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ORIGINAL ARTICLE

Exenatide Therapy and the Risk of Pancreatitis and Pancreatic Cancer in a Privately Insured Population

John A. Romley, Ph.D.,[1,2] Dana P. Goldman, Ph.D.,[1,2,3] Matthew Solomon, M.D., Ph.D.,[4] Daniel McFadden, Ph.D.,[1,5] and Anne L. Peters, M.D.[6]

Abstract

Background: Postmarketing reports have linked exenatide use with acute pancreatitis and pancreatic cancer, but a definitive relationship has yet to be established.
Subjects and Methods: We conducted a retrospective cohort analysis of patients with type 2 diabetes with employer-provided health insurance from 2007 to 2009. Multivariate models estimated the association between exenatide use and acute pancreatitis and pancreatic cancer. We required at least 1 year of exenatide exposure in the pancreatic cancer analysis. Sensitivity analyses were conducted that quasirandomized exenatide use based on patient out-of-pocket costs.
Results: Among 268,561 patients included in the acute pancreatitis analysis, only 2.6% used exenatide. Hospitalization for acute pancreatitis was rare (0.247% of patients). In unadjusted and adjusted analyses, patients who did not use exenatide were more likely to be hospitalized for acute pancreatitis (0.249% vs. 0.196% in unadjusted analysis), but the difference was not statistically significant in either analysis ($P = 0.22$ and $P = 0.70$, respectively). Among 209,306 patients in the pancreatic cancer analysis, 0.070% were diagnosed with pancreatic cancer, and 0.88% had at least 1 year of continuous exenatide exposure prior to the diagnosis. Those with exenatide exposure had higher rates of pancreatic cancer compared with those without (0.081% vs. 0.070% in unadjusted analysis). In both unadjusted and adjusted analyses, the difference was not statistically significant ($P = 0.80$ and $P = 0.46$, respectively). In sensitivity analyses, results were similar.
Conclusions: We found no association between exenatide use and either hospitalization for acute pancreatitis or pancreatic cancer in a large sample of privately insured U.S. patients.

Introduction

Exenatide was introduced into the U.S. market in 2005 to improve glycemic control in patients with type 2 diabetes mellitus who have not achieved adequate glycemic control on metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea.[1] However, postmarketing reports of acute pancreatitis, including severe forms such as hemorrhagic or necrotizing pancreatitis, developing in patients taking exenatide were submitted to the Food and Drug Administration (FDA)[1,2] and have been published in the literature.[3,4] Although these reports do not prove a causal link between exenatide and pancreatitis, the FDA added a warning on the exenatide label in 2007 that was strengthened over the next 2 years to note that the postmarketing reports included episodes of both fatal and nonfatal pancreatitis.[1,2]

The true incidence of exenatide-associated pancreatitis has been difficult to determine, and it is unknown whether exenatide causes pancreatitis. Pancreatitis occurs more frequently in individuals with diabetes,[5] and people with type 2 diabetes often have multiple risk factors for pancreatitis.[6] Analyses of large claims and pharmacy databases have shown no apparent increased risk for pancreatitis in patients taking exenatide,[7–9] while a concern over the possibility of an increased risk of pancreatic cancer from exenatide use has been raised in the FDA adverse event reporting system (AERS) database.[10] However, this analysis has been criticized regarding the limitations of using the AERS database for determining event rates.[11]

In order to better characterize the relationship between exenatide, acute pancreatitis and pancreatic cancer, we analyzed a large commercial claims database of adult U.S residents with private insurance from 2007 through 2009.

[1]Leonard D. Schaeffer Center for Health Policy and Economics; and Price School of Public Policy, University of Southern California, Los Angeles, California.
[2]RAND Corporation, Santa Monica, California.
[3]School of Pharmacy, University of Southern California, Los Angeles, California.
[4]Department of Medicine, Stanford University, Stanford, California.
[5]Department of Economics, University of Southern California, Los Angeles, California.
[6]Division of Endocrinology, Keck School of Medicine of University of Southern California, Los Angeles, California.

Research Design and Methods

The RAND Human Subjects Protection Committee ruled that this research was exempt from institutional review board approval.

Data

A retrospective analysis of a large, administrative claims database of privately insured individuals was performed. The database contained enrollment information as well as pharmacy and medical claims for U.S. health insurance plans provided by 31 Fortune 500 employers over the period 1997–2009. The database included approximately 6.6 million unique covered employees and dependents over this time period. This database has been used in numerous studies of health care utilization and health outcomes, and details of the contents of the claims files have been described elsewhere.[12–15]

Study sample

To identify beneficiaries with type 2 diabetes, we required study participants to have two or more medical claims with an International Classification of Diseases, Ninth Revision (ICD-9) code of 250.xx within a calendar year and fewer than two claims with an ICD-9 code of 250.x1 within each year. To increase the specificity of our assignment, we also required the use of oral antidiabetes medications at any point during the study period. Eligible beneficiaries were enrolled in at least 1 year during the period 2007–2009 and were continuously enrolled throughout each year, with no gaps between years. Users of sitagliptin were excluded, as were patients less than 18 years of age.

Statistical analysis

The unit of analysis was a person-year. Hospitalization for acute pancreatitis was identified by an inpatient claim with an ICD-9 code of 577.0.[8,9] Pancreatic cancer was identified by a claim with an ICD-9 code of 157.xx.[16] Beneficiaries with pancreatic cancer were excluded subsequent to the incident cancer diagnosis. For either outcome, patients were excluded from the analysis if the first event occurred prior to 2007 or prior to the first use of exenatide. Annualized rates of hospitalization for acute pancreatitis and for diagnosis of pancreatic cancer were calculated.

Exenatide use was identified by National Drug Code within pharmacy claims. For the analysis of acute pancreatitis, use of exenatide was classified by at least one fill of an exenatide prescription within a year. For the analysis of pancreatic cancer, sustained use of exenatide was classified by at least 365 days supplied of exenatide from entry into the sample through the end of the calendar year prior to the year analyzed. For example, a patient in 2009 would be considered to have used exenatide if he or she had accrued at least 365 days of exenatide use from their first observation in the sample through the end of 2008.

In sensitivity analyses, sustained use was defined alternatively by 6 months and 18 months of exenatide supply as of the prior year. In additional analyses of both pancreatic cancer and acute pancreatitis, exenatide users were excluded if their cumulative days supplied did not exceed 90 days. Further sensitivity analyses for pancreatitis used a person-half year as the unit of analysis and required a claims history of diabetes for at least 1 year prior to inclusion in the analysis.

Logistic regressions were estimated for each outcome. Multivariate models were constructed that controlled for age, gender, years since diabetes diagnosis, year of analysis, and a set of 19 co-morbid conditions (for example, congestive heart failure, chronic obstructive pulmonary disease, and stroke). These conditions were identified by two or more medical claims with the relevant ICD-9 code in the current or a prior year (see Appendix for specific codes). In addition, the model for pancreatitis included traditional risk factors, such as a history of gallstones or alcohol abuse,[17] identified by a claim in the current or preceding year with ICD-9 codes of 574.xx, 303.xx, or 305.1x. The method of predictive margins was used to predict rates of pancreatitis and pancreatic cancer with and without exenatide use.[18]

In sensitivity analyses, unmeasured confounders—such as body weight or smoking, which are not reliably measured in medical claims—were dealt with by "quasirandomizing" patients into exenatide use based on patient costs. A patient's out-of-pocket costs under the insurance benefit can affect his or her utilization behavior but may be otherwise unrelated to outcomes and also uncorrelated with confounding factors.[13] Then, differences across patients in out-of-pocket costs for exenatide lead to effectively random variation in utilization and allow for valid estimates of the causal effect of utilization on outcomes. This approach was demonstrated in an observational study of the efficacy of intensive treatment of heart attack.[19]

Costs were measured by average 30-day out-of-pocket spending on an exenatide prescription by employer and year, adjusted for medical price inflation. Patients faced either "low" or "high" costs, in comparison with median spending on a 30-day prescription. Specifically, for the analyses of both pancreatitis and pancreatic cancer, a logistic regression of exenatide use on an indicator variable for high out-of-pocket costs was performed. Each outcome was then also regressed on the indicator variable for high out-of-pocket costs. A significant effect of cost on both utilization and an outcome would then indicate a causal relationship between exenatide use and the outcome.

Analyses were performed using Stata version 11 (StataCorp, College Station, TX). Hypothesis tests were conducted with a probability of 0.025 in each tail, or a P value of 0.05. Confidence intervals were adjusted for repeated observation of patients.

Results

For the analysis of acute pancreatitis hospitalization, 268,561 patients with type 2 diabetes met the sample selection criteria (Table 1). There were 209,306 eligible patients in the pancreatic cancer sample. Patients in the pancreatitis sample were 63.1 years old on average, compared with a mean of 64.4 years in the cancer sample. There were slightly more men than women in both samples (54.2% for pancreatitis and 54.9% for cancer).

Hospitalizations for acute pancreatitis were rare. As Table 1 shows, only 0.247% of patients were hospitalized in a given year ($n = 1{,}312$). Utilization of exenatide was less rare but still uncommon, with 2.6% of patients filling at least one prescription in a given year (13,791 patient-years out of 530,574). Table 2 shows that patients who did not use exenatide were slightly more likely to be hospitalized for acute pancreatitis

Table 1. Summary Statistics by Outcome Analyzed

Variable	Outcome	
	Pancreatitis	*Pancreatic cancer*
Patients (*n*)	268,561	209,306
Patient-years (*n*)	530,574	419,613
Acute pancreatitis hospitalization (%)	0.247 (4.967)	—
Incident pancreatic cancer diagnosis (%)	—	0.070 (2.651)
At least 1 exenatide prescription filled (%)	2.6 (15.9)	—
Cumulative use of 365+ days as of prior year (%)	—	0.88 (9.35)
Patient cost of 30-day exenatide supply	$37.94 ($28.61)	—
Patient cost of 30-day supply, prior year	—	$36.56 ($26.99)
Age (years)	63.1 (13.8)	64.4 (13.5)
Male (%)	54.2 (49.8)	54.9 (49.8)
Years since diabetes diagnosis	3.1 (3.0)	4.0 (2.9)
History of gallstones (%)	6.6 (24.5)	—
History of alcohol abuse (%)	5.1 (21.6)	—
Co-morbidity history (%)		
Essential hypertension	61.9 (48.6)	65.5 (47.6)
Congestive heart failure	8.7 (28.2)	9.9 (29.9)
Asthma	5.5 (22.9)	5.8 (23.4)
Hypercholesteremia	50.9 (50.0)	54.0 (49.8)
Ulcer	1.2 (10.8)	1.4 (11.6)
Depression	7.9 (26.9)	8.2 (27.5)
Chronic obstructive pulmonary disease	3.7 (18.8)	4.1 (19.7)
Allergic rhinitis	6.7 (25.0)	7.0 (25.5)
Arthritis	16.4 (37.0)	17.9 (38.3)
Cardiac disease	25.1 (43.4)	27.7 (44.7)
Vascular disease	4.9 (21.6)	5.6 (22.9)
Gastric acid disorder	11.9 (32.4)	12.7 (33.3)
Gout	2.6 (15.9)	2.8 (16.6)
Hyperlipidemia	50.9 (50.0)	54.1 (49.8)
Thyroid disorder	10.6 (30.7)	11.1 (31.4)
Rheumatoid arthritis	1.7 (12.9)	1.8 (13.2)
Human immunodeficiency virus	0.1 (3.9)	0.1 (3.8)
Anemia	11.9 (32.4)	13.3 (34.0)
Stroke	7.1 (25.7)	8.0 (27.1)

In pancreatitis analysis, outcome is hospitalization for acute pancreatitis; in pancreatic cancer analysis, outcome is incident pancreatic cancer diagnosis. SDs are in parentheses. Costs are in 2010 dollars.

than patients who used the drug, with annual rates of 0.249% and 0.196%, respectively. However, the difference in rates was not statistically significant ($P = 0.167$).

Exenatide users were younger than nonusers (57.5 years old on average vs. 63.3 years, $P < 0.001$) and less likely to be male (48.1% vs. 54.4%, $P < 0.001$). Table 2 also shows that exenatide users tended to have had diabetes longer and were less likely than nonusers to have risk factors for pancreatitis (a history of gallstones or alcohol abuse). The results of the multivariate regression analysis are reported in Table 3. Patients with a history of gallstones were significantly more likely to be hospitalized for acute pancreatitis, with an odds ratio (OR) of 7.226 (95% confidence interval [CI], 6.400–8.157); pancreatitis risk was also elevated among patients with a history of alcohol abuse. Of key interest is that there was no significant association between pancreatitis and exenatide use, whose OR of 0.926 was statistically indistinguishable from 1 (95% CI, 0.630–1.361.)

Pancreatic cancer was rarer than hospitalizations for acute pancreatitis. As Table 2 shows, only 0.070% of patients per year received an incident cancer diagnosis ($n = 295$). The proportion of patients with a year or more of exenatide supply through the prior year was 0.88% (3,700 out of 419,613 patient-years). Pancreatic cancer rates were not statistically significantly more common among these patients (0.081% among users vs. 0.070% among users, $P = 0.817$). In multivariate logistic regression, Table 3 shows that pancreatic cancer was not significantly associated with exenatide use, with an OR of 1.543 (95% CI, 0.489–4.869). (Patients with human immunodeficiency virus never had pancreatic cancer; hence, 612 observations associated with these patients were excluded from this logistic analysis.)

Results were similar when 6 and 18 months of prior exenatide supply were considered. Results were also similar when (1) exenatide users were excluded if their cumulative supply did not exceed 90 days, (2) the unit of analysis for pancreatitis was the person-half year, and (3) a history of diabetes for at least 1 year was required for the pancreatitis analysis.

Table 4 shows the results of the sensitivity analyses that used out-of-pocket costs to quasirandomize patients into low and high exenatide utilization rates. For pancreatitis, a higher than median cost of a 30-day supply of exenatide was associated with a decreased likelihood of filling an exenatide prescription, with a logistic OR of 0.711 (95% CI, 0.679–0.745). If all patients faced high out-of-pocket costs for exenatide, the utilization rate would have been 2.2% versus a rate of 3.0% if all patients had faced low costs. But, out-of-pocket costs were not associated with hospitalization for acute pancreatitis (OR, 0.934; 95% CI, 0.835–1.046). For pancreatic cancer, a higher than median cost of exenatide in the prior year was associated with a decreased likelihood of cumulative use of 365 or more days as of the prior year, with an OR of 0.672 (95% CI, 0.614–0.735). Out-of-pocket costs were not associated with an incident cancer diagnosis (OR, 1.072; 95% CI, 0.853–1.347).

Conclusions

In our study of a large, privately insured group of over 200,000 patients with type 2 diabetes, we found no evidence of any positive association between exenatide use and hospitalization for acute pancreatitis or an increased risk of pancreatic cancer. In addition, in a sensitivity analysis that quasirandomized patients into high and low exenatide utilization based on out-of-pocket drug costs, we also found no statistically significant relationship.

Our findings are consistent with other database analyses that examined the risk of exenatide use on acute pancreatitis[7–9] and pancreatic cancer rates.[10,11] Prior analyses used alternate administrative databases, including the i3 Aperio administrative healthcare claims database,[7] the Normative Health Information Database,[9] and the Medco National Integrated Database.[8] These databases differ from ours in terms of the age and geographic distribution of plan

Table 2. Summary Statistics by Exenatide Use

	Outcome, definition of utilization, exenatide use					
	Pancreatitis			*Pancreatic cancer*		
	At least 1 exenatide prescription filled			*Cumulative use of 365+ days as of prior year*		
	No use	*Use*	P *value*	*No use*	*Use*	P *value*
Patient-years (*n*)	516,783	13,791	—		415,913	3,700
Acute pancreatitis hospitalization (%)	0.249	0.196	0.167	—	—	—
Incident pancreatic cancer diagnosis (%)	—	—	—	0.070	0.081	0.817
Patient cost of 30-day exenatide supply	$38.03	$34.60	<0.001	—	—	—
Patient cost of 30-day supply, prior year	—	—	—	$36.60	$31.97	<0.001
Age (years)	63.3	57.5	<0.001	64.4	60.9	<0.001
Male (%)	54.4	48.1	<0.001	54.9	51.4	0.002
Years since diabetes diagnosis	3.1	3.9	<0.001	3.9	6.0	<0.001
History of gallstones (%)	6.6	5.9	0.009	—	—	—
History of alcohol abuse (%)	5.1	3.9	<0.001	—	—	—
Co-morbidity history (%)						
Essential hypertension	61.8	64.7	<0.001	65.4	70.3	<0.001
Congestive heart failure	8.8	6.6	<0.001	9.9	9.5	0.471
Asthma	5.5	6.7	<0.001	5.8	6.8	0.092
Hypercholesteremia	50.7	58.1	<0.001	53.9	64.1	<0.001
Ulcer	1.2	0.8	<0.001	1.4	1.0	0.140
Depression	7.8	9.7	<0.001	8.2	10.9	<0.001
Chronic obstructive pulmonary disease	3.7	2.8	<0.001	4.1	3.7	0.395
Allergic rhinitis	6.7	6.8	0.818	7.0	7.5	0.329
Arthritis	16.4	14.1	<0.001	17.8	20.1	0.014
Cardiac disease	25.2	22.4	<0.001	27.7	28.9	0.222
Vascular disease	4.9	3.0	<0.001	5.6	4.6	0.026
Gastric acid disorder	12.0	9.1	<0.001	12.7	11.5	0.081
Glaucoma	5.4	4.9	0.092	6.0	7.3	0.028
Gout	2.6	2.2	0.020	2.8	3.1	0.580
Hyperlipidemia	50.7	58.2	<0.001	54.0	64.2	<0.001
Thyroid disorder	10.5	11.9	<0.001	11.1	12.9	0.018
Rheumatoid arthritis	1.7	1.2	<0.001	1.8	1.1	0.002
Human immunodeficiency virus	0.2	0.0	<0.001	0.1	0.0	<0.001
Anemia	11.9	9.6	<0.001	13.3	14.7	0.080
Stroke	7.2	4.5	<0.001	8.0	6.6	0.009

"Use" and "No use" columns report means, unless otherwise indicated. Costs are in 2010 dollars.

members. The databases from these other studies included a mostly working age population (<65 years old), with only one study[9] including a small proportion of elderly individuals. Our database included a robust proportion of both working age and elderly individuals, which more accurately reflects the epidemiology of diabetes and exenatide use. (For elderly patients with Medicare coverage as well as employer-sponsored insurance, the database analyzed did include claims from both sources.) Furthermore, one unique aspect of our database is the ability to link members to plans benefits design, allowing for a quasiexperimental method of treatment assignment, which was done in a sensitivity analysis.

Another unique feature of our analysis was the ability to assess rates of pancreatic cancer. Although the number of events was small, there was no significant increase in rates between users and nonusers of exenatide. Our data differ from those of Elashoff et al.,[10] in which the FDA AERS database was examined and a positive association between exenatide and pancreatic cancer was found. However, the AERS is considered inadequate for calculation and comparison of event rates because of possible ascertainment bias, lack of knowledge of duration of exposure to drug, and lack of knowledge of the presence of other co-morbidities,[11] and the authors acknowledge as much in their study.[10] In fact, the FDA specifically advises against use of the AERS database to calculate incidence rates.[20] Thus, our study may be a more accurate assessment of real-world "effectiveness" regarding the impact of exenatide on this outcome.

There are several limitations to our study. First, diagnoses in claims databases are not adjudicated, so the sensitivity and specificity of using claims data to identify both acute pancreatitis and pancreatic cancer are not high, particularly relative to the gold standard, such as clinical imaging and chart review. However, our definitions of the outcomes are consistent with prior analyses.[7,8] In fact, in a 2002 study of Veterans Affairs hospital patients, the use of a single ICD-9 code 577.0 in the primary position had high sensitivity (93%) and adequate specificity (72%) for the accurate diagnosis of acute pancreatitis.[21]

Second, our analysis of the impact of exenatide on pancreatic cancer assumes that a diagnosis of pancreatic cancer

Table 3. Multivariate Logistic Regressions of Outcomes on Exenatide Use

	Outcome	
	Pancreatitis	*Pancreatic cancer*
Odds ratio (95% confidence interval)		
Constant	3.88E-3 (1.60E-3–9.39E-3)‡	7.31E-8 (8.90E-10–6.01E-6)‡
Exenatide use[a]	0.926 (0.630–1.361)	1.543 (0.489–4.869)
Age	0.970 (0.942–0.998)†	1.273 (1.120–1.446)‡
Age squared	1.0002 (1.0000–1.0004)	0.998 (0.998–0.999)‡
Male	0.937 (0.833–1.055)	1.333 (1.039–1.709)[b]
Years since diabetes diagnosis	0.930 (0.910–0.950)‡	0.944 (0.904–0.986)‡
Year of observation	0.979 (0.918–1.044)	0.830 (0.722–0.954)‡
History of gallstones	7.226 (6.400–8.157)‡	—
History of alcohol abuse	1.593 (1.303–1.948)‡	—
Co-morbidity history		
Essential hypertension	1.595 (1.382–1.840)‡	0.971 (0.733–1.285)
Congestive heart failure	1.545 (1.293–1.846)‡	1.033 (0.727–1.467)
Asthma	0.955 (0.760–1.200)	0.886 (0.527–1.491)
Hypercholesteremia	0.262 (0.067–1.019)*	24,178.0 (16,544.4–35,333.7)‡
Ulcer	1.278 (0.939–1.739)	1.863 (1.055–3.290)†
Depression	1.257 (1.055–1.498)†	1.023 (0.664–1.576)
Chronic obstructive pulmonary disease	1.047 (0.829–1.321)	1.147 (0.714–1.843)
Allergic rhinitis	0.912 (0.729–1.142)	0.825 (0.492–1.384)
Arthritis	0.892 (0.768–1.035)	0.980 (0.730–1.316)
Cardiac disease	1.297 (1.119–1.504)‡	1.219 (0.934–1.591)
Vascular disease	1.056 (0.852–1.309)	0.443 (0.253–0.774)‡
Gastric acid disorder	1.624 (1.404–1.879)‡	1.315 (0.945–1.831)
Glaucoma	0.763 (0.588–0.989)†	1.129 (0.743–1.717)
Gout	1.542 (1.180–2.014)‡	0.686 (0.335–1.404)
Hyperlipidemia	3.399 (0.874–13.226)*	3.76E-5 (2.55E-5–5.55E-5)‡
Thyroid disorder	0.948 (0.799–1.124)	1.079 (0.759–1.535)
Rheumatoid arthritis	1.185 (0.823–1.706)	0.272 (0.067–1.113)*
Human immunodeficiency virus	2.132 (0.791–5.746)	—
Anemia	1.756 (1.511–2.041)‡	3.301 (2.474–4.404)‡
Stroke	1.203 (1.001–1.444)†	1.057 (0.733–1.524)
Predictive margins		
No use	0.249%	0.070%
Use	0.196%	0.081%
Other statistics		
Patient-years (*n*)	530,574	419,001

In pancreatitis analysis, outcome is hospitalization for acute pancreatitis; in pancreatic cancer analysis, outcome is incident pancreatic cancer diagnosis.

[a]Exenatide use is defined for pancreatitis as at least one exenatide prescription filled and for pancreatic cancer as cumulative use of 365+ days as of the prior year.

Statistical significance is defined at the *10% level, †5% level, and ‡1% level.

would be observed during our study period. Although the natural history of pancreatic cancer is variable, because the incidence of pancreatic cancer is higher in type 2 diabetes patients than those without,[22,23] it is hypothesized that perhaps certain antidiabetes medication classes may accentuate the cancer risk. It is possible that differential rates in pancreatic cancer may be observed over longer time horizons. However, exenatide was approved in 2005, so there are limited data over which to examine postexposure follow-up. By examining the most recent administrative data available (2009), our analysis examines a time period that is equivalent to the only published analysis that broadly examines exenatide's pancreatic cancer risk.[10] Furthermore, for patients who took 365 days or more of exenatide prior to the year of incident cancer diagnosis—the criterion for identifying sustained exenatide use in our analysis of pancreatic cancer—true exposure was frequently much greater than 1 year. Median use was 1.55 years and often extended back to the time of exenatide approval in 2005.

Finally, our approach allows for robust conclusions by using a quasirandomization approach for exenatide exposure through the use of drug benefit design. By comparing exenatide exposure in this way, we avoid confounding of the exposure–outcome relationship by unobserved factors that affect both exenatide use and the risk of acute pancreatitis or pancreatic cancer. For example, patients with severe alcohol abuse that was not captured in claims might also have been less likely to use exenatide, biasing the baseline logistic analysis against finding a positive association between exenatide use and pancreatitis.

In conclusion, our findings provide further evidence that exenatide is unlikely to be associated with an increased risk of acute pancreatitis. We additionally found no significant

Table 4. Logistic Regressions of Exenatide Use and Health Outcomes on Out-of-Pocket Costs

	Analysis by dependent variable			
	Pancreatitis		*Pancreatic cancer*	
	Exenatide use[a]	*Health outcome*	*Exenatide use*[a]	*Health outcome*
Odds ratio (95% confidence interval)				
Constant	0.031 (0.030–0.032)‡	0.003 (0.002–0.003)‡	0.011 (0.010–0.011)‡	0.0007 (0.0006–0.0008)‡
High out-of-pocket cost[b]	0.711 (0.679–0.745)‡	0.934 (0.835–1.046)	0.672 (0.614–0.735)‡	1.072 (0.853–1.347)
Predictive margins				
Low cost	3.0%	0.256%	1.1%	0.068%
High cost	2.2%	0.239%	0.7%	0.073%
Other statistics				
Patient-years (*n*)	530,574	530,574	419,613	419,613

In pancreatitis analysis, outcome is hospitalization for acute pancreatitis; in pancreatic cancer analysis, outcome is incident pancreatic cancer diagnosis.

[a]Exenatide use is defined for pancreatitis as at least one exenatide prescription filled and for pancreatic cancer as cumulative use of 365+ days as of the prior year.

[b]High out-of-pocket cost is defined as patient cost of 30-day exenatide supply above the median level in the pancreatitis analysis and as cost in the prior year above the median in the pancreatic cancer analysis.

Statistical significance is defined at the ‡1% level.

increase in pancreatic cancer rates comparing exenatide users to nonusers. Future research should continue to assess these potential risks as more longitudinal data become available.

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Author Disclosure Statement

J.A.R. and M.S. have consulted for Amylin. D.P.G. has consulted for Amylin and Eli Lilly. A.L.P. has consulted for Amylin, Eli Lilly, and NovoNordisk, provided expert testimony on behalf of Amylin and Eli Lilly, and received speaking fees from Amylin, Eli Lilly, and NovoNordisk. This study was conducted independently of these activities. No competing financial interests exist for D.M.

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Address correspondence to:
Anne L. Peters, M.D.
Keck School of Medicine
University of Southern California
Los Angeles, CA 90089

E-mail: momofmax@mac.com

(*Appendix follows* →)

Appendix

Table A1. International Classification of Diseases, Ninth Revision Coding

Co-morbidity	*ICD-9 codes*
Essential hypertension	401.xx
Congestive heart failure	428.xx
Asthma	493.xx, excluding 493.2, 493.20, 493.21
Hypercholesteremia	272.0, 272.1, 272.2, 272.4
Ulcer	531.xx, 532.xx, 533.xx
Depression	311.xx, 296.2, 296.3
Chronic obstructive pulmonary disease	491.xx, 492.xx
Allergic rhinitis	477.xx
Arthritis	715.xx
Cardiac disease	402.xx, 404.xx, 410.xx, 411.xx, 412.xx, 413.xx, 414.xx
Vascular disease	440.xx, 443.xx
Gastric acid disorder	531.xx, 532.xx, 533.xx, 534.xx
Gout	274.xx
Hyperlipidemia	272.0, 272.1, 272.2, 272.3, 272.4
Thyroid disorder	240.xx-246.xx
Rheumatoid arthritis	714.xx
Human immunodeficiency virus	042.xx, 079.53, 795.71, V08
Anemia	280.xx-285.xx
Stroke	433.xx, 434.xx, 435.xx