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Research Article

Treatment Modifications and Medical Costs Associated with Use of Exenatide BID or Insulin Glargine in Type 2 Diabetes Patients: A Retrospective Database Analysis

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Abstract

Background: Type 2 diabetes (T2D) is a common and costly illness, associated with significant morbidity and mortality.

Objective: This study examined the association between the treatment modification and medical costs for patients using exenatide BID (exenatide) or insulin glargine (glargine).

Methods: The MarketScan Research Databases were used to identify adult patients with T2D who initiated exenatide (N=9,197) or glargine (N=4,499) between 10/01/2006 and 03/31/2008 with 12 months pre- and 18 months post-index continuous enrollment. Patients were propensity score matched (1:1) to control for baseline differences. Treatment modification was defined as the first instance of treatment intensification, switching or discontinuation of the index medication. Cox-proportional hazard models were used to evaluate treatment modification. Generalized linear models were used to evaluate healthcare costs.

Results: A total of 9,197 exenatide and 4,499 glargine patients met all inclusion and exclusion criteria. Matched exenatide (n=3,774) and glargine (n=3,774) cohorts were well balanced with comparable age (57 years), Deyo Charlson Comorbidity score (1.6), and gender (54% male). Treatment modification was more common among glargine patients (HR=1.33, p<0.0001) than exenatide patients. Glargine patients were 72% more likely to intensify treatment (HR=1.72, p<0.0001), 25% more likely to discontinue (HR=1.25, p<0.0001), but 29% less likely to switch therapies (HR=0.71, p<0.0001). The use of exenatide versus glargine was associated with lower total direct medical costs among all patients ($19,654 versus $21,322, respectively; difference= $1,667, p<0.0001), as well as patients who continued their index therapy ($18,324 versus $19,689; difference= $1,546, p<0.005), or who intensified their index therapy ($19,356 versus $21,828; difference= $2,472, p<0.001). There were no significant differences in costs for patients who switched or discontinued their therapy.

Conclusion: Increased treatment modification was associated with increased healthcare costs. The use of exenatide was associated with lower rates of treatment modification and lower total medical costs compared to the use of glargine.

INTRODUCTION

Type 2 diabetes (T2D) is a common and costly chronic disease, with annual direct medical costs of $116 billion and indirect costs from disability, work loss, and premature mortality of an additional $58 billion [1] in the United States. Diabetes is a leading cause of morbidity and mortality. It is associated with significantly higher rate of microvascular (including neuropathy, retinopathy and nephropathy) and macrovascular complications (including stroke, heart disease) [1].

Glycemic control is a primary treatment goal for patients with type 2 diabetes and has been demonstrated to reduce diabetes-related complications of the disease [2], thus reducing both the clinical and economic burden of the disease. Although, there are several treatment strategies available for the treatment of diabetes, maintaining glycemic control is challenging due, in part, to suboptimal adherence or persistence with diabetes medications [3-6]. Exenatide BID (exenatide) and insulin glargine (glargine) are two therapies for the management of type 2 diabetes. Exenatide is a GLP-1 receptor agonist, acting to enhance glucose-dependent insulin secretion, suppress inappropriate glucagon secretion, and slow gastric emptying [7]. Glargine is a long-acting basal insulin analog that reduces fasting plasma glucose.

Treatment switching, augmentation, or discontinuation can indicate that patients may have failed to achieve glycemic control or that the results of a specific therapy are unpredictable. However there is a scarcity of literature examining the relationship of treatment patterns with the medical costs associated with diabetes therapies. The objective of this study was to examine the rate of treatment modification with exenatide or glargine for management of type 2 diabetes and its association with total medical costs in these patients.

To our knowledge, this is the first study that takes into account association between treatment modifications and healthcare expenditure in patients initiating exenatide or insulin glargine. This study used a large claims database representing US managed care patient population with 18 months follow up period compared to 6 or 12 months follow up period in the previous studies [8,9]. This study used propensity score matching to control for baseline differences in two treatment cohorts as opposed to regression analysis used in a previous study [8].

METHODS

Study design

A claims database was used to select patients with T2D, initiating treatment with exenatide BID. Propensity score matching was used to select a control group of patients with T2D initiating glargine. Treatment modification was assessed through measurement of discontinuation, switching, and intensification of therapy. Generalized Linear Models (GLM) was used to estimate the impact of treatment modification on total healthcare costs for patients initiating exenatide or glargine.

Data sources

Data were derived from the MarketScan® Commercial Claims and Encounters (Commercial) Database and the Medicare Supplemental and Coordination of Benefits (COB) (Medicare) Database. The Commercial Database contains the healthcare experience of several million employees and their dependents annually. The Medicare Database contains the healthcare experience of individuals with Medicare supplemental insurance paid for by employers. Detailed cost, use, and outcomes data are available for both databases, covering inpatient services, outpatient services, and prescription drug claims.

Patient selection

Adult patients (18 years and older) with an exenatide or glargine prescription from October 1, 2006 through September 30, 2007 were selected and screened for continuous eligibility for the 12 and 18 months pre- and post-index date (first exenatide or glargine prescription in the time window). Evidence of type 2 diabetes during the 12 months pre-index was determined using the following criteria: ≥2 prescriptions for an antidiabeties agent; ≥2 outpatient claims with different dates of service with diagnosis codes for type 2 diabetes; ≥1 inpatient admission claims with a type 2 diabetes diagnosis code in the primary diagnosis field; or ≥1 emergency department visit claims with a type 2 diabetes diagnosis code in the primary diagnosis field.

Patients were excluded if they had a medical claim with a diagnosis code for any of the following in the 12 and 18 months pre- and post-index: gestational diabetes, chronic kidney disease, type 1 diabetes, Cushing's syndrome, or acromegaly. Additional exclusion criteria included the presence of a CPT procedure code indicating gastric bypass or banding procedures in the pre- or post-index or occurrence of ≥2 prescription claims for a systemic glucocorticoid in the 12 months prior to the index date. Because the intent of the study was to evaluate treatment modification in those patients not yet experiencing substantive therapy adjustment, patients with prescriptions for pramlintide, vildagliptin, saxagliptin, or sitagliptin in the pre-index were excluded. Finally, patients with a prescription for exenatide or glargine in the pre-index were excluded so as to select only patients initiating therapy with these drugs. Study diagnosis, procedure, and drug codes are available from the authors.

Propensity score matching process

Propensity score matching was used to create similar cohorts of patients initiating exenatide and glargine, reducing potential selection bias that may arise when comparing treatments in a non-randomized, observational study design. Variables used in the matching included: gender, age, health plan type, pre-index comorbid burden as measured by the Charlson Comorbidity Index (CCI) score (Deyo version), and pre-index diabetes related complications. Logistic regression was used to complete a 1:1 match of glargine to exenatide patients. The match was evaluated using the standardized difference (presented in table 1); a standardized difference of less than 10 was interpreted to mean that the two groups were comparable for each measure.

Variables

Demographic variables were measured at index and included gender, mean age and age group, geographic region, and health plan type. Clinical variables measured in the 12 months pre-index included the presence of diabetes related microvascular complications (diabetes retinopathy and macular edema; diabetes neuropathy; amputation and ulceration; renal disease) and macrovascular complications (myocardial infarction; ischemic heart disease; congestive heart failure; peripheral vascular disease; cerebrovascular disease). The presence of comorbidities commonly associated with diabetes (hypertension; dyslipidemia; depression; obesity; hypoglycemia) was also measured. The Deyo Charlson Comorbidity Index (CCI) was calculated using claims from the 12-month pre-index period [10]. As prescription claims do not contain prescribing physician specialty, this variable was determined using the provider specialty from a pre-index type 2 diabetes claim with the closest date of service to the index prescription. Pre-index medication use was measured for three drug categories: antidiabetes, cardiovascular, and other drug therapy. The proportion of patients with ≥1 prescription for any drug within a category was determined, as were the number of patients with prescriptions for specific drug classes within categories.

Treatment modification

Three types of treatment modification were evaluated: discontinuation, switching, or intensification of index therapy. Discontinuation was defined as a 90-day gap between the end of the days supply of an index prescription and the fill date for the next prescription for that medication, ***without*** a prescription for a non-index glucose-lowering therapy in the 90 days.

Switching was defined as a 90-day gap between the end of the days supply of an index prescription and the fill date for the next prescription for that medication, ***with*** a prescription for a non-index glucose-lowering therapy in the 90 days and ***with*** a second prescription for the non-index drug within 90 days of the end of the days supply of the first prescription for the non-index drug. In order to count as a switch, the non-index therapy could not have been used pre-index.

Intensification was defined as the addition of a non-index glucose-lowering medication or an increase in the index medication dosage. Additions were indicated by a non-index glucose-lowering medication prescription with overlap of its days supply with that of the index medication, followed by refills of the index medication and the added medication in the 90 days following the end of the day supply specific to that medication. To be considered intensification, the added, non-index glucose-lowering medication could not have been used pre-index. In addition to adding a therapy, patients on insulin glargine could be classified in the treatment intensification group by increasing their medication dose by at least 100%. Dose was calculated for each glargine prescription by dividing the total insulin units dispensed for a prescription by the number of elapsed days between that dispensing date and the next. The definition for intensification was modified for glargine as glargine dose is escalated upwards before adding on to any new medication.

Healthcare costs

The healthcare costs included medical and pharmacy costs. Healthcare costs were measured as the amount reimbursed by health plans converted to 2008 US dollars using the medical component of the Consumer Price Index.

Statistical analysis

Categorical variables were summarized by frequency. Continuous variables were reported by mean and standard deviation. Differences between treatment groups were tested for statistical significance using chi-square tests for categorical variables and t-tests or Wilcoxon rank tests for continuous variables. Demographic and clinical variables were compared both pre- and post-match; treatment modification measures were compared post-match only. Log-rank statistics and hazard ratios were calculated to assess the probability of treatment modification by time post-index for each types of treatment modification (switching, discontinuation, intensification, and any treatment modification). Total costs per patient during the 18-month post-index period were analyzed using GLM with gamma-distributed error and log link, controlling for pre-index patient demographic and clinical characteristics. Separate models were estimated for each type of treatment modification. All analysis was conducted using SAS 9.1 [11].

RESULTS

Baseline characteristics

A total of 9,197 exenatide and 4,499 glargine patients met all inclusion and exclusion criteria (Table 1). Patients treated with exenatide were younger than patients treated with glargine (54.2 versus 59.6, p<0.0001) and a higher percentage of the exenatide cohort was female (58.3% versus 43.3%, p<0.0001). The two treatment cohorts also had different geographic distributions: 53.2% and 27.4% of exenatide-treated patients lived in the South and North Central regions versus 41.3% and 32.8% ofn glargine-treated patients, respectively. The majority (81%) of both exenatide and glargine-treated patients were covered under a non-capitated/fee-for-service plan.

Propensity score matching resulted in a total of 3,774 matched pairs. Mean age in the exenatide patients was 57.0 years vs. 57.8 years in the glargine patients (standardized difference = 7.8). The percentage of female patients was 45.6% and 45.7% in the exenatide and glargine cohorts, respectively (standardized difference = 0.3). There were significant differences in clinical characteristics of patients between the exenatide and glargine cohorts before matching (Table 1); however, propensity score matching balanced all of these characteristics. After the match, pre-index total healthcare costs were $11,194 for exenatide-treated patients and $11,245 for glargine-treated patients (standardized difference = 0.3). Similarly, approximately 14% of both cohorts had an inpatient admission during the pre-index period.

Treatment modification

Compared to exenatide-treated patients, a significantly higher percentage of glargine-treated patients modified their treatment, defined as any of discontinuation, switching, or intensification (Figure 1). By the end of 18 months follow up period, 76.0% of patients in glargine cohort experienced treatment modification compared to 69.1% of patients in the exenatide cohort (p<0.0001). A higher percentage of glargine patients intensified treatment with other medications compared to exenatide patients (26% vs. 15.9%, p<0.0001). Alternatively, a higher percentage of exenatide patients switched treatment compared to glargine patients (14.9 vs. 10%, p<0.0001).

Similarly, patients treated with glargine were more likely to modify treatment than exenatide-treated patients at any given point in time [hazard ratio (HR) = 1.33, p<0.0001] (Figure 2). Compared to patients treated with exenatide, patients treated with glargine were more likely to intensify therapy (HR = 1.72, p<0.0001), more likely to discontinue index therapy (HR = 1.25, p<0.0001), and less likely to switch therapies (HR = 0.71, p<0.0001).

Medical costs

As reported in (table 2), mean total medical costs were significantly lower for the exenatide cohort ($19,654) compared to the glargine cohort ($21,322) in 18 months follow-up period (difference = $1,667, p<0.0001). Among the subgroup of patients who continued their treatment on index medication without any modification for 18 months, exenatide-treated patients (n=1,127) had significantly lower healthcare costs of $1,546 compared to glargine-treated patients (n=874) ($18,324 vs. $19,869, respectively, p=0.005). Among the subgroup of patients who intensified their therapy, exenatide-treated patients (n=580) had significantly lower costs of $2,472 compared to glargine-treated patients (n=947) ($19,356 vs. $21,828, respectively, p=0.0011). While point estimates suggest lower costs for exenatide-treated

Table 1: Baseline demographic and clinical characteristics, pre- and post-match.

Characteristic	Pre-Match				P-value	Post-Match*				
	Patients Treated With					Patients Treated With				
	Exenatide		Insulin Glargine			Exenatide		Insulin Glargine		
	N = 9,197		N = 4,499			N = 3,774		N = 3,774		
	N/Mean	%/SD	N/Mean	%/SD		N/Mean	%/SD	N/Mean	%/SD	Std. Diff.
Age: Mean (years)	54.2	10.1	59.6	12.6	<0.0001	57.0	10.8	57.8	12.0	7.8
Sex: Female	5,359	58.3%	1,948	43.3%	<0.0001	1,720	45.6%	1,726	45.7%	0.3
Diabetes Complications										
Microvascular	1,521	16.5%	1,109	24.6%	<0.0001	769	20.4%	766	20.3%	0.2
Macrovascular	1,530	16.6%	1,349	30.0%	<0.0001	879	23.3%	906	24.0%	1.7
Deyo Charlson Comorbidity Index	1.4	1.1	1.8	1.5	<0.0001	1.6	1.3	1.6	1.3	0.1
Medication Classes	9.9	4.4	9.9	4.7	0.60	9.7	4.2	9.8	4.6	1.5
Pre-index inpatient admissions	815	8.9%	952	21.2%	<0.0001	530	14.0%	543	14.4%	1.0
Pre-index total healthcare costs	$9,749	$12,251	$14,536	$31,763	<0.0001	$11,194	$15,747	$11,245	$18,254	0.3
Physician Specialty					<0.0001					
Primary care	6,346	69.0%	3,170	70.5%		2,722	72.1%	2,699	71.5%	1.4
Endocrinology	1,168	12.7%	210	4.7%		204	5.4%	198	5.2%	0.7
Other specialist	1,016	11.0%	680	15.1%		524	13.9%	529	14.0%	0.4
Missing/unknown	667	7.3%	439	9.8%		324	8.6%	348	9.2%	2.2
Treatment Pre-Index										
Glucose Lowering	9,188	99.9%	4,402	97.8%	<0.0001	3,765	99.8%	3,766	99.8%	0.6
• Biguanides (metformin)	6,761	73.5%	2,940	65.3%	<0.0001	2,624	69.5%	2,626	69.6%	0.1
• Sulfonylureas	4,252	46.2%	3,011	66.9%	<0.0001	2,445	64.8%	2,428	64.3%	0.9
• Meglitinides	466	5.1%	259	5.8%	0.090	212	5.6%	216	5.7%	0.5
• thiazolidinediones	4,688	51.0%	2,382	52.9%	0.030	2,085	55.2%	2,082	55.2%	0.2
• α glucosidase inhibitors	92	1.0%	69	1.5%	0.0065	44	1.2%	53	1.4%	2.1
• fixed dose therapies	2,293	24.9%	916	20.4%	<0.0001	854	22.6%	840	22.3%	0.9
Cardiovascular	8,493	92.3%	4,111	91.4%	0.049	3,470	91.9%	3,463	91.8%	0.7
• antihyperlipidemics	6,526	71.0%	3,074	68.3%	0.0016	2,648	70.2%	2,638	69.9%	0.6
• antihypertensives	7,693	83.6%	3,814	84.8%	0.091	3,183	84.3%	3,187	84.4%	0.3
Other	3,164	34.4%	1,308	29.1%	<0.0001	1,089	28.9%	1,106	29.3%	1.0
• antidepressants	2,890	31.4%	1,138	25.3%	<0.0001	952	25.2%	978	25.9%	1.6
• antiobesity	82	0.9%	10	0.2%	<0.0001	9	0.2%	10	0.3%	0.5
• antiemetics/antinausea	429	4.7%	260	5.8%	0.0051	202	5.4%	203	5.4%	0.1

*Post-match balance was assessed by evaluating the standardized difference (std. diff.). All standardized differences were less than 2.5, except for mean age, which was 7.8.

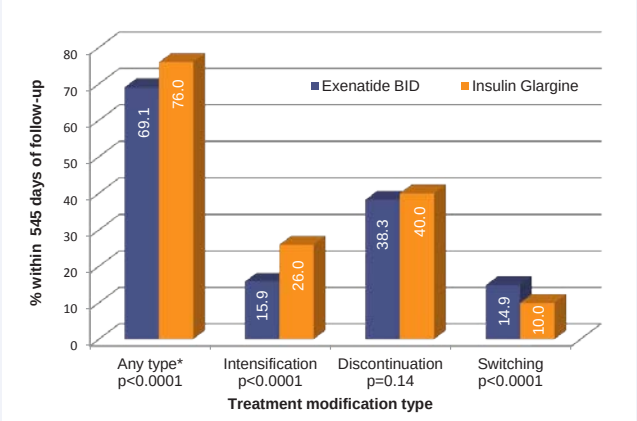

Figure 1 Treatment modification in 18 months follow up period.

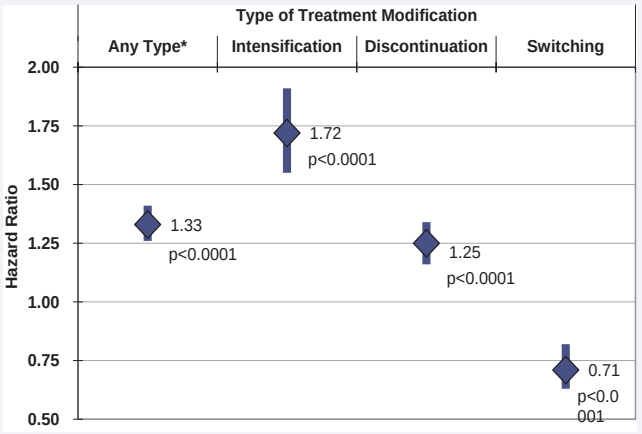

Figure 2 Hazard ratio of treatment modification relative to exenatide BID.

Table 2: Total medical costs in 18 months follow up period.

Patient Cohort	Index Treatment	N	Adjusted** Cost	Incremental cost difference (Insulin Glargine minus Exenatide)	Lower 95% CL	P-value
All patients (matched)	Glargine	3,642	$21,322	$1,667	($939, $2,394)	<0.0001
	Exenatide	3,642	$19,654			
Subset that **Continued** for 18 months	Glargine	874	$19,869	$1,546	($465, $2,631)	0.0050
	Exenatide	1,127	$18,324			
Subset that **Discontinued** within 18 months	Glargine	1,456	$21,324	$948	($422, $2,315)	0.1750
	Exenatide	1,394	$20,376			
Subset that **Intensified** within 18 months	Glargine	947	$21,828	$2,472	($999, $3,913)	0.0011
	Exenatide	580	$19,356			
Subset that **Switched** within 18 months	Glargine	365	$22,623	$1,162	($1,032, $3,392)	0.3014
	Exenatide	541	$21,462			

* Total costs are per-patient for the 18-month period post Index.
** The total cost per patient during the 18-month period post Index was adjusted for differences in patient characteristics between the Index treatments for the following items: pre-period clinical characteristics (Deyo Charlson score, macrovascular complications, microvascular complications, hypertension, dyslipidemia, depression, obesity, hypoglycemia), pre-period utilization (inpatient stay, number of unique prescriptions, ER visit), pre-period expenditure (total costs in 12-months pre Index), and the matching variables (age, gender, geographic region, health plan type) by means of a generalized linear model with gamma-distributed error and log link.

patients, there were no statistically significant differences in costs for patients who switched (difference= $1,162; $21,462 vs. $22,623, respectively, p=0.301). There were no significant differences in costs for exenatide- and glargine-treated patients who discontinued their therapy (difference= $948; $20,376 vs. $21,324, respectively; p=0.175). Figure 3 shows the multivariate adjusted differences in total costs between patients on exenatide and glargine, stratified by type of treatment modification.

CONCLUSIONS

This study suggests that the likelihood of treatment modification and mean total medical costs varied for patients initiating exenatide or glargine in a large real-world United States managed care database. Patients initiating treatment with exenatide had significantly lower rates of treatment modification and lower medical costs than patients initiating glargine treatment in 18 months follow up period.

The lower total direct medical costs for exenatide patients found in this study are consistent with the existing literature. Previous studies have shown that exenatide is a cost effective treatment option compared to insulin glargine [8,12,13]. These findings could be due to various reasons. Lage et al. suggested that one possible reason for the lower costs among exenatide-treated patients may be due to the fact that exenatide is associated with weight loss [14-17], and that weight loss is associated with reduced mortality and cardiovascular disease [12,18,19]. In addition, unlike many other glucose-lowering therapies, exenatide use does not have significantly increased risk of hypoglycemic events [20]. Hypoglycemic events cost an average of $916 per emergency room visit and $15,166 per event that requires an inpatient stay [21].

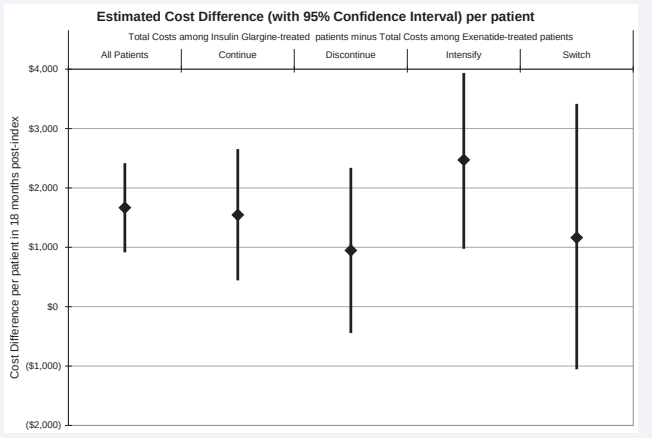

Figure 3 Differences in adjusted total costs: Insulin glargine- exenatide BID.

This study also suggests that increased rate of treatment modification was associated with higher total medical costs. Patients initiating treatment with exenatide had lower rates of treatment modification than patients initiating glargine treatment. Glargine-treated patients were more likely to discontinue or intensify treatment compared to exenatide-treated patients but were less likely to switch therapy. Exenatide-treated patients who continued their therapy also had significantly lower medical costs compared to glargine-treated patients. This finding is consistent with existing literature, suggesting that the use of exenatide is associated with higher adherence than patients using glargine [21]. In a review article, Stephens et al reported a consistent relationship between poorer treatment persistence and/or adherence and increased healthcare utilization and costs among patients with diabetes [22]. Encinosa et al. reported a similar finding, reporting that increasing adherence from 50% to 100% reduces hospitalization rates by 23.3% and emergency room visits by 46.2%, while at the same time increasing diabetes-related drug spending by $776 per patient-per year [23].

This study had several potential limitations. First, the use of a claims database limits the definition of diabetes to the occurrence

of specific diagnosis codes in the claims history, making it dependent on the accuracy of provider diagnosis and coding. To offset this potential limitation, this current study required multiple outpatient claims in the absence of an inpatient or emergency department claim with a diagnosis of type 2 diabetes. Second, the dataset used in this study lacks several clinical variables relevant to the treatment and management of type 2 diabetes, including HbA1c, body weight, body mass index, and compliance with life style modifications. In the absence of this information for use in the propensity score matching, diabetes-related complications, diabetes-related comorbidities and previous medication use were used as a proxy measure of disease severity. Third, treatment modification measures were based on the presence/absence of prescription claims, which may or may not indicate how the medications were used by the patients. It is also important to note that this observational study design does not permit causal inferences. While propensity score matching was used to reduce potential selection bias, and create two comparable patient groups, it does not control for unmeasured confounding variables. These results apply to a population of commercially insured patients, retirees, and their dependents and may not be generalizable to other patient populations. Lastly, further studies are needed to explore the bases for lower direct medical costs observed with exenatide use.

With the advancement of personalized medicine, future studies on type 2 diabetes treatment patterns and outcomes should focus on differential results by patient characteristics. This current study was limited in its ability to stratify by patient race/ethnicity; pharmacogenetic studies suggest that certain genotypes could significantly affect the efficacy of anti-diabetes medications [24-28]. Expanding and evaluating personalized medicine should be able to provide more tailored interventions and better health outcomes.

SUMMARY

Patients initiating treatment with exenatide had lower rates of treatment modification than patients initiating insulin glargine. The use of exenatide was associated with statistically significant reductions in total costs among all patients, patients who continued on their index therapy and patients who intensified their index medication. There was no statistically significant difference in total post-index costs among patients who discontinued their index therapy or who switched their index therapy.

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