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Acute Pancreatitis with Liraglutide

An analysis of MedWatch adverse event reports submitted to the Food and Drug Administration in the first two years following approval

Elizabeth Barbehenn, Ph.D.
Sammy Almashat, M.D., M.P.H.
Anju Nattanmai, B.A.
Sidney Wolfe, M.D.
Michael Carome, M.D.

Public Citizen's Health Research Group

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Executive Summary

Background: There have been conflicting reports concerning the pancreatic adverse effects of the incretin mimetic drug class of diabetes medications, with some studies suggesting a link between the drugs and acute pancreatitis. The present study applies objective criteria to the clinical information contained in Food and Drug Administration (FDA) MedWatch adverse event reports to determine the likelihood that the incretin mimetic drug liraglutide causes acute pancreatitis.

Methods: We requested the individual MedWatch case report forms from the FDA for all cases of "pancreatitis acute" associated with liraglutide in the FDA's Adverse Event Reporting System that were reported to the agency between February 1, 2010, and December 31, 2011, roughly the first two years after liraglutide's approval. Two researchers independently graded the cases for a causal link using the Naranjo adverse drug reaction probability criteria.

Results: There were 278 unique case reports of acute pancreatitis during liraglutide therapy. Pancreatitis occurred relatively soon after initiating therapy: 30% within one month and 72% within four months. Most cases (60%) required hospitalization. There were three deaths, two from complications of acute pancreatitis. Using the Naranjo criteria, we classified liraglutide as the "probable" causative agent in 51 cases, including 12 for which we deemed a causal link to be highly probable. There was one positive rechallenge, which was classified as a "definite" case of liraglutide-induced acute pancreatitis according to the Naranjo criteria.

Conclusions: Applying the Naranjo causality criteria to FDA MedWatch adverse event reports showed that liraglutide was a "probable" cause of 51 cases of acute pancreatitis as well as a "definite" cause of one case, the latter being the first documented report of a positive rechallenge. These results suggest a causal link between liraglutide and the occurrence of acute pancreatitis.

Background

Glucagon-like peptide-1 (GLP-1) agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors constitute a widely used class of medications known as incretin mimetics developed for the treatment of type 2 diabetes mellitus. GLP-1 agonists directly activate GLP-1 receptors, while DPP-4 inhibitors block the degradation of endogenous GLP-1.[1]

GLP-1 reduces serum glucose both by stimulating insulin secretion by pancreatic islet (endocrine) beta cells and by inhibiting secretion of glucagon by pancreatic islet alpha cells.[2] Through these actions, incretin mimetics have been shown to be effective in reducing blood glucose levels.[3] However, concerns have been raised that chronic stimulation of GLP-1 receptors could have adverse effects on the pancreas, potentially through stimulation of GLP-1 receptors on the exocrine cells.[4,5]

The Food and Drug Administration (FDA) issued safety communications in response to reports of acute pancreatitis associated with two incretin mimetics, exenatide (2007) and sitagliptin (2009),[6,7] and warnings about acute pancreatitis are now present in the labels of all incretin mimetics currently on the market.[8]

Three previous analyses, limited to data contained in the FDA's Adverse Event Reporting System (AERS) online database, reported markedly increased rates of acute and chronic pancreatitis associated with incretin mimetics compared with non-incretin diabetes drugs.[9,10,11] However, while these analyses, combined with the existence of a plausible mechanism, suggest

[1] Neumiller JJ. Differential chemistry (structure), mechanism of action, and pharmacology of GLP-1 receptor agonists and DPP-4 inhibitors. J Am Pharm Assoc 2009, 49(Suppl 1): S16-29.
[2] *Ibid.*
[3] Drab SR. Incretin-based therapies for type 2 diabetes mellitus: Current status and future prospects. Pharmacotherapy 2010, 30: 609-24.
[4] Butler PC, Elashoff M, Elashoff R, Gale EA. A critical analysis of the clinical use of incretin-based therapies: Are the GLP-1 therapies safe? Diabetes Care 2013, 36: 2118-25.
[5] Gale EA. GLP-1-based therapies and the exocrine pancreas: more light, or just more heat? Diabetes 2012, 61: 986-8.
[6] FDA. Safety alert: Byetta (exenatide). FDA/CDER, Silver Spring; October 2007. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124712.htm. Accessed April 24, 2014.
[7] FDA. Safety alert: Januvia (sitagliptin). FDA/CDER, Silver Spring; September 2009. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm183764.htm. Accessed April 23, 2014.
[8] FDA. FDA-approved drug products. FDA/CDER, Silver Spring. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed April 17, 2014.
[9] Butler PC, Elashoff M, Elashoff R, Gale EA. A critical analysis of the clinical use of incretin-based therapies: Are the GLP-1 therapies safe? Diabetes Care 2013, 36: 2118-25.
[10] Elashoff M, Matveyenko AV, Gier B, Elashoff R, Butler PC. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. Gastroenterol 2011, 141: 150-156.
[11] Institute for Safe Medication Practices. Perspectives on GLP-1 Agents for Diabetes. QuarterWatch. April 18, 2013 — Partial Data from 2012 Quarter 3. http://www.ismp.org/quarterwatch/pdfs/2012Q3.pdf. Accessed April 17, 2014.

an association between incretin mimetic drugs and pancreatitis, controversy remains as to whether the drugs actually cause an increase in pancreatitis above what would be expected in the general diabetic population.[12,13]

This is the first study to analyze and systematically apply causality criteria to the additional clinical information in MedWatch case reports to determine the likelihood that the incretin mimetic drug liraglutide causes acute pancreatitis.

Methods

Data source

The study utilized data from the FDA's AERS (now known as FAERS), a post-marketing surveillance database that contains spontaneous adverse event and medication error reports submitted to the FDA for drug and therapeutic biologic products.[14]

We searched the AERS database for all reports that listed either liraglutide or Victoza as the "primary suspect" drug in causing "pancreatitis acute" (the coded term for acute pancreatitis in the Medical Dictionary for Regulatory Activities, or MedDRA). We inserted an asterisk before and after each drug name to ensure that all reports using variations of the drug name were captured in the search. Our search included all reports received by the FDA between February 1, 2010, and December 31, 2011, the most recent data available at the time of data collection. The full MedWatch reports from all cases that matched these criteria were subsequently obtained from the FDA through a Freedom of Information request.

Data extraction

From the MedWatch reports, we extracted the following demographic data: age, weight, gender, and country of origin. We also collected the following data pertinent to the adverse drug reaction: dose of liraglutide at the time of the pancreatitis event, the duration on liraglutide before the onset of the event, whether the adverse event subsided after discontinuation of liraglutide (positive dechallenge), whether the adverse event reappeared after reintroduction of liraglutide (positive rechallenge), the presence of objective evidence to confirm the diagnosis of acute pancreatitis, and the outcome of the event (e.g., hospitalization or death).

[12] Butler PC, Elashoff M, Elashoff R, Gale EA. A critical analysis of the clinical use of incretin-based therapies: Are the GLP-1 therapies safe? Diabetes Care 2013, 36: 2118-25.
[13] Nauck MA. A critical analysis of the clinical use of incretin-based therapies: The benefits by far outweigh the potential risks. Diabetes Care 2013, 36: 2126-32.
[14] FDA Adverse Event Reporting System (FAERS; formerly AERS). FDA/CDER, Silver Spring. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm. Accessed April 25, 2014.

Naranjo scale as a measure of causal likelihood

To assess the likelihood that liraglutide caused the acute pancreatitis events described in the MedWatch reports, we used the Naranjo adverse drug reaction probability scale (Table 1). The 10-item Naranjo questionnaire, published in 1981, is a systematic method for determining the likelihood of a causal relationship between a medication and an adverse event in a given patient.[15]

The causal criteria in the Naranjo questionnaire include the presence of a plausible temporal relationship (adverse event occurring after drug administration), a positive dechallenge, a positive rechallenge, plausible alternative causes, and objective evidence to confirm the diagnosis of the adverse event. Points were assessed based on the presence or absence of each of these and other factors, and a final score (range -4 to 13) was generated that indicated the overall likelihood of a causal connection: a score of $\leq$0 is considered "doubtful," 1-4 "possible", 5-8 "probable," and $\geq$9 "definite" evidence of causality.[16]

Objective evidence of acute pancreatitis was defined by either an elevation of amylase or lipase to at least three times the upper limit of the normal range ($\geq$3X ULN) or imaging studies confirming the diagnosis. A patient was considered to have an alternative cause for acute pancreatitis if any of the following were reported: active gallstone disease, alcohol abuse, triglyceride levels >500 mg/dL,[17] concomitant treatment with a medication known to be associated with acute pancreatitis,[18] or a prior history of either chronic pancreatitis or idiopathic acute pancreatitis.

Information provided within each MedWatch report was independently analyzed and rated by two authors (EB and SA) based on the questions and scoring methodology in the Naranjo scale; both reviewers were blinded to each other's initial rating. Disagreements between the two researchers (in 18% of total cases) were resolved through consensus among four authors (EB, SA, MC, and SW).

[15] Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981, 30: 239-45.
[16] *Ibid.*
[17] Murphy MJ, Sheng X, MacDonald TM, Wei L. Hypertriglyceridemia and acute pancreatitis. JAMA Intern Med 2013, 173: 162-4.
[18] We considered two categories of drugs, which were taken concomitantly with liraglutide at the time of the reported event, as alternative drug causes for pancreatitis: 1) any incretin mimetic other than liraglutide, due to the extensively documented association between these drugs and pancreatitis, and 2) any drug with at least one published case of positive rechallenge of acute pancreatitis. A list of such drugs was obtained from the following two sources: a) Drugs classified as a "definite" cause of pancreatitis in Table 2 from: Nitsche C, Maertin S, Scheiber J, et al. Drug-induced pancreatitis. Curr Gastroenterol Rep 2012, 14: 131-8; and b) Class IA and IB drugs in Table 2 from: Badalov N, Baradarian R, Iswara K, et al. Drug-induced acute pancreatitis: an evidence-based review. Clin Gastroenterol Hepatol 2007, 5: 648-61; quiz 644.

Results

We initially received from the FDA a total of 390 MedWatch case report forms of acute pancreatitis associated with liraglutide therapy during the study period. Ninety-eight (98) cases were duplicates, and 13 others were excluded because it was not clear that liraglutide had been used or because no acute pancreatitis adverse event was reported. One additional case was excluded because the case report form was misplaced and a replacement could not be obtained from the FDA. As a result, 278 unique cases represented the final population for analysis.

Patient and case characteristics

Table 2 presents patient and case characteristics. The mean age of patients was 56 years (standard deviation [SD] 10.4), with a mean weight of 104 kilograms (SD 27.7). There were approximately equal numbers of males (49%) and females (51%). Seventy-seven percent of the patients in the reports came from the U.S., with 18% from Europe, 3% from Japan, and 2% from other countries.

Of the cases for which the dose of liraglutide at the time of the acute pancreatitis event was reported, equal numbers of patients (41%) were on 1.2 mg and 1.8 mg daily doses, with 14% on the lower daily dose of 0.6 mg and 4.6% on other doses.

Most patients presented with symptoms of acute pancreatitis soon after beginning liraglutide: 30% during the first month, 50% within the first two months, and 72% within the first four months (Table 2; Figure 1); median duration of therapy before onset of acute pancreatitis was 2.1 months. Approximately half (47%) of the cases reported a confirmation of the diagnosis through a serum amylase or lipase $\geq$3x ULN, imaging studies, or both (Table 2). In most cases (68%), the patient recovered from the acute pancreatitis attack following discontinuation of liraglutide (positive dechallenge). The majority (54%) of cases had no reported alternative cause (not shown in Table 2).

Of the 273 cases that reported outcomes, 164 patients (60%) required hospitalization, 106 (39%) had other (unspecified) serious outcomes, and three (1%) died. Two of the three deaths were due to complications stemming from acute pancreatitis. One of these two patients died of multi-system organ failure and the other from acute respiratory distress syndrome, both deemed by the patients' physicians to be complications of severe acute pancreatitis. Neither patient had a prior history of pancreatitis, gallstone disease, or alcohol abuse; in one of the two cases, the physician stated that there was no other plausible etiology.

Naranjo analyses

Of the 278 unique cases of acute pancreatitis, we classified one as "definitely" caused (Naranjo score of 9), 51 as "probably" caused (score of 5-8), and 226 as "possibly" caused (score of 1-4) by liraglutide (Table 3).

Of the 51 "probable" cases (Naranjo score of 5-8), 12 had a Naranjo score of 7, in which a causal link with liraglutide appeared particularly convincing (Table 4). In these 12 cases, there was no reported history of pancreatitis or evidence of alternative causes, and symptoms resolved following discontinuation of the drug (positive dechallenge). In 11 of the 12 cases, acute pancreatitis occurred within three months of starting liraglutide, and 10 of the 12 cases were confirmed with objective evidence. One of the patients reportedly had a similar reaction to exenatide previously, though the exact nature of that reaction was not further specified.

Positive rechallenge case

There were three cases in which acute pancreatitis recurred following reexposure to liraglutide. However, only one case had no confounding factors, leading us to consider it a positive rechallenge with a "definite" causal relationship to liraglutide (Naranjo score of 9). This case is described here (and in Table 5) in further detail.

A 68-year-old man with a 10-year history of type 2 diabetes mellitus, chronic kidney disease, hypertension, spinal stenosis, and restless leg syndrome began liraglutide and self-titrated up to a daily dose of 1.8 mg. The patient had no prior history of pancreatitis, alcohol abuse, gallstones, or recent infections, and his serum triglyceride levels were stated to always be below 300 mg/dL. The patient had been on exenatide but had been switched to liraglutide due to a lack of efficacy.

Forty-four days after starting liraglutide, he presented with complaints of epigastric pain. Laboratory tests showed an amylase of 179 IU/L (3X ULN = 390) and lipase of 904 IU/L (3X ULN = 285). He was not hospitalized but told to discontinue liraglutide and begin a clear liquid diet. Eight days later, repeat lab values showed that both amylase and lipase had decreased (60 and 184 IU/L, respectively), and he was considered recovered from acute pancreatitis. That same day, the patient was restarted on liraglutide.

Epigastric pain recurred three weeks later, at which time lab work again showed a slightly elevated amylase and markedly increased lipase (100 and 648 IU/L, respectively). He discontinued the drug and, one week later, symptoms had resolved and serum amylase and lipase were again decreasing (89 and 369 IU/L, respectively).

Discussion

This is the first study to assess the likelihood of causality of acute pancreatitis with an incretin mimetic drug using the clinical information present in the original MedWatch case report forms submitted to the FDA. In the first two years following its approval, liraglutide was listed as the primary suspect drug in 278 unique cases of acute pancreatitis reported to the FDA. The majority of cases occurred within the first three months after the initiation of liraglutide and resolved promptly after discontinuation of the drug. Using the Naranjo scale, we identified 51 "probable" cases with enough information reported to suggest a causal link to liraglutide use, including a subgroup of 12 cases in which we deemed a link to be highly probable.

There was, in addition, one "definite" case that, to our knowledge, is the first documented case of recurrent acute pancreatitis following rechallenge with liraglutide. This patient had no prior history of, or risk factors for, pancreatitis, and alternative causes for pancreatitis were excluded at the time of presentation. The recurrence of a rare adverse event, such as acute pancreatitis, after reintroduction of a drug, without other confounding factors in the interim, is considered one of the strongest indicators of causality.[19]

That incretin mimetics have been associated with acute pancreatitis is widely accepted and is included in the drugs' labels.[20] However, there is an ongoing debate as to whether acute pancreatitis cases are due to an inherent property of the drugs or merely to the underlying increased risk from diabetes itself.[21,22] Liraglutide's manufacturer recently claimed that "no cause and effect association has been established…" between liraglutide and pancreatitis.[23]

Acute pancreatitis was identified in randomized clinical trials of liraglutide, before FDA approval, as a potential adverse effect. Summed across all trials, the adjusted rate of acute and chronic pancreatitis was 2.2 cases per 1,000 patient years in liraglutide-treated subjects versus 0.6 cases per 1,000 patient years in diabetic control subjects, a 3.7-fold increase.[24] Following approval, there have been, to our knowledge, five published individual case reports of

[19] FDA. Reviewer guidance: Conducting a clinical safety review of a new product application and preparing a report on the review. FDA/CDER, Silver Spring; February 2005. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072974.pdf. Accessed April 17, 2014.
[20] FDA. FDA-approved drug products. FDA/CDER, Silver Spring. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed April 7, 2014.
[21] Butler PC, Elashoff M, Elashoff R, Gale EA. A critical analysis of the clinical use of incretin-based therapies: Are the GLP-1 therapies safe? Diabetes Care 2013, 36: 2118-25.
[22] Nauck MA. A critical analysis of the clinical use of incretin-based therapies: The benefits by far outweigh the potential risks. Diabetes Care 2013, 36: 2126-32.
[23] Moses A. Novo Nordisk replies to BMJ investigation on incretins and pancreatic damage. BMJ 2013, 347: f4386.
[24] FDA. Liraglutide clinical safety review. FDA/CDER, Silver Spring; July 2009. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000medr_P2.pdf. Accessed April 8, 2014.

liraglutide-associated acute pancreatitis.[25,26,27,28,29] In four of the five cases, the patients had no prior history of pancreatitis, and in all cases, there was prompt resolution of symptoms following discontinuation of liraglutide.

Two recent randomized controlled trials of two other incretin mimetics, saxagliptin and alogliptin, reported numerically (though not statistically significantly) higher rates of acute pancreatitis in incretin mimetic-treated subjects. This included a near-doubling of "definite" cases of acute pancreatitis in those given saxagliptin.[30,31] A recently completed randomized controlled trial of weight loss in more than 3,700 non-diabetic obese and overweight subjects found that a daily dose of 3.0 mg of liraglutide tripled the risk of acute pancreatitis over 56 weeks of use (0.3 vs. 0.1 events per 100 patient-years of exposure in liraglutide- and placebo-treated subjects, respectively).[32] Notably, this trial excluded subjects with diabetes or a prior history of acute or chronic pancreatitis.

Several observational, administrative claims-based studies examining the relationship between acute pancreatitis and use of incretin mimetic drugs have reported mixed results.[33,34,35,36,37] However, the studies used different sample sizes, selection criteria, and analytic approaches, which impede the ability to draw definitive conclusions regarding the association between acute pancreatitis and incretin mimetic drugs.

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[25] Lee PH, Stockton MD, Franks AS. Acute pancreatitis associated with liraglutide. Ann Pharmacother 2011, 45: e22.
[26] Knezevich E, Crnic T, Kershaw S, Drincic A. Liraglutide-associated acute pancreatitis. Am J Health Syst Pharm 2012, 69: 386-389.
[27] Famularo G, Gasbarrone L, Minisola G. Pancreatitis during treatment with liraglutide. JOP 2012, 13: 540-1.
[28] Bourezane H, Kastler B, Kantelip JP. Late and severe acute necrotizing pancreatitis in a patient with liraglutide. Therapie 2012, 67: 539-43.
[29] Nakata H, Sugitani S, Yamaji S, et al. Pancreatitis with pancreatic tail swelling associated with incretin-based therapies detected radiologically in two cases of diabetic patients with end-stage renal disease. Intern Med 2012, 51: 3045-9.
[30] White WB, Cannon CP, Heller SR, et al; EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med 2013, 369: 1327-35.
[31] Scirica BM, Bhatt DL, Braunwald E, et al; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013, 369: 1317-26.
[32] Pi-Sunyer X, Astrup A, Fujioka K, et al. Efficacy and safety of liraglutide 3.0 mg for weight management in overweight and obese adults: the SCALE obesity and prediabetes, a randomized, double-blind and placebo-controlled trial. Abstract #700. American Association of Clinical Endocrinologists 23rd Annual Scientific and Clinical Congress. http://am.aace.com/sites/all/files/Abstract-Book.pdf. Accessed May 20, 2014.
[33] Singh S, Chang HY, Richards TM, et al. Glucagonlike peptide 1-based therapies and risk of hospitalization for acute pancreatitis in type 2 diabetes mellitus: A population-based matched case-control study. JAMA Intern Med 2013, 173: 534-9.
[34] Garg R, Chen W, Pendergrass M. Acute pancreatitis in type 2 diabetes treated with exenatide or sitagliptin: A retrospective observational pharmacy claims analysis. Diabetes Care 2010, 33: 2349-54.
[35] Dore DD, Hussein M, Hoffman C, et al. A pooled analysis of exenatide use and risk of acute pancreatitis. Curr Med Res Opin 2013, 29: 1577-86.
[36] Wenten M, Gaebler JA, Hussein M, et al. Relative risk of acute pancreatitis in initiators of exenatide twice daily compared with other anti-diabetic medication: a follow-up study. Diabet Med 2012, 29: 1412-8.
[37] Romley JA, Goldman DP, Solomon M, McFadden D, Peters AL. Exenatide therapy and the risk of pancreatitis and pancreatic cancer in a privately insured population. Diabetes Technol Ther 2012, 14: 904-11.

If cases of acute pancreatitis with incretin mimetic drugs such as liraglutide were caused merely by the patients' underlying diabetes, one would expect a similar rate of reported cases for all diabetes drugs, incretin mimetics and non-incretin mimetics alike. However, three separate analyses of the FDA's AERS database have demonstrated that reports of acute and chronic pancreatitis were far more likely to be reported in association with incretin mimetic drugs (reporting odds ratios [RORs] of 27-56 with liraglutide) when compared with a control group of non-incretin diabetes drugs and insulin.[38,39,40] A more recent study based on reports to the French Pharmacovigilance Database found a ROR of acute and chronic pancreatitis with incretin mimetics of 14.86 (95 % CI: 9.24–23.92) after adjusting for multiple potential confounders, with no significantly increased signal for pancreatitis seen with any non-incretin diabetes drugs.[41]

We conducted a similar analysis using the same methodology as for our liraglutide search. We retrieved a total of 1,019 cases of "pancreatitis acute" with the five incretin mimetics reported to the FDA from 2005 to 2011, as opposed to only 202 cases for 10, collectively much more widely prescribed[42] non-incretin mimetic oral diabetes drugs reported between 1997 and 2011 (Figure 2).

The precise mechanism by which incretin mimetics may cause pancreatitis is unknown. However, a plausible hypothesis has been suggested based on the proliferative action of GLP-1 on pancreatic ductal epithelium in humans and animal models. Proliferation of ductal epithelium could lead to duct occlusion and an increase in back pressure within the pancreatic acini.[43,44] Such obstruction could cause low-grade, chronic inflammation, which, in the case of predisposed patients, may potentially develop into acute pancreatitis.[45]

A recent study in deceased human organ donors compared pancreata of diabetic patients treated for a year or more with sitagliptin or exenatide to those of diabetic patients not treated with incretin mimetics as well as non-diabetics. The pancreata of those taking incretin mimetics were 40% larger than those of diabetic patients not on incretin mimetic therapy, as a result of

[38] Butler PC, Elashoff M, Elashoff R, Gale EA. A critical analysis of the clinical use of incretin-based therapies: Are the GLP-1 therapies safe? Diabetes Care 2013, 36: 2118-25.
[39] Elashoff M, Matveyenko AV, Gier B, Elashoff R, Butler PC. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. Gastroenterol 2011, 141: 150-156.
[40] Institute for Safe Medication Practices. Perspectives on GLP-1 Agents for Diabetes. QuarterWatch. April 18, 2013 — Partial Data from 2012 Quarter 3. http://www.ismp.org/quarterwatch/pdfs/2012Q3.pdf. Accessed April 8, 2014.
[41] Faillie JL, Babai S, Crépin S, et al. The French Pharmacovigilance Centers Network: The French Pharmacovigilance Centers Network. Pancreatitis associated with the use of GLP-1 analogs and DPP-4 inhibitors: A case/non-case study from the French Pharmacovigilance Database. Acta Diabetol 2013 Dec 19. [Epub ahead of print]
[42] In 2011, there were more than five times as many prescriptions for the non-incretin mimetic metformin than all five incretin mimetics on the market at the time. Source: IMS Health.
[43] Butler PC, Elashoff M, Elashoff R, Gale EA. A critical analysis of the clinical use of incretin-based therapies: Are the GLP-1 therapies safe? Diabetes Care 2013, 36: 2118-25.
[44] Gale EA. GLP-1-based therapies and the exocrine pancreas: more light, or just more heat? Diabetes 2012, 61: 986-8.
[45] Gale EA. GLP-1-based therapies and the exocrine pancreas: more light, or just more heat? Diabetes 2012, 61: 986-8.

increased exocrine cell proliferation.[46] Pancreatic exocrine cell proliferation and/or inflammation in response to incretin mimetic therapy have also been seen in mouse,[47] rat,[48] and monkey[49] pancreata.

There are several limitations to note in this study. The FDA's AERS database depends on voluntary reporting of adverse events. As a result, it is estimated that as few as 2-20% of medication-related adverse events are reported to the agency.[50] This suggests that our study underestimates the number of cases of acute pancreatitis associated with liraglutide therapy.

In addition, the data provided in MedWatch reports are often insufficient to determine whether the adverse event was drug-induced or due to some alternative cause. We made an effort to be conservative in our assessment of potential confounders. We considered as plausible alternative causes significant alcohol use, gallstones (including likely incidental findings on imaging), concomitant medications previously associated with pancreatitis (including those that the patient had been taking longer than liraglutide with no untoward effects), and a prior history of chronic pancreatitis or idiopathic acute pancreatitis.

Nevertheless, diabetes and obesity (mean weight of 104 kg in our sample), both identified as possible risk factors for pancreatitis,[51,52] are examples of potential confounders not accounted for in our analysis. Another possible confounder is the Weber effect, whereby more adverse events are reported with recently-approved drugs, such as liraglutide, than with older diabetes medications.[53] However, neither of these factors is likely to account for the large number of reports with liraglutide, as no signal for acute pancreatitis has appeared with any non-incretin mimetic diabetes drug, at any time following approval (Figure 2).

It is also possible that physicians have been more likely to report cases of pancreatitis with liraglutide and other incretin mimetics than cases with drugs not previously implicated in pancreatitis, a so-called notoriety bias. However, reports to the FDA of acute pancreatitis with

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[46] Butler AE, Campbell-Thompson M, Gurlo T, et al. Marked expansion of exocrine and endocrine pancreas with incretin therapy in humans with increased exocrine pancreas dysplasia and the potential for glucagon-producing neuroendocrine tumors. Diabetes 2013, 62: 2595-604.
[47] Gier B, Matveyenko AV, Kirakossian D, et al. Chronic GLP-1 receptor activation by exendin-4 induces expansion of pancreatic duct glands in rats and accelerates formation of dysplastic lesions and chronic pancreatitis in the Kras(G12D) mouse model. Diabetes 2012, 61: 1250-62.
[48] Nachnani JS, Bulchandani DG, Nookala A, et al. Biochemical and histological effects of exendin-4 (exenatide) on the rat pancreas. Diabetologia 2010, 53: 153-9.
[49] FDA. Liraglutide Pharmacology Review. FDA/CDER, Silver Spring; July 2009. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000pharmr_P1.pdf; and http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000pharmr_P2.pdf. Accessed April 9, 2014.
[50] Hazell L, Shakir SA. Under-reporting of adverse drug reactions: a systematic review. Drug Saf 2006, 29: 385-96.
[51] Solanki NS, Barreto SG, Saccone GT. Acute pancreatitis due to diabetes: the role of hyperglycaemia and insulin resistance. Pancreatology 2012, 12: 234-9.
[52] Hong S, Qiwen B, Ying J, Wei A, Chaoyang T. Body mass index and the risk and prognosis of acute pancreatitis: A meta-analysis. Eur J Gastroenterol Hepatol 2011, 23: 1136-43.
[53] FDA. The clinical impact of adverse event reporting. FDA/CDER, Silver Spring; October 1996. http://www.fda.gov/downloads/Safety/MedWatch/UCM168505.pdf. Accessed April 8, 2014.

the first approved incretin mimetic, exenatide, occurred before concerns of pancreatitis with incretin mimetic drugs became known, and despite the fact that no pre-approval safety signal for acute pancreatitis had been identified (and therefore no label warnings required).[54,55]

Conclusion

A relatively large number of cases of acute pancreatitis with liraglutide therapy were reported to the FDA's AERS during the first two years following its approval. Applying the Naranjo causality criteria to these reports showed that liraglutide was a "probable" cause of 51 cases of acute pancreatitis as well as a "definite" cause of one case, the latter being the first documented report of a positive rechallenge. These findings suggest a causal link between liraglutide and the occurrence of acute pancreatitis. Considered together with results from studies of other incretin mimetics, it appears that this class of drugs increases the risk of acute pancreatitis in patients with diabetes, a population already at an increased risk for the condition.

[54] FDA. Safety alert: Byetta (exenatide). FDA/CDER, Silver Spring; October 2007. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124712.htm. Accessed April 10, 2014.
[55] FDA. Exenatide medical review. FDA/CDER, Silver Spring; March 2005. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/021773_Byetta_medr.PDF. Accessed April 9, 2014.

Table 1. Naranjo adverse drug reaction probability scale.[a]

	Yes	No	Do not know
1. Are there previous *conclusive* reports on this reaction?	+1	0	0
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0
3. Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	+1	0	0
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0
6. Did the reaction reappear when a placebo was given?	-1	+1	0
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
9. Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure?	+1	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0

[a] Total scores can range from -4 to +13, which are then used, as follows, to assign a probability category for causality with the drug: ≤0 ("doubtful"), 1-4 ("possible"), 5-8 ("probable"), ≥9 ("definite"). *Source:* Naranjo CA, Busto U, Sellers EM, *et al*. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; 30(2): 239-45.

Table 2. Liraglutide and acute pancreatitis: patient and case characteristics.[a]

	Mean (SD)	
Age (n=220)	56 (10.4)	
Weight (kg; n=150)	104 (27.7)	
	Number of cases	**Percentage of cases**
Gender (n=260)		
Male	127	49%
Female	133	51%
Country/Region (n=277)		
U.S.	213	77%
Europe	51	18%
Japan	7	2.5%
Other	6	2.2%
Outcome (n=273)		
Hospitalization	164	60%
"Other-Serious"	106	39%
Death	3	1.1%
Dosage (n=194)		
0.6mg/day	27	14%
1.2mg/day	79	41%
1.8mg/day	79	41%
Other	9	4.6%
Time to onset of pancreatitis[b] (n=220; median 62 days)		
<1 month	65	30%
1-2 months	43	20%
2-3 months	27	12%
3-4 months	22	10%
>4 months	63	29%
Positive dechallenge[c] (n = 278)	190	68%
Objective evidence[d] (n = 278)	132	47%

[a] Percentages represent a proportion of reported values (n) for each characteristic, indicated in parentheses. In some cases, percentages do not add up to 100% due to rounding.

[b] Times represent total time on drug before discontinuation. In virtually all cases, patients were discontinued from the medication immediately following the reaction; therefore, these times represent very close approximations of the time between first ingestion of the drug and onset of pancreatitis.

[c] Pancreatitis symptoms and/or signs improved upon drug discontinuation.

[d] See criteria for objective evidence in Methods.

Table 3. Liraglutide and acute pancreatitis: Naranjo scores and likelihood of causality (n = 278).[a]

Naranjo Category	Naranjo Score	Number of cases	Percentage of cases
Possible	**2**	15	5.4%
	3	91	33%
	4	120	43%
Probable	**5**	29	10%
	6	10	3.6%
	7	12	4.3%
	8	0	0%
Definite	**9**	1	0.4%

[a] There were no cases that scored below 2 or above 9.

Table 4. Cases with "probable" causality and a Naranjo score of 7 (n=12).

Age/ Sex	Relevant medical history	Dose at time of event (mg/d)	Duration on drug before event[a] (days)	Reported symptoms	Amylase (IU/L) [b]	Lipase (IU/L)[b]	Confirmed by imaging[b]	Disposition	Positive dechallenge
69 F	No h/o alcohol abuse or gallstones	0.6	4	Severe abdominal pain	508	5,401	Yes	Hospitalized	Yes
42 M[c]	No h/o alcohol abuse or pancreatitis	0.6	20	Not reported	103	391	No	Hospitalized	Yes
39 F	No h/o alcohol abuse, gallstones, or pancreatitis	1.2	29	Substernal pain radiating to back	"elevated"	"elevated"	Yes	Other (Serious)	Yes
73 F	No h/o alcohol abuse, gallstones, or pancreatitis	1.8	32	Abdominal pain radiating to back	217	799	No	Hospitalized	Yes
54 F[c]	No h/o alcohol abuse, gallstones, peptic ulcer disease, or recent infections; previously was hospitalized after similar reaction to exenatide	1.2	35	Abdominal pain, dyspepsia	36	n/a	No	Other (Serious)	Yes
68 M	No h/o alcohol abuse, gallstones, or pancreatitis	1.8	42	Abdominal pain, nausea, vomiting	122	281	No	Hospitalized	Yes
63 F	"Physician stated the patient did not have any known risk factors for the development of pancreatitis"	1.8	46	Not reported	204	1,563	No	Hospitalized	Yes
51 M	No h/o pancreatitis	1.8	46	"Sick feeling"	447	866	No	Other (Serious)	Yes
58 F	No h/o alcohol abuse, gallstones, or pancreatitis	1.8	67	Constant abdominal pain radiating to back	n/a	1,853	No	Hospitalized	Yes
43 M[c]	No h/o pancreatitis; "No biliary tract obstruction"	0.6	74	Abdominal pain	112	n/a	Yes	Hospitalized	Yes
55 F	No h/o alcohol abuse, gallstones, or pancreatitis	1.2	81	Not reported	959	15,254	Yes	Hospitalized	Yes
75 M	Triglycerides "controlled"; "No other risk factors for pancreatitis"	1.8	134	No abdominal pain	230	2,300	No	Other (Serious)	Yes

Abbreviations: h/o, history of; M, male; F, female.

[a] Ordered by duration on drug before discontinuation. In all cases, patients were discontinued from the medication immediately following the reaction; therefore, these times represent very close approximations of the time between first ingestion of the drug and onset of pancreatitis.

[b] See criteria for objective evidence in Methods. Objective evidence was defined as an elevation of either amylase or lipase ≥3x the upper limit of the normal range (ULN) of the reporting laboratory or, if no reference range was provided, of the American College of Physicians' Medical Knowledge Self-Assessment Program, 16th edition (ULN of 130 IU/L for amylase and 95 IU/L for lipase) (Source: American College of Physicians. Medical Knowledge Self-Assessment Program. 16th ed. 2012), or as a finding consistent with acute pancreatitis on imaging.

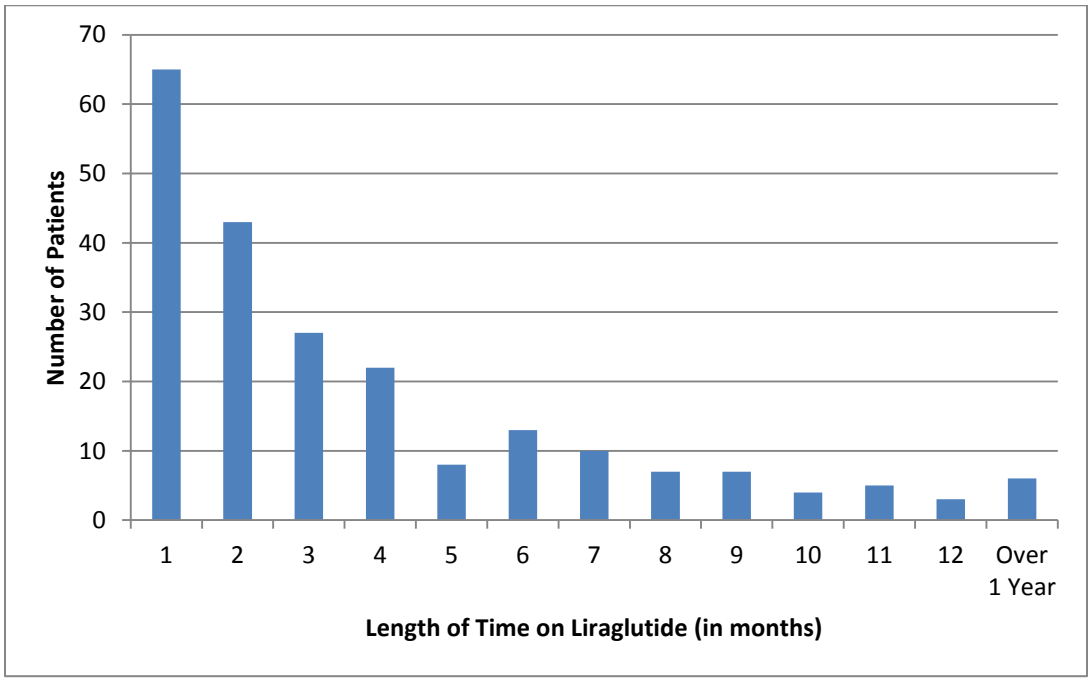
[c] Foreign reports (Lebanon [42yo male], UK [54yo female], and Japan [43yo male]).

Table 5. Acute pancreatitis rechallenge with liraglutide ("definite" causality: Naranjo score of 9).[a]

Age/ Sex	Relevant medical history	Pancreatitis episode/ interim recovery	Dose at time of event (mg/d)	Duration on drug before event/ duration until recovery (days)	Presenting symptoms	Amylase (IU/L)	Lipase (IU/L)	Positive dechallenge	Disposition
68 M	No h/o alcohol abuse, gallstones, or pancreatitis	**1st (first started liraglutide)**	**1.8**	**44**	**Epigastric pain**	**179**	**904**	n/a	**Other (Serious)**
		Interim (off liraglutide)	n/a	8	None	60	184	Yes	Recovered
		2nd (restarted liraglutide)	**0.6**	**20**	**Epigastric pain**	**100**	**648**	n/a	**Other (Serious)**
		Final (off liraglutide)	n/a	6	None	89	369	Yes	Recovered

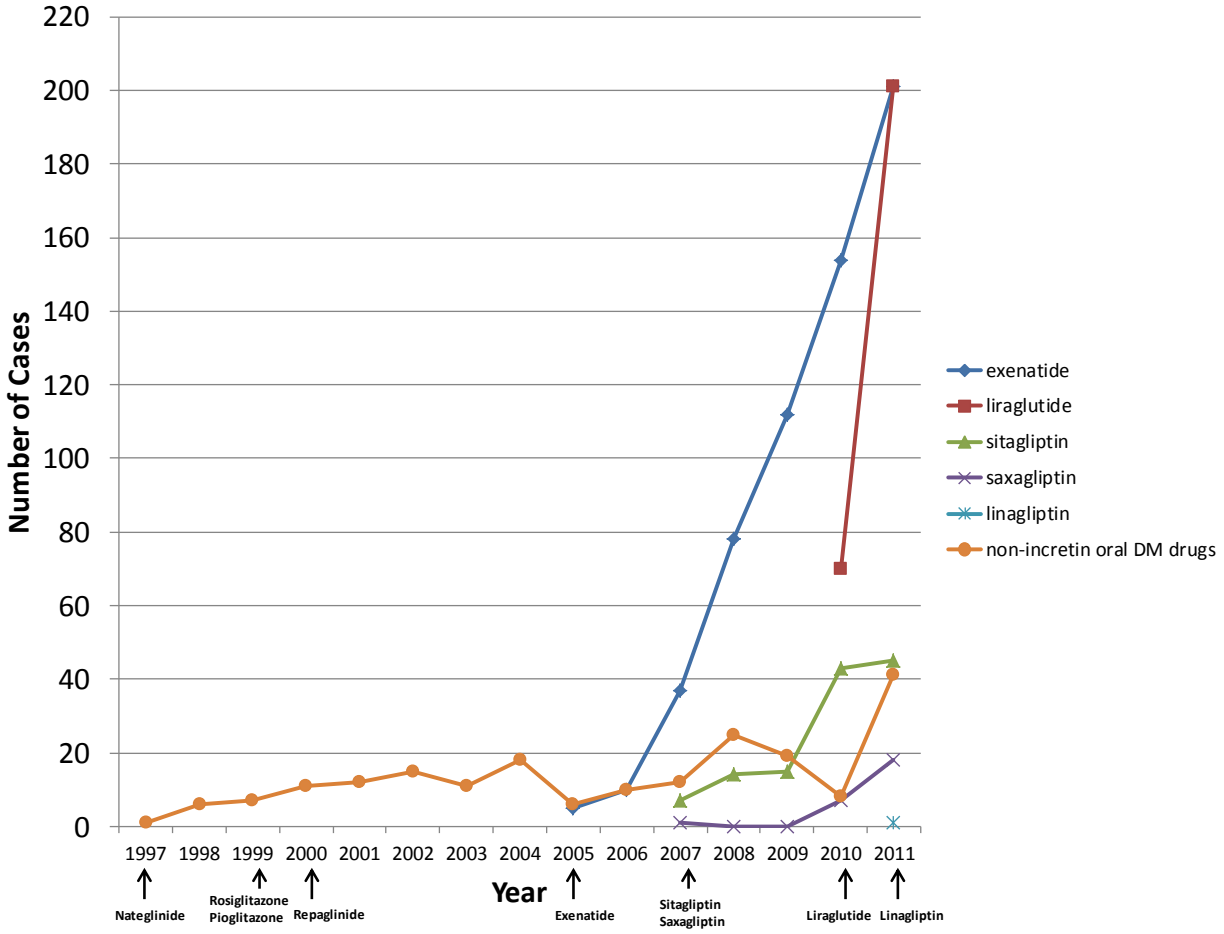
[a] Reappearance of acute pancreatitis upon reinitiating liraglutide. The presiding practitioner diagnosed acute pancreatitis based on abdominal pain plus the objective evidence of an increase in lipase to ≥3x the upper limit of the normal range (ULN). Resolution of symptoms and a decrease in lipase following liraglutide withdrawal constituted a positive dechallenge; reappearance of abdominal pain and elevated lipase to ≥3x ULN constituted a positive rechallenge (ULN of 95 IU/L for lipase and 130 IU/L for amylase; *Source*: American College of Physicians. Medical Knowledge Self-Assessment Program. 16th ed. 2012).

Figure 1. Duration on liraglutide before the onset of acute pancreatitis.[a]



[a] Times represent total time on drug before discontinuation. In virtually all cases, patients were discontinued from the medication immediately following the reaction; therefore, these times represent very close approximations of the time between first use of the drug and the onset of pancreatitis (median 2.1 months).

Figure 2. Acute pancreatitis cases reported to the FDA: incretin mimetics versus non-incretin oral antihyperglycemics.[a]



[a] Arrows indicate year of approval. Analysis comparing the frequency of adverse event reports of acute pancreatitis with incretin mimetic drugs and non-incretin diabetes drugs. Using the same methodology as for our liraglutide search, we searched for unique cases of "pancreatitis acute" reported to the FDA between November 1997 (the earliest date for which these AERS data were available) and December 31, 2011, for all oral diabetes medications deemed "primary suspect" drugs. Incretin mimetic drugs approved through 2011 included liraglutide, exenatide, sitagliptin, saxagliptin, and linagliptin. Non-incretin mimetic oral diabetes drugs included metformin, glyburide, glimepiride, glipizide, rosiglitazone, pioglitazone, nateglinide, repaglinide, acarbose, and miglitol. Arrows indicate the year of FDA approval for drugs approved during or after 1997.

Non-incretin mimetic diabetes drugs are collectively much more widely prescribed than incretin mimetics. Metformin constituted 58% of all cases of acute pancreatitis cases reported with non-incretin mimetic oral diabetes drugs. In 2011, there were 59 million prescriptions filled in the U.S. for metformin. (*Source:* IMS Health. Top 25 Medicines by Dispensed Prescriptions (U.S.). Updated March 22, 2013. http://www.imshealth.com/deployedfiles/imshealth/Global/Content/Corporate/Press%20Room/2012_U.S/Top_25_Medicines_Dispensed_Prescriptions_U.S..pdf. Accessed September 4, 2013.)

In the same year, there were approximately 1.4 million prescriptions for exenatide, 1.4 million for liraglutide, 7.1 million for sitagliptin, 1.4 million for saxagliptin, and 100,000 for linagliptin. (*Source:* IMS Health.)