Efficacy and Safety of Incretin Therapy in Type 2 Diabetes

Systematic Review and Meta-analysis

Renee E. Amori, MD
Joseph Lau, MD
Anastassios G. Pittas, MD, MSc

Context Pharmacotherapies that augment the incretin pathway have recently become available, but their role in the management of type 2 diabetes is not well defined.

Objective To assess the efficacy and safety of incretin-based therapy in adults with type 2 diabetes based on randomized controlled trials published in peer-reviewed journals or as abstracts.

Data Sources We searched MEDLINE (1966–May 20, 2007) and the Cochrane Central Register of Controlled Trials (second quarter, 2007) for English-language randomized controlled trials involving an incretin mimetic (glucagonlike peptide 1 [GLP-1] analogue) or enhancer (dipeptidyl peptidase 4 [DPP4] inhibitor). We also searched prescribing information, relevant Web sites, reference lists and citation sections of recovered articles, and abstracts presented at recent conferences.

Study Selection Randomized controlled trials were selected if they were at least 12 weeks in duration, compared incretin therapy with placebo or other diabetes medication, and reported hemoglobin A_{1c} data in nonpregnant adults with type 2 diabetes.

Data Extraction Two reviewers independently assessed trials for inclusion and extracted data. Differences were resolved by consensus. Meta-analyses were conducted for several efficacy and safety outcomes.

Results Of 355 potentially relevant articles identified, 51 were retrieved for detailed evaluation and 29 met the inclusion criteria. Incretins lowered hemoglobin A_{1c} compared with placebo (weighted mean difference, –0.97% [95% confidence interval {CI}, –1.13% to –0.81%] for GLP-1 analogues and –0.74% [95% CI, –0.85% to –0.62%] for DPP4 inhibitors) and were noninferior to other hypoglycemic agents. Glucagonlike peptide 1 analogues resulted in weight loss (1.4 kg and 4.8 kg vs placebo and insulin, respectively) while DPP4 inhibitors were weight neutral. Glucagonlike peptide 1 analogues had more gastrointestinal side effects (risk ratio, 2.9 [95% CI, 2.0-4.2] for nausea and 3.2 [95% CI, 2.5-4.4] for vomiting). Dipeptidyl peptidase 4 inhibitors had an increased risk of infection (risk ratio, 1.2 [95% CI, 1.0-1.4] for nasopharyngitis and 1.5 [95% CI, 1.0-2.2] for urinary tract infection) and headache (risk ratio, 1.4 [95% CI, 1.1-1.7]). All but 3 trials had a 30-week or shorter duration; thus, long-term efficacy and safety could not be evaluated.

Conclusions Incretin therapy offers an alternative option to currently available hypoglycemic agents for nonpregnant adults with type 2 diabetes, with modest efficacy and a favorable weight-change profile. Careful postmarketing surveillance for adverse effects, especially among the DPP4 inhibitors, and continued evaluation in longer-term studies and in clinical practice are required to determine the role of this new class among current pharmacotherapies for type 2 diabetes.

JAMA. 2007;298(2):194-206 www.jama.com

Author Affiliations: Division of Endocrinology, Diabetes and Metabolism (Drs Amori and Pittas) and Institute for Clinical Research and Health Policy Studies (Dr Lau), Tufts-New England Medical Center, Boston, Massachusetts.

Corresponding Author: Anastassios G. Pittas, MD, MSc, Division of Endocrinology, Diabetes and Metabolism, Tufts-New England Medical Center, 750 Washington St, #268, Boston, MA 02111 (apittas@tufts-nemc.org).

FEWER THAN HALF OF US ADULTS with type 2 diabetes reach a hemoglobin A_{1c} (HbA_{1c}) level of less than 7% despite several available therapies.[1] Ineffective implementation of existing pharmacotherapies is a significant factor contributing to suboptimal care.[2] However, efficacy of available therapies, even when used appropriately, diminishes as the disease progresses because of a steady, relentless decline in pancreatic beta cell function.[3] Furthermore, current therapies for type 2 diabetes are often limited by adverse effects such as weight gain, edema, or hypoglycemia, and most do not target postprandial hyperglycemia effectively. Therefore, therapies targeting the decline in pancreatic beta cell function without causing weight gain and with minimal adverse effects are desirable.

Recently, improved understanding of the incretin effect on the pathophysiology of type 2 diabetes has led to development of new hypoglycemic agents. The incretin effect is the augmentation of glucose-stimulated insulin secretion by intestinally derived peptides, which are released in the presence of glucose or nutrients in the gut.[4] The theory evolved from the observation that an oral glucose load was more effective at releasing insulin compared with the same amount of glucose given intravenously.[5] The actions of incre-

tins depend on glucose concentration, and their function ceases when serum glucose level is less than 55 mg/dL (to convert to millimoles per liter, multiply by 0.0555).[4,6] The incretin effect is composed primarily of 2 peptides, glucose-dependent insulinotropic polypeptide (GIP) and glucagonlike peptide 1 (GLP-1). Incretins are rapidly inactivated by the enzyme dipeptidyl peptidase 4 (DPP4), resulting in a very short half-life (minutes). The incretin pathway appears to be attenuated in type 2 diabetes, making the pathway a target for development of new pharmacologic agents.[7,8]

In April 2005, the US Food and Drug Administration approved the first incretin mimetic, exenatide, a GLP-1 receptor analogue resistant to DPP4 degradation, as adjunctive therapy for patients with type 2 diabetes. Because GLP-1 analogues require injection, considerable effort has been devoted to creating an oral agent targeting the incretin pathway. Inhibition of DPP4 extends the half-life of native incretins, thereby prolonging their effects. In October 2006, the Food and Drug Administration approved the first oral incretin enhancer, sitagliptin, a selective DPP4 inhibitor, for use as monotherapy or in combination with metformin or thiazolidinedione. Additional incretin-based agents are in late-stage development.[8]

The present meta-analysis assesses the efficacy and safety of incretin-based therapy (GLP-1 analogues and DPP4 inhibitors) in nonpregnant adults with type 2 diabetes based on published and unpublished randomized controlled trials.

METHODS

We followed the QUOROM (Quality of Reporting of Meta-analyses) guidelines for reporting our meta-analysis methods and results.[9]

Data Sources and Searches

We conducted a search of MEDLINE (1966–May 20, 2007) and the Cochrane Central Register of Controlled Trials (second quarter, 2007) for English-language randomized controlled trials of incretin therapy (GLP-1 analogues and DPP4 inhibitors) in nonpregnant adults with type 2 diabetes. We used the following search terms: *diabetes*, *blood glucose*, *hyperglycemia*, *glucose*, *glycohemoglobin*, *hemoglobin A1c*, *incretin*, *glucagon like peptide*, *enteroglucagon*, *GLP-1*, *GIP*, *exenatide*, *liraglutide*, *dipeptidyl peptidase*, *DPP*, *LAF237*, *MK-0431*, *sitagliptin*, *vildagliptin*, *saxagliptin*, *human*, and *clinical trial*. We searched for additional trials in the prescribing information documents of approved medications, at relevant Web sites (eg, http://www.clinicalstudyresults.org and http://www.clinicaltrials.gov), and in personal reference lists and citation sections of recovered articles. We also searched abstracts presented at the American Diabetes Association and the European Association Study of Diabetes conferences for 2005-2006. We included abstracts with data that had not been published in peer-reviewed journals because in our search of the relevant literature, we did not find any differences between trial results that were originally described in abstracts and those from the same trials that were subsequently published in peer-reviewed journals.

Study Selection

Two reviewers (R.E.A. and A.G.P.) independently screened abstracts according to the inclusion criteria. An abstract was judged relevant if it reported original data from controlled trials in patients with type 2 diabetes with HbA_{1c} outcomes for an incretin-based vs a non–incretin-based comparator group (placebo or hypoglycemic agent). We excluded studies of less than 12 weeks' duration because such studies would give an inadequate assessment of change in glycemic efficacy, as HbA_{1c} reflects glycemia during the previous 3 months.[10] Full-text articles were retrieved and reviewed if a decision on inclusion could not be made solely based on the abstract. Any discrepancies were resolved by consensus between the 2 independent reviewers or in group conference via referencing the original article.

Data Extraction and Quality Assessment

Participant baseline characteristics of the included studies were extracted and are described in TABLE 1. For glycemic efficacy, we extracted data on change from baseline in HbA_{1c}, fasting plasma glucose, and postprandial glycemia after a mixed-meal test and proportion of patients achieving HbA_{1c} of less than 7%. When available, we also extracted data on change in body weight and lipid profile. To evaluate safety, we extracted data on hypoglycemia (severe or nonsevere) and all reported adverse events. We also extracted data on level of circulating antibodies to incretin analogue. For hypoglycemia, we combined and present data on the total number of patients per treatment group who reported at least 1 episode of hypoglycemia. Differences in baseline characteristics between groups, description of allocation concealment, intention-to-treat analysis, and dropout rate were used to evaluate study quality.

Data Synthesis and Analysis

The primary measure for glycemic efficacy was the treatment group difference in HbA_{1c} change from baseline. Treatment group difference in fasting plasma glucose and the proportion of participants reaching an HbA_{1c} of less than 7% were secondary glycemic efficacy outcomes. For safety, we examined number of participants reporting hypoglycemia and other adverse effects. Because these 2 classes of medications are relatively new, to assess safety, we analyzed all reported adverse events.

For continuous variables (HbA_{1c}, fasting plasma glucose, weight), we calculated weighted mean differences and 95% confidence intervals (CIs) for change from baseline in incretin vs comparator (placebo or hypoglycemic agent) groups. For dichotomous variables (percentages achieving HbA_{1c} $<7\%$ and percentages with hypoglycemia and adverse events), we calculated the risk ratios and 95% CIs for incretin vs comparator groups. If data from more than 2 trials were available,

Table 1. Characteristics of Randomized Controlled Trials of Glucagonlike Peptide 1 Analogues and Dipeptidyl Peptidase 4 Inhibitors Included in the Systematic Review

Source[a]	Study Duration, wk	No. of Participants[b]	Mean Age, y/ Women, %/ White, %	Duration of Diabetes, y	Baseline HbA_{1c} Level, %	Incretin-Based Therapy[c]	Control[c]	Study Quality[d]		
								Allocation Concealment Described?	Data Analysis	Dropout Rate, %
Exenatide										
Buse et al,[11] 2004	30	377	55/40/63	6	8.6	Sulfonylurea + exenatide, 10 μg Sulfonylurea + exenatide, 5 μg[e]	Sulfonylurea + placebo injection (subcutaneous twice daily)	No	ITT	31
DeFronzo et al,[12] 2005	30	336	53/43/76	6	8.2	Metformin + exenatide, 10 μg Metformin + exenatide, 5 μg[e]	Metformin + placebo injection (subcutaneous twice daily)	No	ITT	19
Kendall et al,[13] 2005	30	734	55/42/68	9	8.5	Sulfonylurea/ metformin + exenatide, 5 μg[e] Sulfonylurea/ metformin + exenatide, 10 μg	Sulfonylurea/ metformin + placebo injection (subcutaneous twice daily)	No	ITT	19
Heine et al,[14] 2005[f]	26	551	59/44/80	10	8.2	Sulfonylurea/ metformin + exenatide, 10 μg	Sulfonylurea/ metformin + insulin glargine	Yes	APT	15
Nauck et al,[15] 2007[f]	52	505	59/49/NR	10	8.6	Sulfonylurea/ metformin + exenatide, 10 μg	Sulfonylurea/ metformin + biphasic aspart insulin	Yes	APT	16
Zinman et al,[16] 2007	16	233	56/45/84	8	7.9	Thiazolidinedione (pioglitazone or rosiglitazone)/ metformin + exenatide, 10 μg	Thiazolidinedione (pioglitazone or rosiglitazone)/ metformin + placebo injection (subcutaneous twice daily)	Yes	ITT	22
Kim et al,[17] 2007	15	45	53/40/60	5	8.5	Metformin/diet + exenatide (subcutaneous once/wk), 2.0 mg Metformin/diet + exenatide (subcutaneous once/wk), 0.8 mg[e]	Metformin/diet + placebo injection (subcutaneous once/wk)	No	ITT	4
Liraglutide										
Madsbad et al,[18] 2004	12	193	58/33/100	4	7.4	Liraglutide, 0.75 mg Liraglutide, 0.6 mg[e]	Placebo injection (subcutaneous twice daily)	No	ITT	13
Feinglos et al,[19] 2005	12	210	54/60/78	5	7.0	Liraglutide, 0.75 mg Liraglutide, 0.6 mg[e]	Metformin	No	Completers	15
Sitagliptin										
Scott et al,[20] 2007	12	743	55/45/65	5	7.9	Sitagliptin, 50 mg twice daily Sitagliptin, 5 mg twice daily[e] Sitagliptin, 12.5 mg twice daily[e] Sitagliptin, 25 mg twice daily[e]	Placebo	No	APT	12
Raz et al,[21] 2006	18	521	55/46/68	5	8.1	Sitagliptin, 100 mg once daily Sitagliptin, 200 mg once daily[e]	Placebo	No	APT	11
Ascher et al,[22] 2006	24	741	54/46/51	4	8.0	Sitagliptin, 100 mg once daily Sitagliptin, 200 mg once daily[e]	Placebo	No	APT	14
Charbonnel et al,[23] 2006	24	701	55/43/64	6	8.0	Metformin + sitagliptin, 100 mg once daily	Metformin + placebo	No	APT	13

(continued)

we combined data from trials within a class (GLP-1 analogues or DPP4 inhibitors) and explored heterogeneity between comparable trials with prespecified subgroup analyses by type of comparator group (placebo vs hypoglycemic agent), duration of intervention (12 vs >12 weeks), and available formulation within each class. For dose-dependent outcomes, such as glycemic efficacy (HbA_{1c}, percentage achieving HbA_{1c} >7%), weight change, and hypoglycemia, only data from the approved maximum dose entered the meta-analyses (10 µg twice daily for exenatide and 100 mg/d for sitagliptin). For nonapproved medications, the highest dose was used (0.75 mg/d for liraglutide, 2.0 mg once weekly for exenatide given subcutaneously, and 100 mg/d for vildagliptin). For adverse-event outcomes, we included data from all available doses to increase the statistical power to detect differences between treatment groups of uncommon events.

For postprandial glycemia, lipid profile, and antibody development, we did not perform meta-analyses because of the diverse methods used to assess out-

Table 1. Characteristics of Randomized Controlled Trials of Glucagonlike Peptide 1 Analogues and Dipeptidyl Peptidase 4 Inhibitors Included in the Systematic Review (cont)

Source[a]	Study Duration, wk	No. of Participants[b]	Mean Age, y/ Women, %/ White, %	Duration of Diabetes, y	Baseline HbA_{1c} Level, %	Incretin-Based Therapy[c]	Control[c]	Study Quality[d]		
								Allocation Concealment Described?	Data Analysis	Dropout Rate, %
Sitagliptin										
Rosenstock et al,[24] 2006	24	353	56/44/73	6	8.1	Pioglitazone + sitagliptin, 100 mg once daily	Pioglitazone + placebo	No	APT	13
Nauck et al,[25] 2007[f]	52	1172	57/41/74	6	7.7	Metformin + sitagliptin, 100 mg once daily	Metformin + glipizide	No	APT	32
Nonaka et al,[26] 2006[g]	12	151	55/49/NR	4	7.6	Sitagliptin, 100 mg once daily	Placebo	No	APT	NR
Hanefeld et al,[27] 2005[g]	12	555	56/48/NR	4	7.7	Sitagliptin, 100 mg once daily Sitagliptin 50 mg twice daily[e] Sitagliptin, 25 mg once daily[e] Sitagliptin, 50 mg once daily[e]	Placebo	No	APT	NR
Vildagliptin										
Ahren et al,[28] 2004	12	107	57/32/99	6	7.8	Metformin + vildagliptin, 50 mg once daily	Metformin + placebo	No	ITT	10
Ristic et al,[29] 2005	12	279	56/46/80	3	7.7	Vildagliptin, 100 mg once daily Vildagliptin, 25 mg twice daily[e] Vildagliptin, 25 mg once daily[e] Vildagliptin, 50 mg once daily[e]	Placebo	No	ITT	NR
Pratley et al,[30] 2006	12	100	56/57/47	4	8.0	Vildagliptin, 25 mg twice daily	Placebo	No	ITT	9
Pi-Sunyer et al,[31] 2007	24	354	51/45/54	2	8.4	Vildagliptin, 100 mg once daily Vildagliptin, 50 mg once daily[e] Vildagliptin, 50 mg twice daily[e]	Placebo	No	APT	23
Dejager et al,[32] 2007	24	632	54/53/73	2	8.4	Vildagliptin, 100 mg once daily Vildagliptin, 50 mg once daily[e] Vildagliptin, 50 mg twice daily[e]	Placebo	No	ITT	19
Garber et al,[33] 2007	24	463	54/50/80	5	8.7	Pioglitazone + vildagliptin, 50 mg twice daily Pioglitazone + vildagliptin, 50 mg once daily[e]	Pioglitazone + placebo	No	APT	19

(continued)

comes and/or because of insufficiently reported data. For all meta-analyses, we used a random-effects model that weighs studies by the inverse of the within-study and between-studies variances.[40] Most studies reported differences in the mean changes and the corresponding 95% CIs (or standard errors) between comparison groups. For studies that reported only the mean changes and the corresponding standard errors of the mean change, we calculated the differences and the standard errors of the differences between comparison groups using these data. We used the I^2 statistic to quantify the degree of heterogeneity among trials in each meta-analysis.[41] Event rates of single groups across studies (eg, hypoglycemia, adverse events) were calculated using a random-effects model to combine the logits of the event rates then transforming back to the rates (percentages).

RESULTS

Search Results and Study Characteristics

Search results are summarized in FIGURE 1. The characteristics of the 29 included trials (articles and abstracts) are summarized in Table 1. Only 3 of the 29 studies had durations of longer than 30 weeks.

There were 8 published trials (n=3139; age range, 19-78 years) in which a GLP-1 analogue was added to existing inadequate therapy (lifestyle or oral hypoglycemic therapy) and compared with a double-blind injectable placebo,[11-13,16,18] metformin,[19] or open-label subcutaneous insulin (glargine or biphasic aspart).[14,15] There was also 1 small study (n=45) with a long-acting formulation of a GLP-1 analogue.[17]

There were 13 published double-blind trials (n=4780; age range, 18-80 years) in which a placebo was compared with a DPP4 inhibitor given as monotherapy[20-22,29-32] or as add-on therapy to oral hypoglycemic

Table 1. Characteristics of Randomized Controlled Trials of Glucagonlike Peptide 1 Analogues and Dipeptidyl Peptidase 4 Inhibitors Included in the Systematic Review (cont)

Source[a]	Study Duration, wk	No. of Participants[b]	Mean Age, y/ Women, %/ White, %	Duration of Diabetes, y	Baseline HbA_{1c} Level, %	Incretin-Based Therapy[c]	Control[c]	Study Quality[d]		
								Allocation Concealment Described?	Data Analysis	Dropout Rate, %
Vildagliptin										
Rosenstock et al,[34] 2007[f]	24	786	54/42/80	2	8.7	Vildagliptin, 50 mg twice daily	Rosiglitazone, 8 mg once daily	No	APT	14
Bosi et al,[35] 2007	24	544	54/43/74	6	8.4	Metformin + vildagliptin, 50 mg twice daily Metformin + vildagliptin, 50 mg once daily[e]	Metformin + placebo	No	APT	15
Rosenstock et al,[36] 2007[h]	24	315	52/36/42	2	8.7	Vildagliptin, 100 mg once daily	Pioglitazone, 30 mg once daily	No	APT	15
Fonseca et al,[37] 2007	24	296	59/49/71	15	8.4	Unspecified insulin therapy + vildagliptin, 50 mg twice daily	Unspecified insulin therapy + placebo	No	APT	19
Schweizer et al,[38] 2007[f]	52	780	53/46/68	1	8.7	Vildagliptin, 50 mg twice daily	Metformin, 1000 mg twice daily	No	APT	27
Mimori et al,[39] 2006[g]	12	219	59/NR/NR	NR	7.4	Vildagliptin, 50 mg twice daily Vildagliptin, 10 mg twice daily[e] Vildagliptin, 25 mg twice daily[e]	Placebo	No	NR	NR

Abbreviations: HbA_{1c}, hemoglobin A_{1c}; NR, not reported.
[a] All studies were multinational except Buse et al,[11] Defronzo et al,[12] and Kendall et al.[13] Women who were pregnant or breastfeeding or those with reproductive potential who were not using contraceptives were excluded.
[b] The total number of participants randomized to all groups is different from the number of participants used in meta-analyses of glycemic efficacy, weight change, and hypoglycemia outcomes because most articles reported a modified ITT analysis ("all patients treated") that did not include all randomized participants and because only the highest available dose entered these meta-analyses.
[c] Plus sign indicates that the study medication (active or control) was added to existing therapy. Neither glucagonlike peptide 1 analogues nor dipeptidyl peptidase 4 inhibitors were titrated according to study-specific glucose goals. Exenatide or placebo injection was given subcutaneously twice daily approximately 15 minutes before a meal, titrated to the higher dose after an acclimation period, unless otherwise specified. Liraglutide or placebo injection was given subcutaneously once daily approximately 15 minutes before breakfast. When not specified, sulfonylurea drug was glyburide, glipizide, or glibenclamide.
[d] Few studies reported whether they tested for balanced baseline characteristics between comparison groups. No differences were noted in the most important characteristics (age, weight, HbA_{1c}, and duration of diabetes) except in the studies by Buse et al,[11] Defronzo et al,[12] Madsbad et al,[18] and Dejager et al,[32] in which small differences were noted between groups at baseline. Intention-to-treat (ITT) analyses were defined as those in which all randomized patients who received at least 1 dose of study treatment were included in the analysis; "all patients treated" (APT) analyses were defined as those in which all randomized patients who received at least 1 dose of study treatment and who had both a baseline and at least 1 postbaseline measurement were included; "completers" analyses were defined as those in which participants with complete data at the last follow-up visit were included.
[e] Study groups with lower doses or nonapproved doses were used in meta-analyses for adverse events only.
[f] Noninferiority trials.
[g] Data were available from abstracts only.
[h] Study had 2 additional groups (vildagliptin, 100 mg daily, combined with pioglitazone, 30 mg daily; and vildagliptin, 50 mg daily, combined with pioglitazone, 15 mg daily), which were not used in the meta-analyses.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.