.02%)<br>Severe hypoglycemia: 7 (1.2%)<br>Osteoarthritis: 4 (0.68%)<br>Pain in extremities: 8 (1.37%)<br>Dizziness: 12 (2.05%)<br>Fatigue: 5 (0.86%) | 379 pts excluded from PP analysis, 96% were excluded because of missing txmt data at Week 52.<br><br>More pts in the sitagliptin group dc'd txmt compared w/ glipizide group; this difference was mainly bc of a higher number of sitagliptin-treated patients dc'ing for lack of efficacy, which was based on prespecified FBG and/or HbA1c criteria throughout the txmt period. Pts who dc'd bc of lack of efficacy had more severe hyperglycaemia at baseline than those who completed the study (baseline HbA1c: 8.6 vs. 7.5%, respectively); dc'd pts also tended to be slightly older than pts who completed the study (57 vs. 55 years, respectively) and had a slightly more body weight (93 vs. 90 kg, respectively).<br><br>There were 3 deaths (2-glipizide arm and 1-sitagliptin arm)<br>Incidence of overall gastrointestinal events was similar in sitagliptin and glipizide arms (20.4% vs. 19.3%)<br><br>Gastrointestinal AE were prespecified<br><br>2 SAE considered related to study drug by the investigator in the glipizide group (myocardial infarction and spontaneous abortion) and none in the sitagliptin group. |
| | Sitagliptin +MET | Total sample size: 588<br>Withdrawals, total: 202 (34.35%)<br>Withdrawals for AEs: 25 (4.25%) | Abdominal pain: 16 (2.72%)<br>Diarrhea: 34 (5.78%)<br>Nausea: 15 (2.55%)<br>Vomiting: 5 (0.85%)<br>Nasopharyngitis: 62 (10.54%)<br>Sinusitis: 19 (3.23%)<br>Urinary Tract Infection: 32 (5.44%)<br>Hypoglycemia (unspecified): 29 (4.93%)<br>Severe hypoglycemia: 1 (0.17%)<br>Osteoarthritis: 15 (2.55%)<br>Pain in extremities: 20 (3.4%)<br>Dizziness: 22 (3.74%)<br>Fatigue: 18 (3.06%) | |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| | | | | 3 deaths occurred in this 52-week study. 2 in the glipizide group (sudden cardiac death and myocardial infarction) and 1 in the sitagliptin group (because of trauma) (table 3); none was considered related to study drug.<br><br>For APT-cohort: At 52 weeks, weight decr'd w/ sitagliptin [] and incr'd w/ glipizide relative to baseline, with |
| **Nelson 2007**<br>US<br>open label extension<br>N/A | Exenatide (Byetta) | Total sample size: 127<br>Withdrawals, total: 40 (31.5%)<br>Withdrawals for AEs: (%) | | Withdrawal due to AEs not reported. Withdrawal of consent 14%. Withdrawal due to loss of glucose control 2%.<br><br>No cases of severe hypoglycemia were reported. Hypoglycemia 5-9%, but follow-up interval unclear for this outcome. Nausea reported at 22% witih 10ug over 4-week RCT; no data for OLE; discussion section section states drug well tolerated over the OLE of 30 wks |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| **Nonaka 2007**<br>Japan<br>placebo-controlled<br>Fair | Sitagliptin (Januvia) | Total sample size: 75<br>Withdrawals, total: 2 (2.67%)<br>Withdrawals for AEs: 0 (0%) | Gastrointestinal disorders (unspecified): 16 (21.33%)<br>Nervous system disorders (unspecified): 8 (10.67%) | No hypoglycemic events<br>Sitagliptin and placebo groups had similar incidences of clinical AE, drug-related AE, and SAE. |
| | Placebo | Total sample size: 76<br>Withdrawals, total: 8 (10.53%)<br>Withdrawals for AEs: 2 (2.63%) | Gastrointestinal disorders (unspecified): 13 (17.11%)<br>Nervous system disorders (unspecified): 5 (6.58%) | There was 1-SAE with sitagliptin (overdose) that did not result in hypoglycemic symptoms. There were 2-SAE in the placebo group (myocardial infarction and overdose) which were not considered to be drug-related; however 1-SAE in the placebo arm (exfoliative dermatitis) was considered drug-related. |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| **Ratner 2002**<br>U.S.<br>placebo-controlled<br>Fair-Poor | Pramlintide (Symlin) 150 mcgTID+Insulin | Total sample size: 144<br>Withdrawals, total: 54 (37.5%)<br>Withdrawals for AEs: 26 (18.06%) | Nausea: 33 (22.92%)<br>Severe nausea: 4 (2.78%)<br>Sinusitis: 14 (9.72%)<br>Hypoglycemia (unspecified): 93 (64.58%)<br>Severe hypoglycemia: 4 (2.78%)<br>Headache: 23 (15.97%)<br>Inflicted injury: 15 (10.42%) | Larger proportion of subjects in the Pram 150 arm withdrew due to AE.<br>High differential between those in placebo arm versus Pram 150 arm.<br><br>No evidence of cardiac, hepatic or renal toxicity, or changes in serum lipid parameters with pramlinitide treatment. |
| | Pramlintide (Symlin) 30mcg TID+Insulin | Total sample size: 122<br>Withdrawals, total: 32 (26.23%)<br>Withdrawals for AEs: 9 (7.38%) | Nausea: 18 (14.75%)<br>Severe nausea: 1 (0.82%)<br>Sinusitis: 16 (13.11%)<br>Hypoglycemia (unspecified): 82 (67.21%)<br>Severe hypoglycemia: 5 (4.1%)<br>Headache: 15 (12.3%)<br>Inflicted injury: 22 (18.03%)<br>Retinal disorder: 7 (5.74%) | |
| | Pramlintide (Symlin) 75mcgTID+Insulin | Total sample size: 136<br>Withdrawals, total: 34 (25.0%)<br>Withdrawals for AEs: 14 (10.29%) | Nausea: 36 (26.47%)<br>Severe nausea: 1 (0.74%)<br>Sinusitis: 25 (18.38%)<br>Hypoglycemia (unspecified): 92 (67.65%)<br>Severe hypoglycemia: 3 (2.21%)<br>Headache: 26 (19.12%)<br>Inflicted injury: 18 (13.24%)<br>Retinal disorder: 8 (5.88%) | |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| | Placebo+Insulin | Total sample size: 136<br>Withdrawals, total: 37 (27.21%)<br>Withdrawals for AEs: 14 (10.29%) | Nausea: 23 (16.91%)<br>Severe nausea: 2 (1.47%)<br>Sinusitis: 11 (8.09%)<br>Hypoglycemia (unspecified): 96 (70.59%)<br>Severe hypoglycemia: 2 (1.47%)<br>Headache: 18 (13.24%)<br>Inflicted injury: 17 (12.5%)<br>Retinal disorder: 7 (5.15%) | |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| **Ratner 2004**<br>U.S., & Canada<br>placebo-controlled<br>Fair-poor | Pramlintide 60 mcg QID+insulin | Total sample size: 161<br>Withdrawals, total: 55 (34.16%)<br>Withdrawals for AEs: 22 (13.66%) | Nausea: 47 (29.19%)<br>Severe nausea: 11 (6.83%)<br>Severe vomiting: 1 (0.62%)<br>Vomiting: 11 (6.83%)<br>Anorexia: 11 (6.83%)<br>Severe anorexia: 3 (1.86%) | High differential for overall and for WD due to AE<br><br>Pramlinitide therapy was not associated with increased incidence of cardiovascular, hepatic or renal adverse events. There were no differences in fasting lipids, heart rate, or systolic or diastolic blood pressure between 4 treatment groups. Most of the AEs were mild or moderate intensity, transient in nature and tended to occur early in the course of treatment. |
| | Pramlintide 60 mcg TID+insulin | Total sample size: 164<br>Withdrawals, total: 69 (42.07%)<br>Withdrawals for AEs: 32 (19.51%) | Nausea: 47 (28.66%)<br>Severe nausea: 14 (8.54%)<br>Severe vomiting: 3 (1.83%)<br>Vomiting: 10 (6.1%)<br>Anorexia: 18 (10.98%)<br>Severe anorexia: 2 (1.22%) | |
| | Pramlintide 90 mcg Tid+Insulin | Total sample size: 172<br>Withdrawals, total: 86 (50%)<br>Withdrawals for AEs: 38 (22.09%) | Nausea: 59 (34.3%)<br>Severe nausea: 10 (5.81%)<br>Severe vomiting: 2 (1.16%)<br>Vomiting: 12 (6.98%)<br>Anorexia: 16 (9.3%)<br>Severe anorexia: 1 (0.58%) | |
| | Placebo+insulin | Total sample size: 154<br>Withdrawals, total: 51 (33.12%)<br>Withdrawals for AEs: 6 (3.9%) | Anorexia: 3 (1.95%)<br>Nausea: 12 (7.79%)<br>Severe nausea: 2 (1.3%)<br>Severe vomiting: 1 (0.65%)<br>Vomiting: 6 (3.9%)<br>Severe anorexia: 0 (0%) | |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| **Ratner 2005**<br>USA<br>Pooled analysis<br>N/A | Pramlintide (Symlin)+Insulin | Total sample size: 281<br>Withdrawals, total: 93 (33.1%)<br>Withdrawals for AEs: 48 (17.08%) | Nausea: 122 (43.42%)<br>Anorexia: 45 (16.01%) | High differential between the arms for total withdrawn and for AE<br>Total withdrawal rate 27.7% |
| | Placebo+Insulin | Total sample size: 196<br>Withdrawals, total: 39 (19.9%)<br>Withdrawals for AEs: 10 (5.1%) | Nausea: 20 (10.2%)<br>Anorexia: 3 (1.53%) | The overall severe hypoglycemia event rates were slightly higher than that observed in the original studies which included less well controlled subjects. There was no evidence of cardiovascular, hepatic or renal toxicity or changes in the lab safety parameters or ECG variables |
| **Ratner 2006**<br>US<br>Open label extension<br>N/A | Exenatide 10 mcg | Total sample size: 92<br>Withdrawals, total: (*see comments%)<br>Withdrawals for AEs: (*see comments%) | Diarrhea: 14 (9.33%)<br>Diarrhea: 6 (4%)<br>Diarrhea: 8 (5.33%)<br>Nausea: 50 (33.33%)<br>Nausea: 45 (30%)<br>Nausea: 21 (14%)<br>Vomiting: 9 (6%)<br>Vomiting: 2 (1.33%)<br>Vomiting: 8 (5.33%)<br>Upper Respiratory Tract Infection: 8 (5.33%)<br>Upper Respiratory Tract Infection: 15 (10%)<br>Upper Respiratory Tract Infection: 6 (4%)<br>Dizziness: 3 (2%)<br>Dizziness: 9 (6%)<br>Dizziness: 6 (4%) | Total withdrawals based on ITT population= 58 (39%)<br>Withdrawals due to AE based on ITT population= 11 (7%)<br><br>No evidence of pulmonary, hepatic, renal, or cardiovascular toxicity, or idiosyncratic side effects<br><br>No severe hypoglycemic events. |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| **Raz 2006**<br>Multinational<br>placebo-controlled<br>Fair | Sitagliptin 100 mg | Total sample size: 205<br>Withdrawals, total: 17 (8.29%)<br>Withdrawals for AEs: 5 (2.44%) | Hypertension: 2 (0.98%)<br>Abdominal pain: 4 (1.95%)<br>Constipation: 4 (1.95%)<br>Diarrhea: 9 (4.39%)<br>Diarrhea: 8 (3.9%)<br>Nausea: 2 (0.98%)<br>Vomiting: 0 (0%)<br>Influenza: 8 (3.9%)<br>Nasopharyngitis: 7 (3.41%)<br>Sinus headache: 1 (0.49%)<br>Sinusitis: 4 (1.95%)<br>Upper Respiratory Tract Infection: 8 (3.9%)<br>Urinary Tract Infection: 4 (1.95%)<br>Blood glucose increase: 4 (1.95%)<br>Hypoglycemia (unspecified): 3 (1.46%)<br>Arthralgia: 1 (0.49%)<br>Back pain: 10 (4.88%)<br>Osteoarthritis: 4 (1.95%)<br>Pain in extremities: 4 (1.95%)<br>Dizziness: 4 (1.95%)<br>Fatigue: 2 (0.98%)<br>Headache: 7 (3.41%)<br>Vertigo: 4 (1.95%)<br>Cough: 2 (0.98%) | Prespecified AEs: hypoglycemia, nausea, vomiting, diarrhea, abdominal pain, change in body weight.<br>**Note: there are 2-reports of diarrhea (1-report of 'prespecified' diarrhea from Table 2 in article and the other from Table 2 in appendix)<br><br>Analyses of body weight and GI AE excluded data obtained after patients received rescue therapy. |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| | Sitagliptin 200 mg | Total sample size: 206<br>Withdrawals, total: 22 (10.68%)<br>Withdrawals for AEs: 0 (0%) | Hypertension: 2 (0.97%)<br>Abdominal pain: 3 (1.46%)<br>Constipation: 4 (1.94%)<br>Diarrhea: 2 (0.97%)<br>Diarrhea: 2 (0.97%)<br>Nausea: 3 (1.46%)<br>Vomiting: 1 (0.49%)<br>Influenza: 6 (2.91%)<br>Nasopharyngitis: 6 (2.91%)<br>Sinus headache: 0 (0%)<br>Sinusitis: 5 (2.43%)<br>Upper Respiratory Tract Infection: 6 (2.91%)<br>Urinary Tract Infection: 6 (2.91%)<br>Blood Gluc Increase: 1 (0.49%)<br>Hypoglycemia (unspecified): 2 (0.97%)<br>Arthralgia: 5 (2.43%)<br>Back pain: 7 (3.4%)<br>Osteoarthritis: 0 (0%)<br>Pain in extremities: 2 (0.97%)<br>Dizziness: 1 (0.49%)<br>Fatigue: 4 (1.94%)<br>Headache: 7 (3.4%)<br>Vertigo: 0 (0%)<br>Cough: 5 (2.43%) | |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| | Placebo | Total sample size: 110<br>Withdrawals, total: 19 (17.27%)<br>Withdrawals for AEs: 4 (3.64%) | Hypertension: 4 (3.64%)<br>Abdominal pain: 3 (2.73%)<br>Constipation: 2 (1.82%)<br>Diarrhea: 6 (5.45%)<br>Diarrhea: 4 (3.64%)<br>Nausea: 0 (0%)<br>Vomiting: 1 (0.91%)<br>Influenza: 5 (4.55%)<br>Nasopharyngitis: 0 (0%)<br>Sinus headache: 3 (2.73%)<br>Sinusitis: 3 (2.73%)<br>Upper Respiratory Tract Infection: 3 (2.73%)<br>Urinary Tract Infection: 3 (2.73%)<br>Blood Gluc Increase: 5 (4.55%)<br>Hypoglycemia (unspecified): 0 (0%)<br>Arthralgia: 4 (3.64%)<br>Back pain: 2 (1.82%)<br>Osteoarthritis: 0 (0%)<br>Pain in extremities: 0 (0%)<br>Dizziness: 4 (3.64%)<br>Fatigue: 4 (3.64%)<br>Headache: 3 (2.73%)<br>Vertigo: 0 (0%)<br>Cough: 2 (1.82%) | |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| **Raz 2008**<br>Multinational<br>placebo-controlled<br>Fair | Sitagliptin + MET | Total sample size: 96<br>Withdrawals, total: 17 (17.71%)<br>Withdrawals for AEs: 2 (2.08%) | Angina pectoris: 3 (3.12%)<br>Hypertension: 2 (2.08%)<br>Abdominal pain: 2 (2.08%)<br>Diarrhea: 6 (6.25%)<br>Gastritis: 2 (2.08%)<br>Nausea: 2 (2.08%)<br>Vomiting: 0 (0%)<br>Influenza: 1 (1.04%)<br>Nasopharyngitis: 7 (7.29%)<br>Pharyngitis: 4 (4.17%)<br>Pharyngotonsillitis: 3 (3.12%)<br>Tinea Pedis: 4 (4.17%)<br>Upper Respiratory Tract Infection: 0 (0%)<br>Urinary Tract Infection: 4 (4.17%)<br>Blood glucose increase: 6 (6.25%)<br>Hyperglycemia: 0 (0%)<br>Hypoglycemia (unspecified): 1 (1.04%)<br>Pain in extremities: 3 (3.12%)<br>Diabetic neuropathy: 4 (4.17%)<br>Headache: 4 (4.17%) | No serious AE or dicontinuations due to clinical AE were reported in the sitagliptin group. In the placebo arm, 6 serious clinic AE were reported in 5 patients (including fatal MI, 3 neoplasms, a limb fracture, and an upper GI hemorrhage) and were responsible for 1-death and 2-discontinuations. There were all regarded by the investigators as not drug-related.<br><br>Incidence of severe hypoglycemia not reported. |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| | Placebo + MET | Total sample size: 94<br>Withdrawals, total: 14 (14.89%)<br>Withdrawals for AEs: 2 (2.13%) | Angina pectoris: 0 (0%)<br>Hypertension: 4 (4.26%)<br>Abdominal pain: 0 (0%)<br>Diarrhea: 5 (5.32%)<br>Gastritis: 3 (3.19%)<br>Nausea: 2 (2.13%)<br>Vomiting: 1 (1.06%)<br>Influenza: 3 (3.19%)<br>Nasopharyngitis: 7 (7.45%)<br>Pharyngitis: 6 (6.38%)<br>Pharyngotonsillitis: 1 (1.06%)<br>Tinea Pedis: 2 (2.13%)<br>Upper Respiratory Tract Infection: 3 (3.19%)<br>Urinary Tract Infection: 3 (3.19%)<br>Blood glucose increase: 15 (15.96%)<br>Hyperglycemia: 3 (3.19%)<br>Hypoglycemia (unspecified): 0 (0%)<br>Pain in extremities: 2 (2.13%)<br>Diabetic neuropathy: 2 (2.13%)<br>Headache: 4 (4.26%) | |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| **Riddle 2006**<br>US<br>Open label extension<br>N/A | Exenatide 10 mcg | Total sample size: 222<br>Withdrawals, total: (*see comments%)<br>Withdrawals for AEs: (*see comments%) | Nausea: 108 (26.93%)<br>Nausea: 60 (14.96%)<br>Nausea: 140 (34.91%)<br>Hypoglycemia (unspecified): 60 (14.96%)<br>Hypoglycemia (unspecified): 56 (13.97%)<br>Hypoglycemia (unspecified): 56 (13.97%) | Total withdrawals based on ITT population, n=401; (45%)<br>Withdrawals due to AE based on ITT population, n= 401; (7%)<br><br>4-severe hypoglycemic events<br><br>No AE in VS or PE findings; did not report whether or not there were no effects on CV, pulmon, renal, etc<br><br>There was no correlation between nausea and weight loss. |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| **Riddle 2007**<br>US<br>placebo-controlled<br>Fair | Pramlintide > 8.5% + glargine (+/- OHA) | Total sample size: 42<br>Withdrawals, total: 7 (16.67%)<br>Withdrawals for AEs: 1 (2.38%) | | More patients in the Pram arm withdrew due to AE (appears that most came from the Pram <8.5% arm).<br><br>1-severe hypoglycemic event occurred in the Pram arm which was deemed not to be related to study medication by the investigator (patient injected rapid-acting insulin instead of glargine?). |
| | Pramlintide ≤ 8.5% + glargine (+/- OHA) | Total sample size: 63<br>Withdrawals, total: 11 (17.46%)<br>Withdrawals for AEs: 3 (4.76%) | | |
| | Total Placebo + glargine (+/- OHA) | Total sample size: 106<br>Withdrawals, total: 16 (15.09%)<br>Withdrawals for AEs: 1 (0.94%) | Nausea: 11 (10.38%)<br>MIld/moderate hypoglycemia: 50 (47.17%)<br>Severe hypoglycemia: 0 (0%)<br>Injection site reaction: 1 (0.94%) | |
| | Total Pramlintide + glargine (+/- OHA) | Total sample size: 105<br>Withdrawals, total: 18 (17.14%)<br>Withdrawals for AEs: 4 (3.81%) | Nausea: 33 (31.43%)<br>MIld/moderate hypoglycemia: 46 (43.81%)<br>Severe hypoglycemia: 1 (0.95%)<br>Injection site reaction: 1 (0.95%) | |
| | Placebo >8.5% + glargine (+/- OHA) | Total sample size: 48<br>Withdrawals, total: 8 (16.67%)<br>Withdrawals for AEs: 0 (0%) | | |
| | Placebo ≤ 8.5% + glargine (+/- OHA) | Total sample size: 58<br>Withdrawals, total: 8 (13.79%)<br>Withdrawals for AEs: 1 (1.72%) | | |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| **Rosenstock 2006**<br>multinational<br>placebo-controlled<br>Fair | Sitagliptin + Pioglitazone | Total sample size: 175<br>Withdrawals, total: 26 (14.86%)<br>Withdrawals for AEs: 11 (6.29%) | Abdominal pain: 6 (3.43%)<br>Diarrhea: 3 (1.71%)<br>Nausea: 2 (1.14%)<br>Vomiting: 1 (0.57%)<br>Influenza: 7 (4%)<br>Nasopharyngitis: 7 (4%)<br>Upper Respiratory Tract Infection: 11 (6.29%)<br>Hypoglycemia (unspecified): 2 (1.14%)<br>Weight increase: 5 (2.86%)<br>Arthralgia: 5 (2.86%)<br>Back pain: 3 (1.71%)<br>Pain in extremities: 4 (2.29%)<br>Peripheral edema: 7 (4%)<br>Depression: 4 (2.29%)<br>Headache: 10 (5.71%) | Higher % of withdrawals due to Aes in the Sita +Pioglitazone arm (6.3%) than placebo + Piolgitazone arm (1.1%)<br><br>There was 1-serious in the Sitagliptin arm (urticaria and angioedema)<br><br>No serious hypoglycemia.<br><br>Prespecified AE are hypoglycemia and selected gastrointestinal-related events (abdominal pain, nausea, vomiting, and diarrhea). Analyses of change in body weight and the incidence of gastrointestinal AE were excluded after the initiation of rescue therapy.<br><br>Note: Authors list additional adverse events leading to study discontinuation but NO actual data was reported. These AE include: blurred vision, palpitation, hypersensitivity, and suicide attempt. |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| | Placebo + Pioglitazone | Total sample size: 178<br>Withdrawals, total: 20 (11.24%)<br>Withdrawals for AEs: 2 (1.12%) | Abdominal pain: 0 (0%)<br>Diarrhea: 2 (1.12%)<br>Nausea: 0 (0%)<br>Vomiting: 1 (0.56%)<br>Influenza: 5 (2.81%)<br>Nasopharyngitis: 7 (3.93%)<br>Upper Respiratory Tract Infection: 6 (3.37%)<br>Hypoglycemia (unspecified): 0 (0%)<br>Weight increase: 5 (2.81%)<br>Arthralgia: 5 (2.81%)<br>Back pain: 5 (2.81%)<br>Pain in extremities: 3 (1.69%)<br>Peripheral edema: 6 (3.37%)<br>Depression: 2 (1.12%)<br>Headache: 7 (3.93%) | |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| **Scott 2007** Multinational active-control Fair | Glipizide | Total sample size: 123<br>Withdrawals, total: 23 (18.7%)<br>Withdrawals for AEs: 7 (5.69%) | Hypoglycemia (unspecified): 21 (17.07%) | Did not collect all data for sitagliptin 5 mg, 12.5 mg, 25 mg arms.<br><br>AE were abstracted for sitagliptin 50 mg Bid, placebo, glipizide arms only.<br><br>Patients also check home BG; only hypoglycemia was reported. Authors did not specify whether these were severe hypo events. |
| | Sitagliptin (Januvia) 12.5 mg | Total sample size: 123<br>Withdrawals, total: 7 (5.69%)<br>Withdrawals for AEs: (%) | | |
| | Sitagliptin (Januvia) 25mg | Total sample size: 123<br>Withdrawals, total: 15 (12.2%)<br>Withdrawals for AEs: (%) | | |
| | Sitagliptin (Januvia) 50 mg | Total sample size: 124<br>Withdrawals, total: 12 (9.68%)<br>Withdrawals for AEs: 2 (1.61%) | Hypoglycemia (unspecified): 2 (1.64%) | |
| | Sitagliptin (Januvia) 5mg | Total sample size: 125<br>Withdrawals, total: 18 (14.4%)<br>Withdrawals for AEs: (%) | | |
| | Placebo | Total sample size: 125<br>Withdrawals, total: 17 (13.6%)<br>Withdrawals for AEs: 1 (0.8%) | Hypoglycemia (unspecified): 3 (2.4%) | |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author<br>Year<br>Country<br>Trial type<br>Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| **Scott 2008**<br>Multinational<br>active-control<br><br>Fair | Rosiglitazone + MET monotherapy | Total sample size: 87<br>Withdrawals, total: 2 (2.3%)<br>Withdrawals for AEs: 2 (2.3%) | Abdominal pain: 1 (1.15%)<br>Diarrhea: 3 (3.45%)<br>Nausea: 1 (1.15%)<br>Vomiting: 1 (1.15%)<br>Hypoglycemia (unspecified): 1 (1.15%)<br>Edema: 4 (4.6%) | Overall incidence of clinical adverse experiences for sitagliptin (39%) and rosiglitazone (44%) relative to placebo (30%). No meaningful differences were observed among the sitagliptin, rosiglitazone and placebo groups with respect to the incidences of serious clinical adverse experiences and drug-related clinical adverse experiences. |
| | Sitagliptin + MET monotherapy | Total sample size: 94<br>Withdrawals, total: 9 (9.57%)<br>Withdrawals for AEs: 3 (3.19%) | Abdominal pain: 0 (0%)<br>Diarrhea: 3 (3.19%)<br>Nausea: 1 (1.06%)<br>Vomiting: 1 (1.06%)<br>Hypoglycemia (unspecified): 1 (1.06%)<br>Edema: 1 (1.06%) | |
| | Placebo + MET monotherapy | Total sample size: 92<br>Withdrawals, total: 9 (9.78%)<br>Withdrawals for AEs: 1 (1.09%) | Abdominal pain: 1 (1.1%)<br>Diarrhea: 1 (1.1%)<br>Nausea: 2 (2.2%)<br>Vomiting: 1 (1.1%)<br>Hypoglycemia (unspecified): 2 (2.2%)<br>Edema: 1 (1.1%) | |
| **Whitehouse 2002**<br>US<br>Open label extension<br><br>N/A | Original Pramlintide arm + insulin | Total sample size: 125<br>Withdrawals, total: 37 (29.6%)<br>Withdrawals for AEs: 8 (6.4%) | Nausea: 18 (14.4%)<br>Anorexia: 2 (1.6%) | Large proportion of withdrawals even in the OLE |
| | Switched to pramlintide from placebo + insulin | Total sample size: 111<br>Withdrawals, total: 38 (34.23%)<br>Withdrawals for AEs: 18 (16.22%) | Nausea: 45 (40.54%)<br>Anorexia: 14 (12.61%) | |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| **Whitehouse 2002**<br>US<br>placebo-controlled<br>Fair-poor | Pramlintide 30 mcg + 60 mcg (combined) + insulin | Total sample size: 174<br>Withdrawals, total: 69 (28.4%)<br>Withdrawals for AEs: 31 (12.76%) | Nausea: 113 (46.5%)<br>Severe nausea: 15 (6.17%)<br>Severe vomiting: 5 (2.06%)<br>Vomiting: 28 (11.52%)<br>Anorexia: 43 (17.7%)<br>Severe anorexia: 6 (2.47%) | *There was an outlier patient in the placebo arm who was excluded from evaluation of severe hypoglycemia (the patient reported > 100 episodes of severe hypoglycemia). |
| | Placebo + insulin | Total sample size: 168<br>Withdrawals, total: 69 (29.11%)<br>Withdrawals for AEs: 19 (8.02%) | Nausea: 52 (21.94%)<br>Severe nausea: 4 (1.69%)<br>Severe vomiting: 1 (0.42%)<br>Vomiting: 19 (8.02%)<br>Anorexia: 5 (2.11%)<br>Severe anorexia: 0 (0%) | |

## Evidence Table 3. Adverse events of trials and studies of newer drugs for the treatment of diabetes mellitus

| Author Year Country Trial type Quality | Intervention | Withdrawals | Adverse Event | Comments |
|---|---|---|---|---|
| **Zinman 2007**<br>Canada, Spain,<br>placebo-controlled<br>Fair | Exenatide 10 mcg | Total sample size: 121<br>Withdrawals, total: 35 (28.93%)<br>Withdrawals for AEs: 19 (15.7%) | Allergic alveolitis: 1 (0.83%)<br>Chest pain: 1 (0.83%)<br>Diarrhea: 7 (5.79%)<br>Dyspepsia: 9 (7.44%)<br>Nausea: 48 (39.67%)<br>Vomiting: 16 (13.22%)<br>Influenza: 6 (4.96%)<br>Nasopharyngitis: 16 (13.22%)<br>MIld/moderate hypoglycemia: 13 (10.74%)<br>Peripheral edema: 7 (5.79%)<br>Headache: 7 (5.79%) | At the monthly visits, investigators examined patients for pedal edema and asked them to report AE. Patients were given diaries and glucose monitors; they were to keep track of sxs, med changes, etc.<br><br>Significantly more reports of nausea in exenatide arm.<br><br>2 serious adverse events: 1-case of allergic alveolitis probably associated with study drug; 1-case of chest pain probably not associated with study drug |
| | Placebo | Total sample size: 112<br>Withdrawals, total: 16 (14.29%)<br>Withdrawals for AEs: 2 (1.79%) | Diarrhea: 3 (2.68%)<br>Dyspepsia: 1 (0.89%)<br>Nausea: 17 (15.18%)<br>Vomiting: 1 (0.89%)<br>Influenza: 5 (4.46%)<br>Nasopharyngitis: 9 (8.04%)<br>MIld/moderate hypoglycemia: 8 (7.14%)<br>Peripheral edema: 9 (8.04%)<br>Headache: 5 (4.46%) | |

## Evidence Table 4. Quality assessment of efficacy trials of newer drugs for the treatment of diabetes mellitus

**Aronne, 2007** **Trial type:** placebo-controlled **Design:** RCT - Parallel group, DB, NR **Quality rating:** Poor

| Internal validity | |
|---|---|
| 1. Randomization adequate? | Method not described |
| 2. Allocation adequate? | Method not described |
| 3. Groups similar at baseline? | NR |
| 4. Eligibility criteria specified? | Yes |
| 5. Loss to follow-up, differential? | Unable to determine |
| 6. Outcome assessors masked? | Unclear, reported as double blind |
| 7. Care provider masked? | Unclear, reported as double blind |
| 8. Patients masked? | Unclear, reported as double blind |
| 9. Intention-to-treat analysis? | No |
| 10. Postrandomization exclusions? | Unable to determine |
| 11. Reporting of Attrition | Yes |
| Crossover | No |
| Adherence | No |
| Contamination | No |

| External validity | |
|---|---|
| 1. Number Screened/Eligible/Enrolled: | NR/NR/44 |
| 2. Run-in/Washout: | Yes/No |
| 3. Exclusion criteria reported? | Yes |
| 4. Funding: | NR |

**Comments:**

QA performed on 44 patients in DM2 subgroup, not for entire study population

**Aschner, 2006** **Trial type:** placebo-controlled **Design:** RCT - Parallel group, DB, NR **Quality rating:** Fair

| Internal validity | |
|---|---|
| 1. Randomization adequate? | Yes* |
| 2. Allocation adequate? | Yes* |
| 3. Groups similar at baseline? | Yes |
| 4. Eligibility criteria specified? | Yes |
| 5. Loss to follow-up, differential? | No |
| 6. Outcome assessors masked? | Yes* |
| 7. Care provider masked? | Yes* |
| 8. Patients masked? | Yes* |
| 9. Intention-to-treat analysis? | Yes |
| 10. Postrandomization exclusions? | No |
| 11. Reporting of Attrition | Yes |
| Crossover | No |
| Adherence | No |
| Contamination | No |

| External validity | |
|---|---|
| 1. Number Screened/Eligible/Enrolled: | 1807/NR/741 |
| 2. Run-in/Washout: | Yes/Yes |
| 3. Exclusion criteria reported? | Yes |
| 4. Funding: | Merck |

**Comments:**

*This information was not provided in the publication but was provided by the manufacturer

**Barnett, 2007** **Trial type:** active-control **Design:** Other, Open, Crossover **Quality rating:** Fair-poor

| Internal validity | External validity |
|---|---|

## Evidence Table 4. Quality assessment of efficacy trials of newer drugs for the treatment of diabetes mellitus

**Barnett, 2007** **Trial type:** active-control **Design:** Other, Open, Crossover **Quality rating:** Fair-poor

| Internal validity | | External validity | |
|---|---|---|---|
| 1. Randomization adequate? | Yes | 1. Number Screened/Eligible/Enrolled: | 196/NR/141 |
| 2. Allocation adequate? | Yes | 2. Run-in/Washout: | No/No |
| 3. Groups similar at baseline? | No | 3. Exclusion criteria reported? | No |
| 4. Eligibility criteria specified? | Yes | 4. Funding: | Eli Lilly |
| 5. Loss to follow-up, differential? | No | | |
| 6. Outcome assessors masked? | No | **Comments:** | |
| 7. Care provider masked? | No | | |
| 8. Patients masked? | No | | |
| 9. Intention-to-treat analysis? | Yes | | |
| 10. Postrandomization exclusions? | Yes | | |
| 11. Reporting of Attrition | Yes | | |
| Crossover | No | | |
| Adherence | No | | |
| Contamination | No | | |

**Blonde, 2006** **Trial type:** Open label extension **Design:** NA **Quality rating:** NA

| Internal validity | | External validity | |
|---|---|---|---|
| 1. Randomization adequate? | | 1. Number Screened/Eligible/Enrolled: | NR/NR/974 |
| 2. Allocation adequate? | | 2. Run-in/Washout: | No/No |
| 3. Groups similar at baseline? | | 3. Exclusion criteria reported? | |
| 4. Eligibility criteria specified? | | 4. Funding: | Amylin Pharmaceuticals, Eli Lilly |
| 5. Loss to follow-up, differential? | | | |
| 6. Outcome assessors masked? | | **Comments:** | |
| 7. Care provider masked? | | | |
| 8. Patients masked? | | | |
| 9. Intention-to-treat analysis? | | | |
| 10. Postrandomization exclusions? | | | |
| 11. Reporting of Attrition | | | |
| Crossover | | | |
| Adherence | | | |
| Contamination | | | |

**Buse, 2004** **Trial type:** placebo-controlled **Design:** RCT - Parallel group, Triple blind, NR **Quality rating:** Fair

| Internal validity | External validity |
|---|---|

## Evidence Table 4. Quality assessment of efficacy trials of newer drugs for the treatment of diabetes mellitus

**Buse, 2004** **Trial type:** placebo-controlled **Design:** RCT - Parallel group, Triple blind, NR **Quality rating:** Fair

| Internal validity | | External validity | |
|---|---|---|---|
| 1. Randomization adequate? | Method not described | 1. Number Screened/Eligible/Enrolled: | NR/NR/377 |
| 2. Allocation adequate? | Method not described | 2. Run-in/Washout: | Yes/No |
| 3. Groups similar at baseline? | Yes | 3. Exclusion criteria reported? | Yes |
| 4. Eligibility criteria specified? | Yes | 4. Funding: | Eli Lilly & Amylin Pharmaceuticals |
| 5. Loss to follow-up, differential? | No | | |
| 6. Outcome assessors masked? | Unclear, reported as triple blind | **Comments:** | |
| 7. Care provider masked? | Unclear, reported as triple blind | | |
| 8. Patients masked? | Yes | | |
| 9. Intention-to-treat analysis? | Yes | | |
| 10. Postrandomization exclusions? | Yes | | |
| 11. Reporting of Attrition | Yes | | |
| Crossover | No | | |
| Adherence | No | | |
| Contamination | No | | |

**Buse, 2007** **Trial type:** Open label extension **Design:** NA **Quality rating:** NA

| Internal validity | | External validity | |
|---|---|---|---|
| 1. Randomization adequate? | | 1. Number Screened/Eligible/Enrolled: | NR/NR/974 |
| 2. Allocation adequate? | | 2. Run-in/Washout: | No/No |
| 3. Groups similar at baseline? | | 3. Exclusion criteria reported? | |
| 4. Eligibility criteria specified? | | 4. Funding: | Amylin Pharmaceuticals, Eli Lilly |
| 5. Loss to follow-up, differential? | | | |
| 6. Outcome assessors masked? | | **Comments:** | |
| 7. Care provider masked? | | | |
| 8. Patients masked? | | | |
| 9. Intention-to-treat analysis? | | | |
| 10. Postrandomization exclusions? | | | |
| 11. Reporting of Attrition | | | |
| Crossover | | | |
| Adherence | | | |
| Contamination | | | |

**Charbonnel, 2006** **Trial type:** placebo-controlled **Design:** RCT - Parallel group, DB, NR **Quality rating:** Fair

| Internal validity | External validity |
|---|---|

## Evidence Table 4. Quality assessment of efficacy trials of newer drugs for the treatment of diabetes mellitus

**Charbonnel, 2006** **Trial type:** placebo-controlled **Design:** RCT - Parallel group, DB, NR **Quality rating:** Fair

| Internal validity | |
|---|---|
| 1. Randomization adequate? | Yes* |
| 2. Allocation adequate? | Yes* |
| 3. Groups similar at baseline? | Yes |
| 4. Eligibility criteria specified? | Yes |
| 5. Loss to follow-up, differential? | No |
| 6. Outcome assessors masked? | Yes* |
| 7. Care provider masked? | Yes* |
| 8. Patients masked? | Yes* |
| 9. Intention-to-treat analysis? | Yes |
| 10. Postrandomization exclusions? | Yes |
| 11. Reporting of Attrition | Yes |
| Crossover | No |
| Adherence | No |
| Contamination | No |

| External validity | |
|---|---|
| 1. Number Screened/Eligible/Enrolled: | 1464/NR/701 |
| 2. Run-in/Washout: | Yes/No |
| 3. Exclusion criteria reported? | Yes |
| 4. Funding: | Merck |

**Comments:**

*This information was not provided in the publication but was provided by the manufacturer

**Davis, 2007** **Trial type:** active-control **Design:** RCT - Parallel group, Open, Parallel **Quality rating:** Fair-poor

| Internal validity | |
|---|---|
| 1. Randomization adequate? | Method not described |
| 2. Allocation adequate? | Method not described |
| 3. Groups similar at baseline? | Yes |
| 4. Eligibility criteria specified? | Yes |
| 5. Loss to follow-up, differential? | No |
| 6. Outcome assessors masked? | No |
| 7. Care provider masked? | No |
| 8. Patients masked? | No |
| 9. Intention-to-treat analysis? | No |
| 10. Postrandomization exclusions? | Yes |
| 11. Reporting of Attrition | Yes |
| Crossover | No |
| Adherence | No |
| Contamination | No |

| External validity | |
|---|---|
| 1. Number Screened/Eligible/Enrolled: | 99/51/51 |
| 2. Run-in/Washout: | No/No |
| 3. Exclusion criteria reported? | Yes |
| 4. Funding: | Eli Lilly & Amylin |

**Comments:**

**DeFronzo, 2005** **Trial type:** placebo-controlled **Design:** RCT - Parallel group, DB, Parallel **Quality rating:** Fair

| Internal validity | External validity |
|---|---|

## Evidence Table 4. Quality assessment of efficacy trials of newer drugs for the treatment of diabetes mellitus

**DeFronzo, 2005** **Trial type:** placebo-controlled **Design:** RCT - Parallel group, DB, Parallel **Quality rating:** Fair

| Internal validity | | External validity | |
|---|---|---|---|
| 1. Randomization adequate? | Method not described | 1. Number Screened/Eligible/Enrolled: | NR/NR/336 |
| 2. Allocation adequate? | Method not described | 2. Run-in/Washout: | Yes/No |
| 3. Groups similar at baseline? | Yes | 3. Exclusion criteria reported? | Yes |
| 4. Eligibility criteria specified? | Yes | 4. Funding: | Pharmaceutical (Amylin & Eli Lilly) |
| 5. Loss to follow-up, differential? | No | | |
| 6. Outcome assessors masked? | Yes | **Comments:** | |
| 7. Care provider masked? | Yes | ITT-LOCF used | |
| 8. Patients masked? | Yes | | |
| 9. Intention-to-treat analysis? | Yes | | |
| 10. Postrandomization exclusions? | Yes | | |
| 11. Reporting of Attrition | Yes | | |
| Crossover | No | | |
| Adherence | No | | |
| Contamination | No | | |

**Edelman, 2006** **Trial type:** placebo-controlled **Design:** RCT - Parallel group, DB, NR **Quality rating:** Fair

| Internal validity | | External validity | |
|---|---|---|---|
| 1. Randomization adequate? | Method not described | 1. Number Screened/Eligible/Enrolled: | NR/NR/296 |
| 2. Allocation adequate? | Method not described | 2. Run-in/Washout: | No/No |
| 3. Groups similar at baseline? | Yes | 3. Exclusion criteria reported? | Yes |
| 4. Eligibility criteria specified? | Yes | 4. Funding: | NR; Amylin Pharmaceuticals? |
| 5. Loss to follow-up, differential? | No | | |
| 6. Outcome assessors masked? | Unclear, reported as double blind | **Comments:** | |
| 7. Care provider masked? | Unclear, reported as double blind | | |
| 8. Patients masked? | Unclear, reported as double blind | | |
| 9. Intention-to-treat analysis? | Unable to determine | | |
| 10. Postrandomization exclusions? | Yes | | |
| 11. Reporting of Attrition | Yes | | |
| Crossover | No | | |
| Adherence | No | | |
| Contamination | No | | |

**Goldstein, 2007** **Trial type:** placebo-controlled **Design:** RCT - Parallel group, DB, **Quality rating:** Fair

| Internal validity | External validity |
|---|---|

## Evidence Table 4. Quality assessment of efficacy trials of newer drugs for the treatment of diabetes mellitus

**Goldstein, 2007** **Trial type:** placebo-controlled **Design:** RCT - Parallel group, DB, **Quality rating:** Fair

| Internal validity | | External validity | |
|---|---|---|---|
| 1. Randomization adequate? | Yes* | 1. Number Screened/Eligible/Enrolled: | 3544/1208/1091 |
| 2. Allocation adequate? | Yes* | 2. Run-in/Washout: | Yes/Yes |
| 3. Groups similar at baseline? | Yes | 3. Exclusion criteria reported? | Yes |
| 4. Eligibility criteria specified? | Yes | 4. Funding: | Merck |
| 5. Loss to follow-up, differential? | No | | |
| 6. Outcome assessors masked? | Yes* | **Comments:** | |
| 7. Care provider masked? | Yes* | *This information was not provided in the publication but was provided by the manufacturer | |
| 8. Patients masked? | Yes* | | |
| 9. Intention-to-treat analysis? | Yes | | |
| 10. Postrandomization exclusions? | Yes | | |
| 11. Reporting of Attrition | Yes | | |
| Crossover | No | | |
| Adherence | No | | |
| Contamination | No | | |
| 1. Randomization adequate? | | 1. Number Screened/Eligible/Enrolled: | NR/NR/117 |
| 2. Allocation adequate? | | 2. Run-in/Washout: | No/No |
| 3. Groups similar at baseline? | | 3. Exclusion criteria reported? | |
| 4. Eligibility criteria specified? | | 4. Funding: | |
| 5. Loss to follow-up, differential? | | | |
| 6. Outcome assessors masked? | | **Comments:** | |
| 7. Care provider masked? | | | |
| 8. Patients masked? | | | |
| 9. Intention-to-treat analysis? | | | |
| 10. Postrandomization exclusions? | | | |
| 11. Reporting of Attrition | | | |
| Crossover | | | |
| Adherence | | | |
| Contamination | | | |

**Heine, 2005** **Trial type:** active-control **Design:** RCT - Parallel group, Open, NR **Quality rating:** Fair

| Internal validity | External validity |
|---|---|

## Evidence Table 4. Quality assessment of efficacy trials of newer drugs for the treatment of diabetes mellitus

**Heine, 2005** **Trial type:** active-control **Design:** RCT - Parallel group, Open, NR **Quality rating:** Fair

| Internal validity | | External validity | |
|---|---|---|---|
| 1. Randomization adequate? | Yes | 1. Number Screened/Eligible/Enrolled: | 844/555/551 |
| 2. Allocation adequate? | Yes | 2. Run-in/Washout: | No/No |
| 3. Groups similar at baseline? | Yes | 3. Exclusion criteria reported? | Yes |
| 4. Eligibility criteria specified? | Yes | 4. Funding: | Amylin & Eli Lilly |
| 5. Loss to follow-up, differential? | No | | |
| 6. Outcome assessors masked? | No (open label) | **Comments:** | |
| 7. Care provider masked? | No (open label) | | |
| 8. Patients masked? | No (open label) | | |
| 9. Intention-to-treat analysis? | Yes | | |
| 10. Postrandomization exclusions? | Yes | | |
| 11. Reporting of Attrition | Yes | | |
| Crossover | No | | |
| Adherence | No | | |
| Contamination | No | | |

**Hermansen, 2007** **Trial type:** placebo-controlled **Design:** RCT - Parallel group, DB, Parallel **Quality rating:** Fair

| Internal validity | | External validity | |
|---|---|---|---|
| 1. Randomization adequate? | Yes* | 1. Number Screened/Eligible/Enrolled: | 1098/NR/441 |
| 2. Allocation adequate? | Yes* | 2. Run-in/Washout: | Yes/Yes |
| 3. Groups similar at baseline? | Yes | 3. Exclusion criteria reported? | Yes |
| 4. Eligibility criteria specified? | Yes | 4. Funding: | Merck |
| 5. Loss to follow-up, differential? | No | | |
| 6. Outcome assessors masked? | Yes* | **Comments:** | |
| 7. Care provider masked? | Yes* | *This information was not provided in the publication but was provided by the manufacturer | |
| 8. Patients masked? | Yes* | | |
| 9. Intention-to-treat analysis? | Yes | | |
| 10. Postrandomization exclusions? | Yes | | |
| 11. Reporting of Attrition | Yes | | |
| Crossover | No | | |
| Adherence | No | | |
| Contamination | No | | |

**Hollander, 2003** **Trial type:** placebo-controlled **Design:** RCT - Parallel group, DB, NR **Quality rating:** Fair

| Internal validity | External validity |
|---|---|

## Evidence Table 4. Quality assessment of efficacy trials of newer drugs for the treatment of diabetes mellitus

**Hollander, 2003** **Trial type:** placebo-controlled **Design:** RCT - Parallel group, DB, NR **Quality rating:** Fair

| Internal validity | | External validity | |
|---|---|---|---|
| 1. Randomization adequate? | Method not described | 1. Number Screened/Eligible/Enrolled: | NR/NR/656 |
| 2. Allocation adequate? | Method not described | 2. Run-in/Washout: | Yes/No |
| 3. Groups similar at baseline? | Yes | 3. Exclusion criteria reported? | Yes |
| 4. Eligibility criteria specified? | Yes | 4. Funding: | NR |
| 5. Loss to follow-up, differential? | Unable to determine | | |
| 6. Outcome assessors masked? | Unclear, reported as double blind | **Comments:** | |
| 7. Care provider masked? | Unclear, reported as double blind | | |
| 8. Patients masked? | Yes | | |
| 9. Intention-to-treat analysis? | Yes | | |
| 10. Postrandomization exclusions? | Unable to determine | | |
| 11. Reporting of Attrition | Yes | | |
| Crossover | No | | |
| Adherence | No | | |
| Contamination | No | | |
| 1. Randomization adequate? | | 1. Number Screened/Eligible/Enrolled: | NR/NR/NR |
| 2. Allocation adequate? | | 2. Run-in/Washout: | No/No |
| 3. Groups similar at baseline? | | 3. Exclusion criteria reported? | |
| 4. Eligibility criteria specified? | | 4. Funding: | NR |
| 5. Loss to follow-up, differential? | | | |
| 6. Outcome assessors masked? | | **Comments:** | |
| 7. Care provider masked? | | | |
| 8. Patients masked? | | | |
| 9. Intention-to-treat analysis? | | | |
| 10. Postrandomization exclusions? | | | |
| 11. Reporting of Attrition | | | |
| Crossover | | | |
| Adherence | | | |
| Contamination | | | |

**Hollander, 2004** **Trial type:** Pooled analysis **Design:** NA **Quality rating:** NA

| Internal validity | External validity |
|---|---|

## Evidence Table 4. Quality assessment of efficacy trials of newer drugs for the treatment of diabetes mellitus

**Hollander, 2004** **Trial type:** Pooled analysis **Design:** NA **Quality rating:** NA

| Internal validity | External validity | |
|---|---|---|
| 1. Randomization adequate? | 1. Number Screened/Eligible/Enrolled: | NR/NR/NR |
| 2. Allocation adequate? | 2. Run-in/Washout: | No/No |
| 3. Groups similar at baseline? | 3. Exclusion criteria reported? | |
| 4. Eligibility criteria specified? | 4. Funding: | NR |
| 5. Loss to follow-up, differential? | | |
| 6. Outcome assessors masked? | **Comments:** | |
| 7. Care provider masked? | | |
| 8. Patients masked? | | |
| 9. Intention-to-treat analysis? | | |
| 10. Postrandomization exclusions? | | |
| 11. Reporting of Attrition | | |
| Crossover | | |
| Adherence | | |
| Contamination | | |

**Karl, 2007** **Trial type:** Open-label cohort **Design:** NA **Quality rating:** NA

| Internal validity | External validity | |
|---|---|---|
| 1. Randomization adequate? | 1. Number Screened/Eligible/Enrolled: | NR/NR/NR |
| 2. Allocation adequate? | 2. Run-in/Washout: | No/No |
| 3. Groups similar at baseline? | 3. Exclusion criteria reported? | |
| 4. Eligibility criteria specified? | 4. Funding: | NR |
| 5. Loss to follow-up, differential? | | |
| 6. Outcome assessors masked? | **Comments:** | |
| 7. Care provider masked? | | |
| 8. Patients masked? | | |
| 9. Intention-to-treat analysis? | | |
| 10. Postrandomization exclusions? | | |
| 11. Reporting of Attrition | | |
| Crossover | | |
| Adherence | | |
| Contamination | | |

**Kendall, 2005** **Trial type:** placebo-controlled **Design:** RCT - Parallel group, DB, NR **Quality rating:** Fair

| Internal validity | External validity |
|---|---|

## Evidence Table 4. Quality assessment of efficacy trials of newer drugs for the treatment of diabetes mellitus

**Kendall, 2005** **Trial type:** placebo-controlled **Design:** RCT - Parallel group, DB, NR **Quality rating:** Fair

| Internal validity | | External validity | |
|---|---|---|---|
| 1. Randomization adequate? | Method not described | 1. Number Screened/Eligible/Enrolled: | NR/NR/733 |
| 2. Allocation adequate? | Method not described | 2. Run-in/Washout: | Yes/No |
| 3. Groups similar at baseline? | Yes | 3. Exclusion criteria reported? | Yes |
| 4. Eligibility criteria specified? | Yes | 4. Funding: | Eli Lilly & Amylin Pharmaceuticals |
| 5. Loss to follow-up, differential? | Unable to determine | | |
| 6. Outcome assessors masked? | Unclear, reported as double blind | **Comments:** | |
| 7. Care provider masked? | Unclear, reported as double blind | | |
| 8. Patients masked? | Unclear, reported as double blind | | |
| 9. Intention-to-treat analysis? | Yes | | |
| 10. Postrandomization exclusions? | Yes | | |
| 11. Reporting of Attrition | Yes | | |
| Crossover | No | | |
| Adherence | No | | |
| Contamination | No | | |

**King, 2006** **Trial type:** retrospective uncontrol **Design:** Other, Open, NA **Quality rating:** Poor

| Internal validity | | External validity | |
|---|---|---|---|
| 1. Randomization adequate? | | 1. Number Screened/Eligible/Enrolled: | NR/NR/200 |
| 2. Allocation adequate? | | 2. Run-in/Washout: | No/No |
| 3. Groups similar at baseline? | | 3. Exclusion criteria reported? | |
| 4. Eligibility criteria specified? | | 4. Funding: | NR |
| 5. Loss to follow-up, differential? | | | |
| 6. Outcome assessors masked? | | **Comments:** | |
| 7. Care provider masked? | | | |
| 8. Patients masked? | | | |
| 9. Intention-to-treat analysis? | | | |
| 10. Postrandomization exclusions? | | | |
| 11. Reporting of Attrition | | | |
| Crossover | | | |
| Adherence | | | |
| Contamination | | | |

**Klonoff, 2008** **Trial type:** Pooled analysis **Design:** NA **Quality rating:** NA

| Internal validity | External validity |
|---|---|

## Evidence Table 4. Quality assessment of efficacy trials of newer drugs for the treatment of diabetes mellitus

**Klonoff, 2008** **Trial type:** Pooled analysis **Design:** NA **Quality rating:** NA

| Internal validity | External validity | |
|---|---|---|
| 1. Randomization adequate? | 1. Number Screened/Eligible/Enrolled: | NR/NR/NR |
| 2. Allocation adequate? | 2. Run-in/Washout: | No/No |
| 3. Groups similar at baseline? | 3. Exclusion criteria reported? | |
| 4. Eligibility criteria specified? | 4. Funding: | |
| 5. Loss to follow-up, differential? | | |
| 6. Outcome assessors masked? | **Comments:** | |
| 7. Care provider masked? | | |
| 8. Patients masked? | | |
| 9. Intention-to-treat analysis? | | |
| 10. Postrandomization exclusions? | | |
| 11. Reporting of Attrition | | |
| Crossover | | |
| Adherence | | |
| Contamination | | |

**Maggs, 2003** **Trial type:** Pooled analysis **Design:** NA **Quality rating:** NA

| Internal validity | External validity | |
|---|---|---|
| 1. Randomization adequate? | 1. Number Screened/Eligible/Enrolled: | NR/NR/NR |
| 2. Allocation adequate? | 2. Run-in/Washout: | No/No |
| 3. Groups similar at baseline? | 3. Exclusion criteria reported? | |
| 4. Eligibility criteria specified? | 4. Funding: | Amylin Pharmaceuticals |
| 5. Loss to follow-up, differential? | | |
| 6. Outcome assessors masked? | **Comments:** | |
| 7. Care provider masked? | | |
| 8. Patients masked? | | |
| 9. Intention-to-treat analysis? | | |
| 10. Postrandomization exclusions? | | |
| 11. Reporting of Attrition | | |
| Crossover | | |
| Adherence | | |
| Contamination | | |

**Nauck, 2007** **Trial type:** active-control **Design:** RCT - Parallel group, Open, NR **Quality rating:** Fair

| Internal validity | External validity |
|---|---|

## Evidence Table 4. Quality assessment of efficacy trials of newer drugs for the treatment of diabetes mellitus

**Nauck, 2007** **Trial type:** active-control **Design:** RCT - Parallel group, Open, NR **Quality rating:** Fair

| Internal validity | | External validity | |
|---|---|---|---|
| 1. Randomization adequate? | Yes | 1. Number Screened/Eligible/Enrolled: | 641/NR/505 |
| 2. Allocation adequate? | Yes | 2. Run-in/Washout: | No/No |
| 3. Groups similar at baseline? | Yes | 3. Exclusion criteria reported? | Yes |
| 4. Eligibility criteria specified? | Yes | 4. Funding: | Eli Lilly & Amylin |
| 5. Loss to follow-up, differential? | Unable to determine | | |
| 6. Outcome assessors masked? | | **Comments:** | |
| 7. Care provider masked? | | | |
| 8. Patients masked? | | | |
| 9. Intention-to-treat analysis? | Yes | | |
| 10. Postrandomization exclusions? | Yes | | |
| 11. Reporting of Attrition | Yes | | |
| Crossover | No | | |
| Adherence | No | | |
| Contamination | No | | |
| 1. Randomization adequate? | Yes* | 1. Number Screened/Eligible/Enrolled: | 2141/NR/1172 |
| 2. Allocation adequate? | Yes* | 2. Run-in/Washout: | Yes/No |
| 3. Groups similar at baseline? | Yes | 3. Exclusion criteria reported? | Yes |
| 4. Eligibility criteria specified? | Yes | 4. Funding: | Merck |
| 5. Loss to follow-up, differential? | No | | |
| 6. Outcome assessors masked? | Yes* | **Comments:** | |
| 7. Care provider masked? | Yes* | *This information was not provided in the publication but was provided by the manufacturer | |
| 8. Patients masked? | Yes* | | |
| 9. Intention-to-treat analysis? | No | | |
| 10. Postrandomization exclusions? | Yes | | |
| 11. Reporting of Attrition | Yes | | |
| Crossover | No | | |
| Adherence | No | | |
| Contamination | No | | |

**Nelson, 2007** **Trial type:** open label extension **Design:** NA **Quality rating:** NA

| Internal validity | External validity |
|---|---|

## Evidence Table 4. Quality assessment of efficacy trials of newer drugs for the treatment of diabetes mellitus

**Nelson, 2007** **Trial type:** open label extension **Design:** NA **Quality rating:** NA

| Internal validity | |
|---|---|
| 1. Randomization adequate? | |
| 2. Allocation adequate? | |
| 3. Groups similar at baseline? | |
| 4. Eligibility criteria specified? | |
| 5. Loss to follow-up, differential? | |
| 6. Outcome assessors masked? | |
| 7. Care provider masked? | |
| 8. Patients masked? | |
| 9. Intention-to-treat analysis? | |
| 10. Postrandomization exclusions? | |
| 11. Reporting of Attrition | |
| Crossover | |
| Adherence | |
| Contamination | |

| External validity | |
|---|---|
| 1. Number Screened/Eligible/Enrolled: | 156/141/127 |
| 2. Run-in/Washout: | No/No |
| 3. Exclusion criteria reported? | |
| 4. Funding: | Amylin Pharmaceuticals, Eli Lilly |

**Comments:**

**Nonaka, 2007** **Trial type:** placebo-controlled **Design:** RCT - Parallel group, DB, Parallel **Quality rating:** Fair

| Internal validity | |
|---|---|
| 1. Randomization adequate? | Yes* |
| 2. Allocation adequate? | Yes* |
| 3. Groups similar at baseline? | Yes |
| 4. Eligibility criteria specified? | Yes |
| 5. Loss to follow-up, differential? | Unable to determine |
| 6. Outcome assessors masked? | Yes* |
| 7. Care provider masked? | Yes* |
| 8. Patients masked? | Yes* |
| 9. Intention-to-treat analysis? | Yes |
| 10. Postrandomization exclusions? | No |
| 11. Reporting of Attrition | Yes |
| Crossover | No |
| Adherence | No |
| Contamination | No |

| External validity | |
|---|---|
| 1. Number Screened/Eligible/Enrolled: | 262/NR/152 |
| 2. Run-in/Washout: | Yes/Yes |
| 3. Exclusion criteria reported? | Yes |
| 4. Funding: | Banyu Pharmaceutical and Merck |

**Comments:**

*This information was not provided in the publication but was provided by the manufacturer

**Ratner, 2002** **Trial type:** placebo-controlled **Design:** RCT - Parallel group, DB, Parallel **Quality rating:** Fair-Poor

| Internal validity | External validity |
|---|---|

## Evidence Table 4. Quality assessment of efficacy trials of newer drugs for the treatment of diabetes mellitus

**Ratner, 2002** **Trial type:** placebo-controlled **Design:** RCT - Parallel group, DB, Parallel **Quality rating:** Fair-Poor

| Internal validity | | External validity | |
|---|---|---|---|
| 1. Randomization adequate? | Method not described | 1. Number Screened/Eligible/Enrolled: | NR/NR/538 |
| 2. Allocation adequate? | Method not described | 2. Run-in/Washout: | Yes/No |
| 3. Groups similar at baseline? | Yes | 3. Exclusion criteria reported? | Yes |
| 4. Eligibility criteria specified? | Yes | 4. Funding: | NR (but 6 of 8 authors are from Amylin Pharma) |
| 5. Loss to follow-up, differential? | No | | |
| 6. Outcome assessors masked? | Unclear, reported as double blind | **Comments:** | |
| 7. Care provider masked? | Unclear, reported as double blind | | |
| 8. Patients masked? | Unclear, reported as double blind | | |
| 9. Intention-to-treat analysis? | Unable to determine | | |
| 10. Postrandomization exclusions? | Yes | | |
| 11. Reporting of Attrition | Yes | | |
| Crossover | No | | |
| Adherence | No | | |
| Contamination | No | | |

**Ratner, 2004** **Trial type:** placebo-controlled **Design:** RCT - Parallel group, DB, Parallel **Quality rating:** Fair-poor

| Internal validity | | External validity | |
|---|---|---|---|
| 1. Randomization adequate? | Method not described | 1. Number Screened/Eligible/Enrolled: | NR/NR/651 |
| 2. Allocation adequate? | Method not described | 2. Run-in/Washout: | Yes/No |
| 3. Groups similar at baseline? | Yes | 3. Exclusion criteria reported? | Yes |
| 4. Eligibility criteria specified? | Yes | 4. Funding: | NR |
| 5. Loss to follow-up, differential? | No | | |
| 6. Outcome assessors masked? | Unclear, reported as double blind | **Comments:** | |
| 7. Care provider masked? | Unclear, reported as double blind | | |
| 8. Patients masked? | Yes | | |
| 9. Intention-to-treat analysis? | Yes | | |
| 10. Postrandomization exclusions? | Yes | | |
| 11. Reporting of Attrition | Yes | | |
| Crossover | No | | |
| Adherence | No | | |
| Contamination | No | | |

**Ratner, 2005** **Trial type:** Pooled analysis **Design:** NA **Quality rating:** NA

| Internal validity | | External validity | |
|---|---|---|---|

## Evidence Table 4. Quality assessment of efficacy trials of newer drugs for the treatment of diabetes mellitus

**Ratner, 2005** **Trial type:** Pooled analysis **Design:** NA **Quality rating:** NA

| Internal validity | External validity | |
|---|---|---|
| 1. Randomization adequate? | 1. Number Screened/Eligible/Enrolled: | NR/NR/477 |
| 2. Allocation adequate? | 2. Run-in/Washout: | No/No |
| 3. Groups similar at baseline? | 3. Exclusion criteria reported? | |
| 4. Eligibility criteria specified? | 4. Funding: | NR |
| 5. Loss to follow-up, differential? | | |
| 6. Outcome assessors masked? | **Comments:** | |
| 7. Care provider masked? | | |
| 8. Patients masked? | | |
| 9. Intention-to-treat analysis? | | |
| 10. Postrandomization exclusions? | | |
| 11. Reporting of Attrition | | |
| Crossover | | |
| Adherence | | |
| Contamination | | |

**Ratner, 2006** **Trial type:** Open label extension **Design:** NA **Quality rating:** NA

| Internal validity | External validity | |
|---|---|---|
| 1. Randomization adequate? | 1. Number Screened/Eligible/Enrolled: | NR/183/150 |
| 2. Allocation adequate? | 2. Run-in/Washout: | No/No |
| 3. Groups similar at baseline? | 3. Exclusion criteria reported? | |
| 4. Eligibility criteria specified? | 4. Funding: | Amylin Pharmaceuticals, Eli Lilly and Company |
| 5. Loss to follow-up, differential? | | |
| 6. Outcome assessors masked? | **Comments:** | |
| 7. Care provider masked? | | |
| 8. Patients masked? | | |
| 9. Intention-to-treat analysis? | | |
| 10. Postrandomization exclusions? | | |
| 11. Reporting of Attrition | | |
| Crossover | | |
| Adherence | | |
| Contamination | | |

**Raz, 2006** **Trial type:** placebo-controlled **Design:** RCT - Parallel group, DB, NR **Quality rating:** Fair

| Internal validity | External validity |
|---|---|

## Evidence Table 4. Quality assessment of efficacy trials of newer drugs for the treatment of diabetes mellitus

**Raz, 2006** **Trial type:** placebo-controlled **Design:** RCT - Parallel group, DB, NR **Quality rating:** Fair

| Internal validity | | External validity | |
|---|---|---|---|
| 1. Randomization adequate? | Yes* | 1. Number Screened/Eligible/Enrolled: | 1387/NR/521 |
| 2. Allocation adequate? | Yes* | 2. Run-in/Washout: | Yes/Yes |
| 3. Groups similar at baseline? | Yes | 3. Exclusion criteria reported? | Yes |
| 4. Eligibility criteria specified? | Yes | 4. Funding: | Merck |
| 5. Loss to follow-up, differential? | No | | |
| 6. Outcome assessors masked? | Yes* | **Comments:** | |
| 7. Care provider masked? | Yes* | *This information was not provided in the publication but was provided by the manufacturer | |
| 8. Patients masked? | Yes* | | |
| 9. Intention-to-treat analysis? | Yes | | |
| 10. Postrandomization exclusions? | Unable to determine | | |
| 11. Reporting of Attrition | Yes | | |
| Crossover | No | | |
| Adherence | No | | |
| Contamination | No | | |

**Raz, 2008** **Trial type:** placebo-controlled **Design:** RCT - Parallel group, DB, NR **Quality rating:** Fair

| Internal validity | | External validity | |
|---|---|---|---|
| 1. Randomization adequate? | Yes | 1. Number Screened/Eligible/Enrolled: | 544/NR/190 |
| 2. Allocation adequate? | Method not described | 2. Run-in/Washout: | Yes/Yes |
| 3. Groups similar at baseline? | Yes | 3. Exclusion criteria reported? | Yes |
| 4. Eligibility criteria specified? | Yes | 4. Funding: | Merck |
| 5. Loss to follow-up, differential? | No | | |
| 6. Outcome assessors masked? | Unclear, reported as double blind | **Comments:** | |
| 7. Care provider masked? | Unclear, reported as double blind | | |
| 8. Patients masked? | Unclear, reported as double blind | | |
| 9. Intention-to-treat analysis? | Yes | | |
| 10. Postrandomization exclusions? | Yes | | |
| 11. Reporting of Attrition | Yes | | |
| Crossover | No | | |
| Adherence | Yes | | |
| Contamination | No | | |

**Riddle, 2006** **Trial type:** Open label extension **Design:** NA **Quality rating:** NA

| Internal validity | External validity |
|---|---|

## Evidence Table 4. Quality assessment of efficacy trials of newer drugs for the treatment of diabetes mellitus

**Riddle, 2006** **Trial type:** Open label extension **Design:** NA **Quality rating:** NA

| Internal validity | | External validity | |
|---|---|---|---|
| 1. Randomization adequate? | | 1. Number Screened/Eligible/Enrolled: | NR/591/518 |
| 2. Allocation adequate? | | 2. Run-in/Washout: | No/No |
| 3. Groups similar at baseline? | | 3. Exclusion criteria reported? | |
| 4. Eligibility criteria specified? | | 4. Funding: | Amylin Pharmaceuticals, Eli Lilly |
| 5. Loss to follow-up, differential? | | | |
| 6. Outcome assessors masked? | | **Comments:** | |
| 7. Care provider masked? | | | |
| 8. Patients masked? | | | |
| 9. Intention-to-treat analysis? | | | |
| 10. Postrandomization exclusions? | | | |
| 11. Reporting of Attrition | | | |
| Crossover | | | |
| Adherence | | | |
| Contamination | | | |

**Riddle, 2007** **Trial type:** placebo-controlled **Design:** RCT - Parallel group, DB, NR **Quality rating:** Fair

| Internal validity | | External validity | |
|---|---|---|---|
| 1. Randomization adequate? | Method not described | 1. Number Screened/Eligible/Enrolled: | NR/NR/212 |
| 2. Allocation adequate? | Method not described | 2. Run-in/Washout: | No/No |
| 3. Groups similar at baseline? | Yes | 3. Exclusion criteria reported? | Yes |
| 4. Eligibility criteria specified? | Yes | 4. Funding: | NR |
| 5. Loss to follow-up, differential? | No | | |
| 6. Outcome assessors masked? | Unclear, reported as double blind | **Comments:** | |
| 7. Care provider masked? | Unclear, reported as double blind | | |
| 8. Patients masked? | Unclear, reported as double blind | | |
| 9. Intention-to-treat analysis? | Yes | | |
| 10. Postrandomization exclusions? | Yes | | |
| 11. Reporting of Attrition | Yes | | |
| Crossover | No | | |
| Adherence | No | | |
| Contamination | No | | |

**Rosenstock, 2006** **Trial type:** placebo-controlled **Design:** RCT - Parallel group, DB, NR **Quality rating:** Fair

| Internal validity | | External validity | |
|---|---|---|---|

## Evidence Table 4. Quality assessment of efficacy trials of newer drugs for the treatment of diabetes mellitus

**Rosenstock, 2006** **Trial type:** placebo-controlled **Design:** RCT - Parallel group, DB, NR **Quality rating:** Fair

| Internal validity | |
|---|---|
| 1. Randomization adequate? | Yes* |
| 2. Allocation adequate? | Yes* |
| 3. Groups similar at baseline? | Yes* |
| 4. Eligibility criteria specified? | Yes |
| 5. Loss to follow-up, differential? | No |
| 6. Outcome assessors masked? | Yes* |
| 7. Care provider masked? | Yes* |
| 8. Patients masked? | Yes* |
| 9. Intention-to-treat analysis? | Yes |
| 10. Postrandomization exclusions? | Yes |
| 11. Reporting of Attrition | Yes |
| Crossover | No |
| Adherence | No |
| Contamination | No |

| External validity | |
|---|---|
| 1. Number Screened/Eligible/Enrolled: | 928/458/353 |
| 2. Run-in/Washout: | Yes/No |
| 3. Exclusion criteria reported? | Yes |
| 4. Funding: | Merck |

**Comments:**

* This information was not provided in the publication but was provided by the manufacturer

**Scott, 2007** **Trial type:** active-control **Design:** RCT - Parallel group, DB, NR **Quality rating:** Fair

| Internal validity | |
|---|---|
| 1. Randomization adequate? | Yes |
| 2. Allocation adequate? | Yes* |
| 3. Groups similar at baseline? | Yes |
| 4. Eligibility criteria specified? | Yes |
| 5. Loss to follow-up, differential? | No |
| 6. Outcome assessors masked? | Yes* |
| 7. Care provider masked? | Yes* |
| 8. Patients masked? | Yes* |
| 9. Intention-to-treat analysis? | Yes |
| 10. Postrandomization exclusions? | Yes |
| 11. Reporting of Attrition | Yes |
| Crossover | No |
| Adherence | No |
| Contamination | No |

| External validity | |
|---|---|
| 1. Number Screened/Eligible/Enrolled: | 2186/NR/743 |
| 2. Run-in/Washout: | Yes/Yes |
| 3. Exclusion criteria reported? | Yes |
| 4. Funding: | Merck |

**Comments:**

* This information was not found in the publication but was provided by the manufacturer

**Scott, 2008** **Trial type:** active-control **Design:** RCT - Parallel group, DB, NR **Quality rating:** Fair

| Internal validity | External validity |
|---|---|

## Evidence Table 4. Quality assessment of efficacy trials of newer drugs for the treatment of diabetes mellitus

**Scott, 2008** **Trial type:** active-control **Design:** RCT - Parallel group, DB, NR **Quality rating:** Fair

| Internal validity | |
|---|---|
| 1. Randomization adequate? | Yes* |
| 2. Allocation adequate? | Yes* |
| 3. Groups similar at baseline? | Yes |
| 4. Eligibility criteria specified? | Yes |
| 5. Loss to follow-up, differential? | No |
| 6. Outcome assessors masked? | Yes* |
| 7. Care provider masked? | Yes* |
| 8. Patients masked? | Yes* |
| 9. Intention-to-treat analysis? | Yes |
| 10. Postrandomization exclusions? | Yes |
| 11. Reporting of Attrition | Yes |
| Crossover | No |
| Adherence | Yes |
| Contamination | No |

| External validity | |
|---|---|
| 1. Number Screened/Eligible/Enrolled: | 486/NR/273 |
| 2. Run-in/Washout: | Yes/No |
| 3. Exclusion criteria reported? | Yes |
| 4. Funding: | Merck |

**Comments:**

* This information was not found in the publication but was provided by the manufacturer.

**Whitehouse, 2002** **Trial type:** Open label extension **Design:** NA **Quality rating:** NA

| Internal validity | |
|---|---|
| 1. Randomization adequate? | |
| 2. Allocation adequate? | |
| 3. Groups similar at baseline? | |
| 4. Eligibility criteria specified? | |
| 5. Loss to follow-up, differential? | |
| 6. Outcome assessors masked? | |
| 7. Care provider masked? | |
| 8. Patients masked? | |
| 9. Intention-to-treat analysis? | |
| 10. Postrandomization exclusions? | |
| 11. Reporting of Attrition | |
| Crossover | |
| Adherence | |
| Contamination | |

| External validity | |
|---|---|
| 1. Number Screened/Eligible/Enrolled: | NR/NR/236 |
| 2. Run-in/Washout: | No/No |
| 3. Exclusion criteria reported? | |
| 4. Funding: | NR; Amylin Pharmaceuticals? |

**Comments:**

## Evidence Table 4. Quality assessment of efficacy trials of newer drugs for the treatment of diabetes mellitus

**Whitehouse, 2002** **Trial type:** Open label extension **Design:** NA **Quality rating:** NA

| Internal validity | | External validity | |
|---|---|---|---|
| 1. Randomization adequate? | Method not described | 1. Number Screened/Eligible/Enrolled: | NR/NR/480 |
| 2. Allocation adequate? | Method not described | 2. Run-in/Washout: | No/No |
| 3. Groups similar at baseline? | Yes | 3. Exclusion criteria reported? | Yes |
| 4. Eligibility criteria specified? | Yes | 4. Funding: | NR; Amylin Pharmaceuticals? |
| 5. Loss to follow-up, differential? | Unable to determine | | |
| 6. Outcome assessors masked? | Unclear, reported as double blind | **Comments:** | |
| 7. Care provider masked? | Unclear, reported as double blind | | |
| 8. Patients masked? | Unclear, reported as double blind | | |
| 9. Intention-to-treat analysis? | No | | |
| 10. Postrandomization exclusions? | Yes | | |
| 11. Reporting of Attrition | Yes | | |
| Crossover | No | | |
| Adherence | No | | |
| Contamination | No | | |

**Zinman, 2007** **Trial type:** placebo-controlled **Design:** RCT - Parallel group, DB, NR **Quality rating:** Fair

| Internal validity | | External validity | |
|---|---|---|---|
| 1. Randomization adequate? | Yes | 1. Number Screened/Eligible/Enrolled: | 435/250/233 |
| 2. Allocation adequate? | Yes | 2. Run-in/Washout: | Yes/No |
| 3. Groups similar at baseline? | Yes | 3. Exclusion criteria reported? | No |
| 4. Eligibility criteria specified? | Yes | 4. Funding: | Eli Lilly & Amylin |
| 5. Loss to follow-up, differential? | No | | |
| 6. Outcome assessors masked? | Unclear, reported as double blind | **Comments:** | |
| 7. Care provider masked? | Unclear, reported as double blind | | |
| 8. Patients masked? | Yes | | |
| 9. Intention-to-treat analysis? | Yes | | |
| 10. Postrandomization exclusions? | Yes | | |
| 11. Reporting of Attrition | Yes | | |
| Crossover | Yes | | |
| Adherence | No | | |
| Contamination | No | | |

**Evidence Table 5. Systematic review of newer drugs for the treatment of diabetes mellitus by Amori et al 2007**

| Author Year | Aims | Databases searched; Literature search dates; Other data sources | Eligibility criteria | Number of trials/ Number of patients | Characteristics of identified articles: study designs | Characteristics of identified articles: populations | Characteristics of identified articles: interventions |
|---|---|---|---|---|---|---|---|
| Amori 2007 | To assess efficacy and safety of GLP-1 analogues and DPP4 inhibitors in adults with DM2 | MEDLINE (1966–May 20, 2007); Cochrane Central Register of Controlled Trials (second quarter, 2007); prescribing information documents; in personal reference lists and citation sections of recovered articles; abstracts presented at the American Diabetes Association and the European Association Study of Diabetes conferences for 2005-2006. | English-language, randomized controlled trials and conference abstracts that reported original data in patients with DM2 with A1c outcomes for an incretin-based vs a non–incretin-based comparator group (placebo or hypoglycemic agent).<br><br>Excluded studies <12 wks duration | 29 RCTs (12 included in DERP report; 14 were excluded because the drugs are not yet FDA approved; 3 others were excluded because they did not meet DERP report inclusion criteria) | Exenatide- 7 studies total; 5 placebo-controlled and 2 active-controlled trials; there was 1 small study looking at long-acting formulation that is not yet FDA approved<br><br>Liraglutide- 2 studies total; 1 placebo-controlled and 1 active-controlled trials; not yet FDA approved<br><br>Sitagliptin- 8 studies total; 7 placebo-controlled and 1 active-controlled trials<br><br>Vildagliptin- 12 studies total; 9 placebo-controlled and 3 active-controlled trials<br><br>*some studies with an insulin comparator were open-label | Nonpregnant adults with varying severity and durations of DM2; patients were either inadequately controlled by diet/exercise, oral medications, insulin therapy, or combinations of diet/exercise, oral, and insulin therapy. | 3 of 29 studies had study durations >30 wks<br><br>8 published trials in which a GLP-1 analogue was added to existing inadequate therapy (lifestyle or OHA) and compared with a DB injectable placebo, MET, or open-label subcutaneous insulin<br><br>1 small study with a LA formulation of a GLP-1 analogue<br><br>13 DB, placebo-controlled trials compared a DPP4 inhibitor given as monotherapy or as add-on therapy to OHA or insulin<br><br>4 trials compared a DPP4 inhibitor with an OHA, including glipizide titrated to glycemic goals, metformin, or a TZD<br><br>3 abstracts concerning a DPP4 inhibitor with data contributing only to certain meta-analyses |

**Evidence Table 5. Systematic review of newer drugs for the treatment of diabetes mellitus by Amori et al 2007**

| Main efficacy outcome | Main efficacy results | Harms results | Quality assessment method | Limitations of primary studies | Data synthesis methods | Comments |
|---|---|---|---|---|---|---|
| Change A1c from baseline<br><br>If data from more than 2 trials were available for A1c, data from these trials within a class were combined and heterogeneity explored<br><br>Treatment differences in FPG and the proportion of patients achieving HbA1c< 7% | Individual study results are listed in Figures 2 and 3 in the Amori article.<br><br>GLP-1 analogues and DPP4 inhibitors (mean difference in change in A1c versus control, 95% CI)<br><br>GLP-1 vs. placebo= -0.97 (-1.13, -0.81); $I^2$ 44%<br>Exenatide vs. placebo= -1.01 (-1.18, -0.84); $I^2$ 45%<br>Exenatide vs. insulin= -0.06 (-0.22, -0.10); $I^2$ 59%<br><br>DPP4 vs. placebo= –0.74 (–0.85 to –0.62); $I^2$ 77%<br>Sitagliptin vs. placebo= –0.74 (–0.84 to –0.63); $I^2$ 54%<br>Vildagliptin vs placebo= –0.73 (–0.94 to –0.52); $I^2$ 85%<br>Duration 12 wk vs placebo= –0.78 (–1.00 to –0.56); $I^2$ 82%<br>Duration 12-24 wk vs placebo= –0.70 (–0.83 to –0.58); $I^2$ 72%<br>DPP4 vs hypoglycemic agent= +0.21 (0.02 to 0.39); $I^2$ 66% | Data from all available doses were included to increase statistical power between treatment groups of uncommon events.<br><br>(See Table 3 in Amori, et al for more information on harms, Results reported as Risk Ratio between incretin therapy vs. control, 95% CI)<br><br>For GLP-1 analogues: **Hypoglycemia**= Exenatide vs placebo injection 2.30 (1.08-4.88); Exenatide vs insulin 1.02 (0.46-2.26), **Nausea**= All GLP-1 analogues vs comparator 2.92 (2.02-4.24), **Vomiting**=All GLP-1 analogues vs comparator 3.32 (2.51-4.41), **Diarrhea**= All GLP-1 analogues vs comparator 2.23 (1.72-2.89)<br><br>For DPP4 inhibitors: **Hypoglycemia**= All DPP4 inhibitors vs comparator 0.97 (0.50-1.86), **Nausea**= All DPP4 inhibitors vs comparator 0.89 (0.58-1.36), vomiting, **Diarrhea**= All DPP4 inhibitors vs comparator 0.80 (0.42-1.54), abdominal pain, cough, influenza, **Nasopharyngitis**=All DPP4 inhibitors vs comparator 1.17 (0.98-1.40), upper respiratory tract infection, sinusitis, **Urinary tract infection**= All DPP4 inhibitors vs comparator 1.52 (1.04-2.21), **Headache**= All DPP4 inhibitors vs comparator 1.38 (1.10-1.72) | Oxman, et al criteria (minimal flaws in this SR= 6 of 7) | Short duration of follow-up which limits long-term assessment of efficacy/effectiveness and harms<br><br>Most studies included larger proportion of white patients with relatively lower baseline A1c levels compared to previous clinical trials. Most of the included studies did not use 'true' intent-to-treat populations for statistical analyses.<br><br>Results do not apply to children | For dose-dependent outcomes, such as glycemic efficacy (A1c, percentage achieving A1c < 7%), weight change, and hypoglycemia, only data from the approved maximum dose entered the meta-analyses. For nonapproved medications, the highest dose was used.<br><br>Used a random-effects model that weighs studies by the inverse of the within-study and between-studies variability. Also used the $I^2$ statistic to quantify the degree of heterogeneity among trials. | For postprandial glycemia, lipid profile, and antibody development, meta-analyses were not performed because of the diverse methods used to assess outcomes and/or because of insufficiently reported data. |

**Evidence Table 6. Quality assessment of systematic reviews of newer drugs for the treatment of diabetes mellitus**

| Study | Searches through | 1. Search methods reported? | 2. Comprehensive search? | 3. Inclusion criteria reported? | 4. Selection bias avoided? | 5. Validity criteria reported? | 6. Validity assessed appropriately? | 7. Methods used to combine studies reported? | 8. Findings combined appropriately? | 9. Conclusions supported by data? | 10. Overall scientific quality (score 1-7) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Amori, 2007 | Medline 1966-May 20, 2007 | Yes;<br><br>Medline, Cochrane Library, conference abstracts, personal reference lists, websites | Yes; (see box 1) | Yes;<br><br>English-language, RCTs; abstracts with data not included in RCTs (from ADA and Europena Assoc Study of DM for 2005-2006); nonpregnant adults with DM2; included drugs that are not yet FDA approved<br><br>Excluded studies <12 wks duration | Yes (see quorum tree);<br><br>Dual abstract review and consensus based on inclusion criteria | Yes;<br><br>Reported certain internal validity characteristics of RCTs in Table 1 and some in the text. | Yes<br><br>Reported how many studies mentioned allocation concealment, role of funding source in the study, etc. Did not specify whether sensitivity analyses were done; did not report whether they excluded poor quality studies for their analyses; they did mention that random-effects model was used and also reported I^2 heterogeneity percentage. | Yes<br><br>Reported individual study results and combined different incretin therapies comparing them to controls | Yes;<br><br>Though sensitivity analyses could have been done by removing outliers since I^2 was fairly high. Could have discussed heterogeneity issues observed. | Yes | 6 of 7 |
| Barnett, 2007 | Jan 2004 - Sept 2006 | Yes<br><br>Medline, hand-searching references; meeting/ conference abstracts; search terms were reported | No<br><br>Only 1-database searched (Medline) with some hand-searching of reference lists | Yes<br><br>The authors listed exclusion criteria: review articles, studies without documented mean wt change, DM1, adolescents, cildren | No | No<br><br>nothing mentioned | No<br><br>nothing mentioned | No | No | Unknown (results were in a narrative format) | 1-major flaws (validity criteria or assessment not reported; high potential for selection bias) |