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Who Uses Exenatide for Glucose Control in Diabetes Mellitus? A Retrospective Cohort Study of a New Therapy

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Abstract

Background: Exenatide was approved by the Food and Drug Administration (FDA) in April, 2005 as adjunctive therapy for type 2 diabetes mellitus (DM). We evaluated whether early use of this drug was consistent with the FDA-approved indications for use.

Methods: We assembled a retrospective cohort of patients with DM from among a population of employed persons and their dependents. The data, from i3Innovus, includes pharmacy claims and inpatient and outpatient services. The dataset included patients with a diagnosis of DM, or a claim for a drug used to treat DM, between June 1, 2004 and December 31, 2005. We categorized patients by medication use and by their first fill-date of exenatide, and described the patients prior to exenatide use.

Results: We studied 206,345 individuals ages18 to 64 years (mean 51.3 years); 54% were male. Exenatide was filled by 3,225 people, beginning in June 2005. Fifty-three percent of the early users (first 3 months) were female. Twenty-two percent of users were obese, compared to 11 to 15% using other medications. Fourteen percent of users had used no other medication for DM in the preceding year, suggesting that exenatide was their initial therapy. Thirty percent filled a thiazolidinedione prescription within 60 days of filling exenatide.

Conclusions: Exenatide was used frequently early after its approval as monotherapy or with a thiazolidinedione; neither is an FDA approved indication. Exenatide-users had a higher prevalence of obesity than patients using other therapies, suggesting that its weight-lowering benefits may be widely known.

Introduction

In 2003, the Centers for Disease Control and Prevention (CDC) estimated that 13.8 million Americans had a diagnosis of DM, with nearly 40% of these people 65 years or older.[1] New therapies are continually in development to improve treatment of this challenging disease. Exenatide, manufactured as Byetta by Amylin Pharmaceuticals, Inc. (San Diego, CA), was approved by the FDA on April 28, 2005.[2] Exenatide is a first-in-class drug that acts through a novel mechanism; it is a peptide that is a partial analog of glucagon-like peptide-1 (GLP-1). The therapeutic target is restoration of first phase insulin secretion via the "incretin effect" in which the diabetic pancreas responds with insulin secretion in a glucose-dependent fashion. The indication for which exenatide was approved is "to improve glycemic control in patients with type 2 DM who have not achieved adequate glycemic control on metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea."[3] This twice daily injectable drug is approved for use only in adults, pending pediatric studies, and has not been tested in patients with type 1 DM. The approval is only for its use as an adjunctive therapy pending further clinical trials of its efficacy as a monotherapy. Early efficacy trials of this drug demonstrated its superiority relative to placebo for glycemic control,[4-9] and its non-inferiority relative to insulin glargine[10] and insulin aspart.[11] These trials also demonstrated weight loss in patients on this drug.

As part of our evaluation of the comparative effectiveness of this new therapy, we investigated whether use of this drug soon after its approval was consistent with the FDA-approved indications for its use.

Methods

This was a retrospective cohort study using existing, observational data from a population of employed, commercially-insured patients and their dependents in the U.S.

Data

The study employed healthcare utilization data collected by i3Innovus, an Ingenix company (Eden Prairie, MN). The data is encrypted so that no patient is uniquely identifiable; the project received exemption from review from the Johns Hopkins Institutional Review Board.

The data set is called Ingenix LabRx® and contains data from UnitedHealthcare which has beneficiaries in all 50 states and the District of Columbia. LabRx® currently includes approximately 24 million insured lives, all of whom have both medical and pharmacy coverage. Forty-six percent of the beneficiaries are in a health maintenance organization, 23% in a preferred provider organization, and 21% in a point-of-service plan. LabRx® is updated monthly with information on enrollee age, sex, enrollment dates, and claims for reimbursement for billable health care services. It includes information on enrollee age, sex, enrollment dates, and claims for reimbursement for billable health care services. Included in this data are patient diagnoses as identified by International Classification of Diseases, Ninth Revision (ICD-9) codes and medical procedures using several classification systems. Additionally, a separate, linkable file is available which includes pharmacy claims for prescription drugs, including the drug name, prescription fill date and the number of days supply provided. Results from laboratory evaluations are also available on a subset of the enrollees.

We requested data on all patients with an ICD-9 code of 250.xx (DM) or a prescription filled for a drug used to treat DM between June 1, 2004 and December 31, 2005. Additionally,

we requested data on patients with an ICD-9 code of 278.xx (obesity) regardless of whether there was also a diagnosis of DM, and any patient filling a prescription for exenatide within this time period, in order to assess early off-label use of this medication. We requested all available data from the medical claims file and the prescription drug file, and limited laboratory data (specifically, hemoglobin A1c, fasting glucose, and lipids), from June 1, 2003 and through December 31, 2005.

Defining the Cohort

We defined the cohort by requiring patients to meet the following criteria:

- Have a claim with a code for diabetes mellitus (ICD-9-CM 250.xx) at least twice[12,13]
- Have 12 months of continuous coverage prior to the index date, which was defined as the date at which the patient first filled exenatide or October 15, 2005 for those not filling exenatide
- Age between 18 years and 64 years, inclusive
- Not be on dialysis
- Not be in a managed Medicaid health plan
- Have at least one visit after June 1, 2005

Creating Variables

From the claims data, we created variables to describe our patient population. These variables fit into the broad categories of demographic characteristics (age, sex, census division of residence), utilization variables (hospitalizations, outpatient visits, provider specialty, total health care charges, co-payments for prescriptions, medication use), and clinical variables (DM-associated complications, achievement of Health Employer Data Information System (HEDIS) indicators of high quality care, side-effects, HbA1c, fasting glucose, and Johns Hopkins University ACG Case-Mix System Predictive Model (v. 8.0 beta) (www.acg.jhsph.edu) measures for description of case mix. For variables that change with time (time-varying), a unique variable was created for each month from June 2004 through December 2005. For example, total health care charges vary by month, so there are 19 variables for each patient representing total health care charges. Similarly, the number of visits to an endocrinologist varies by month. Other variables, such as an ICD-9 code for obesity, were considered *always* to be present after the month in which they were first coded. Similarly, the presence of a DM-associated complication, such as retinopathy, was considered always to be present once coded. The medication use indicator variables were constructed so that if patient filled a 30 day prescription for an oral hypoglycemic medication, the month in which he filled it would have an indicator variable demonstrating that he did so. If it was a 90-day supply, the patient would have an indicator signifying that he had the medication in the subsequent two months as well.

The construction of the variables indicating use of exenatide and of insulin was as follows: the number of days that the patient had exenatide (or any type of insulin product) "on-hand" was calculated using the fill date for the prescription and the number of days supplied. The medication "on-hand" was credited to the appropriate month. If the patient filled a prescription early, i.e., before he should have run out of medication from the prior prescription, this was *not* credited at the end of the next supply. To use these variables in the statistical models, we collapsed the data into two-month intervals (i.e., May-June 2005, July-August 2005, September-October 2005, and November-December 2005). If the patient had sufficient drug-on-hand for

more than 50% of the days within the two-month interval, he was considered to have been on this drug for that interval. An indicator variable was made to indicate whether during the two-month interval the patient was on (a) no injectable medications (i.e., was on oral medications or no medications), (b) insulin, (c) exenatide, or (d) both insulin and exenatide. Patients in all four of these groups may, additionally, have been on oral medications concurrently.

Descriptive Statistics

We stratified the population of patients with DM into six groups to see how users of exenatide compared to other diabetic patients. Most patients in all of the groups were also using oral hypoglycemic medications. The first three groups were patients who never filled exenatide: (1) patients *never* on exenatide and *never* on insulin, (2) patients *never* filling exenatide who were on insulin *before* June 2005, (3) patients *never* filling exenatide who were on insulin first *after* June 2005. The second three groups were patients who filled exenatide: (4) patients *ever* filling a prescription for exenatide, (5) patients *ever* filling exenatide with previous or concurrent use of insulin, and (6) patients *ever* filling exenatide who *never* were on insulin. The fifth and six groups are subsets of the fourth. We hypothesized that the most comparable groups would be groups 3 and 6, as these were patients on oral medication who had recent *intensification* of therapy with either exenatide or insulin. We also stratified patients using exenatide by the period in which they initiated therapy (June through August 2005, September through October 2005, and November through December 2005). For descriptive purposes, we reported the means and percentages of the variables described above. We did not test for statistical differences across groups as even small differences are statistically significant with this large sample size.

Results

Description of the Cohort

We received data on 1,234,540 individuals meeting the broad criteria specified in our data request. Many individuals met two or more criteria for exclusion leaving 206,345 individuals for study. This population was, by design, almost exclusively patients with DM, although we included 1,104 individuals (0.5%) with diagnoses of obesity without DM. Patients ranged in age from 18 to 64 years with a mean of 51.3 years. The population was generally healthy with a mean of only 1.3 DM related comorbidities, out of a possible of 8; and had few comorbid conditions which would be expected to be costly in the next year.

Use of Exenatide

We received data on 5,601 patients who filled prescriptions for exenatide. After creating the cohort, as described in the methods, we studied the 3,225 patients who filled exenatide among these 206,345 individuals. The first prescription for exenatide was filled in June 2005, slightly more than one month after the drug was approved.

Description of Individuals Using Exenatide by Treatment Period

In Table 1 is a description of the patients using exenatide stratified by the period during which the prescription was first filled. Data in this table illustrate how the medication diffused into use across the population. Slightly more females were early users of this medication; the sex difference narrowed in the later period. The proportion of users of the medication who were

obese increased after the first period, from 19% in the first interval to 24% and 22% in the second two intervals, respectively.

A greater proportion of the early users had filled a prescription for insulin in the 60 day window around the first fill of exenatide. Only 12% of the earliest users had not filled prescriptions for other hypoglycemic medication in the preceding year (i.e., exenatide was prescribed as a monotherapy), while 16% of the later users had not been on other medications, suggesting that exenatide was increasingly common as an initial therapy.

Comparison of Individuals by Their Use of Other Medications for DM

In Table 2, we describe the population stratified by medication use. The last two columns are subsets of the fourth column, i.e., subsets of patients using exenatide stratified by whether they had previously used insulin or not. The mean age was fairly comparable across groups. The insulin users were slightly younger; this group is likely to include young adults with type 1 DM. The proportion of individuals who were obese was much higher among the exenatide users (21.9% with an ICD-9 code for obesity compared to 11-15% in the other groups). The group having the greatest number of DM-associated complications was the group of users of exenatide who previously, or concurrently, were on insulin. The group with the fewest complications was the group on no injectable medications or on no medications at all for DM.

The proportion of patients meeting all of the HEDIS indicators for high quality care was highest in the group begun on exenatide (26% compared to 16-21% in the other groups). The exenatide users had more outpatient visits than any other group, including a much higher number of visits to endocrinologists (1.73 per year compared to 0.20 for those on no injectable medication, and 0.60 for those newly on insulin). Doctors who prescribed exenatide often did so for multiple patients—67% of the patients among the exenatide users had a doctor who had at least five patients on exenatide.

In Table 3, we provide details about the other drugs for DM used by these patients. The groups were similar in the mean number of monthly prescriptions filled and the out-of-pocket costs for these medications. Regarding use of oral hypoglycemic medications, 75% and 58% of patients had been on metformin and a sulfonylurea, respectively. Thirty-percent had filled a prescription for a thiazolidinedione within the 60-day window surrounding the first fill of exenatide. While it is possible that use of the thiazolidinedione was discontinued when exenatide was begun, it is probable that there was concurrent use of these medications. Fourteen percent of the patients on exenatide had not filled a prescription for other medications for DM in the preceding year, suggesting that exenatide was the initial therapy for these 450 patients.

Discussion

The early users of this new drug (in the first six months since approval) were largely middle-aged patients with few DM-associated complications, and few comorbid conditions expected to be costly in the subsequent year. Those prescribed the drug later in this six month period tended to have more comorbid illnesses, and more of them had a diagnosis code for obesity.

The results have good face validity—the patients prescribed exenatide were those who we anticipated would use this drug. Patients on exenatide who were concurrently or previously on insulin had the greatest number of DM-associated complications, suggesting that their disease was not adequately managed with lifestyle interventions or oral agents. Similarly, the proportion of individuals with obesity was highest in the group prescribed exenatide, an anticipated finding

as weight loss is a known effect of therapy with exenatide. Patients in the group prescribed exenatide had more visits to endocrinologists, suggesting that this medication diffused into use through prescription by subspecialists before generalist physicians began to use it.

An important observation is that this new drug was used for off-label indications very early after approval; it was used as a monotherapy in 14% of the patients despite not having an indication as monotherapy, and was used an adjunct to thiazolidinediones and to insulin, also not FDA-approved indications. Important future research would investigate whether patients receiving medications for off-label use differ systematically from other patients, and whether they have similar outcomes. It would also be useful to know whether this extent of early off-label use is unique to this medication, or to diabetes medications, or is seen with other classes of medication.[14] A comprehensive study by Radley, et al, suggests that off-label use of diabetes medications is rare,[15] although it is not clear if they would have considered use of a medication as a monotherapy when it is approved for use as an adjunctive therapy as off-label use. We suspect that use of a medication indicated as adjunctive therapy as monotherapy may be common and could be driven by economic concerns, such as medication co-payments by patients. Mechanistically, this drug should be an acceptable monotherapy, although the cost and inconvenience of an injectable medication may make this an unlikely choice as a first-line agent.

Our observation that the "healthiest" diabetic patients were the first to receive this new medication may have broad implications. One might expect that use of a new medication would be highest in patients who have failed to respond adequately to established therapies. This was not the case for exenatide. Additionally, with the added burden of an injectable medication, we think it is unlikely that patients switched from an oral hypoglycemic that was adequately controlling the disease to an injectable medication. The known side-effect of weight loss could have motivated use of this medication, although we cannot know this from this study. Appropriately, there was not yet consumer-directed advertising of this fact, so this would not have drawn patients to its use.

A limitation of this study is under-coding of diagnoses in claims data; obesity is often under-coded and it may have been more likely to be coded for users of this new medication. Additionally, we were not able to reliably exclude patients with type 1 DM from our cohort because the accuracy of the 4th and 5th digits in the ICD-9-CM code for DM is not established.

Our observations have implications for research on the effectiveness of new therapies. These early users of exenatide differed substantially from patients with diabetes using other medications, and the earliest users differed from the later users. We expect that these differences affect outcomes. In summary, exenatide became widely-used in the United States in the months following its approval. Its place in among the array of treatments for diabetes is not yet established as trials are currently underway testing its use with thiazolidinediones and testing its use as a monotherapy, which may alter its indications. We have published an observational study regarding the effectiveness of exenatide;[16] however, controlled trials of its effectiveness in the population have yet to be done.

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Tables

Table 1. Description of individuals with diabetes mellitus by date of first exenatide use

Covariates	First Used Exenatide in June or July or August, 2005	First Used Exenatide in September or October, 2005	First Used Exenatide in November or December, 2005
N	674	1,198	1,363
Mean age(yrs)	51.3	51.7	51.6
Males (%)	47	48	49
Disease Characteristics			
Diabetes-related comorbidities documented in preceding year, mean # [range 0 to 8]	1.62	1.70	1.68
Obesity, ICD-9-CM 278.xx, in preceding year (%)	18.7	24.0	21.6
All HEDIS indicators of high quality care met in preceding year (%)	24.8	27.0	25.4
Mean JHH-ACG score (probability of high costs in subsequent year)	0.22	0.23	0.21
Mean hemoglobin A1c, in preceding year (%) (n=1,080)	8.2	8.2	8.0
Mean fasting glucose, in preceding year (mg/dl) (n=434)	162	168	165
Health Care Utilization			
Mean monthly total health care charges per person in preceding year ($)	1191	1333	1303
Mean monthly copay for exenatide per person ($)	27	31	42
Mean monthly total number of prescriptions per person filled in one year preceding index date	3.8	3.7	3.6
Outpatient visits: Mean number of outpatient visits per person in preceding year	16.5	16.2	15.8
Visits to internist: Mean number of outpatient visits per person to internist in preceding year	2.7	2.6	2.9
Visits to endocrinologist: Mean number of outpatient visits per person in preceding year	1.8	1.9	1.5
Hospitalization in preceding year (%)	12.0	12.6	12.3
Emergency room visit in preceding year (%)	13.9	13.4	11.7
Hospital admission with hyperglycemia in preceding year (%)	0.2	0.3	0.2
Hospital admission with hypoglycemia in preceding year (%)	0.0	0.1	0.0

Table 1. Description of individuals with diabetes mellitus by date of first exenatide use (continued)

Covariates	First Used Exenatide in June or July or August, 2005	First Used Exenatide in September or October, 2005	First Used Exenatide in November or December, 2005
Medication Usage			
% of patients taking exenatide who filled another diabetes medication within a 60 day window surrounding the date of the first fill of exenatide	76.1	70.5	71.0
filled insulin (%)	22.0	18.9	17.0
filled metformin (%)	48.3	45.0	50.3
filled a sulfonylurea (%)	33.0	30.2	25.8
filled a thiazolidinedione (%)	31.9	27.9	30.6
% of patients taking exenatide who never filled a medication for diabetes in preceding year	12.2	13.4	15.6
% of patients filling insulin in preceding year	37.2	36.9	33.2
% of patients filling metformin in preceding year	75.9	73.7	76.8
% of patients filling a sulfonylurea in preceding year	59.5	57.4	56.8
% of patients filling a thiazolidinedione in preceding year	61.0	57.7	58.5
Mean number of patients on exenatide per doctor if doctor prescribed any exenatide	3.2	3.3	2.8

Abbreviations: HEDIS=Health Employer Data Information System, ICD-9-CM=International Classification of Disease, Ninth Revision - Clinical Modification, JHH-ACG=Johns Hopkins Hospital ACG Predictive Model (version 8 beta)

Table 2. Description of individuals with diabetes mellitus stratified by injectable medication use

Covariates	No Exenatide, No Insulin Ever	No Exenatide; Filled Insulin before June 2005	No Exenatide; Newly Filled Insulin after June 2005	Filled Exenatide
N	159,558	40,217	3,345	3,225
Mean age(yrs)	52.1	48.2	49.0	51.6
Males (%)	54.8	51.9	53.8	48.3
Disease Characteristics				
Diabetes-related comorbidities documented in preceding year, mean # [range 0 to 8]	1.3	1.6	1.6	1.7
Obesity, ICD-9-CM 278.xx, in preceding year (%)	11.7	10.9	15.1	21.9
Mean JHH-ACG score (probability of high costs in subsequent year)	0.13	0.28	0.29	0.22
Mean hemoglobin A1c, in preceding year (%)	7.1 (n=44,936)	8.2 (n=11,194)	9.1 (n=924)	8.1 (n=1,080)
Mean fasting glucose, in preceding year (mg/dl)	138 (n=19,348)	170 (n=4,238)	212 (n=384)	165 (n=434)
Health Care Utilization				
Mean monthly total health care charges per person in preceding year ($)	1,138	1,802	2,907	1,291
Outpatient visits: Mean number of outpatient visits per person in preceding year	12.10	14.90	14.95	16.09
Visits to internist: Mean number of outpatient visits per person to internist in preceding year	2.14	2.38	2.63	2.76

Table 2. Description of individuals with diabetes mellitus stratified by injectable medication use (continued)

Covariates	No Exenatide, No Insulin Ever	No Exenatide; Filled Insulin before June 2005	No Exenatide; Newly Filled Insulin after June 2005	Filled Exenatide	Filled Exenatide, Had Prior Insulin Use	Filled Exenatide, No Prior Insulin Use
Visits to endocrinologist: Mean number of outpatient visits per person in preceding year	0.20	1.18	0.60	1.73	2.21	1.46
Hospitalization in preceding year (%)	11.1	19.2	29.9	12.3	17.4	9.6
Emergency room visit in preceding year (%)	10.3	12.4	11.3	12.8	13.7	12.3
Hospital admission with hyperglycemia in preceding year (%)	0.06	1.85	2.90	0.25	0.61	0.05
Hospital admission with hypoglycemia in preceding year (%)	0.01	0.01	0.03	0.03	0.09	0.00
Mean number of patients on exenatide per doctor if doctor prescribed exenatide	5.0	5.2	5.6	3.1	3.4	2.8
All HEDIS indicators of high quality care met in preceding year (%)	16.0	21.0	16.9	25.9	27.3	25.1

Abbreviations: HEDIS=Health Employer Data Information System, ICD-9-CM=International Classification of Disease, Ninth Revision-Clinical Modification, JHH-ACG=Johns Hopkins Hospital ACG Predictive Model (version 8 beta), * n refers to the number of individuals having this laboratory data element

Table 3. Description of oral hypoglycemic medication use by patients with diabetes mellitus stratified by injectable medication use

Covariates	No Exenatide, No Insulin Ever	No Exenatide; Filled Insulin before June 2005	No Exenatide; Newly Filled Insulin after June 2005	Filled Exenatide	Filled Exenatide, Had Prior Insulin Use	Filled Exenatide, No Prior Insulin Use
N	159,558	40,217	3,345	3,225	1,141	2,084
Medication Usage in Preceding Year						
% of patients who never filled a medication for diabetes	—	—	—	14.1	—	—
% of patients filling insulin	0.0	93.2	68.2	35.4	100.0	0.0
% of patients filling metformin	48.8	31.8	58.9	75.5	69.1	78.9
% of patients filling a sulfonylurea	32.8	20.6	55.3	57.6	51.7	60.8
% of patients filling a thiazolidinedione	27.7	25.0	41.8	58.7	58.0	59.1
Mean monthly total number of prescriptions per person filled in one year preceding index date	3.74	3.77	3.65	3.67	3.64	3.71
Mean monthly prescription copays per person in preceding year ($)	59	59	57	57	58	57
Concurrent Medication Usage						
% of exenatide users who filled drug within a 60 day window surrounding the first-fill date for exenatide	—	—	—	71.8	79.5	67.7
filled insulin (%)	—	—	—	18.8	53.0	0.0
filled metformin (%)	—	—	—	47.9	41.7	51.3
filled a sulfonylurea (%)	—	—	—	28.9	23.3	32.0
filled a thiazolidinedione (%)	—	—	—	29.9	27.2	31.3