

A retrospective database analysis of insulin use patterns in insulin-naïve patients with type 2 diabetes initiating basal insulin or mixtures

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Objective: To describe insulin persistence among patients with type 2 diabetes initiating insulin therapy with basal insulin or insulin mixtures and determine factors associated with nonpersistence.

Research design and methods: The Thomson Reuters MarketScan[®] databases were used to retrospectively analyze insulin-naïve patients with type 2 diabetes by initiating insulin therapy. Insulin use was described using a variety of measures. The persistence to insulin was described using both a gap-based measure and the number of claims measure.

Results: Patients in the basal insulin cohort (N = 15,255) primarily used insulin analogs (88.1%) and vial and syringe (97%). Patients in the mixture cohort (N = 2,732) were more likely to initiate on human insulin mixtures (62.5%) and vial and syringe (68.1%). Average time between insulin refills was 80 and 71 days for basal and mixture initiators, respectively. Nearly, 75% of basal insulin initiators and 65% of insulin mixture initiators had a 90-day gap in insulin prescriptions. More than half of all the patients had at least one insulin prescription per quarter. Patients initiating with insulin analogs were more likely to be persistent compared with those initiating with human insulin across both cohorts and measures of persistence ($P < 0.001$).

Conclusion: Persistence to insulin therapy is poorer than one would anticipate, but appears to be higher in users of insulin analogs and insulin mixtures.

Keywords: insulin persistence, basal insulin, insulin mixtures

Introduction

Type 2 diabetes is a common and expensive disease, with 17.5 million diagnosed cases and \$174 billion in acute-care costs in the United States in 2007.¹ The goal of type 2 diabetes treatment is to maintain a glycosylated hemoglobin (HbA1c) of <7%.² To meet this goal, many patients with type 2 diabetes eventually require insulin therapy to maintain glycemic control because of progressive β -cell dysfunction. Health care providers and patients are often reluctant to initiate insulin therapy, as this therapy is intended to be a permanent change and requires strict adherence and persistence to diet and medication compared with oral antihyperglycemic agents. A significant percent of patients with diabetes experiences difficulty in taking insulin as prescribed by their doctor. For example, in a review article, Cramer³ reported that persistence to insulin varies but is often quite low and three reviewed studies reported that 16%–49% of patients are persistent at 6–12 months.^{4–6} Research also suggests that factors related to injection,⁷ complexity of the medication regimen,³ and higher frequency dosing schedules^{8,9} are key barriers to insulin therapy. Thus, several treatment-related factors may be significant barriers to successful long-term treatment for some patients.

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The primary objective of this study was to describe the persistence to insulin among insulin-naïve patients with type 2 diabetes, who initiated insulin therapy with basal (long-acting) insulin or mixtures. The secondary objective was to determine risk factors for poor persistence with insulin therapy.

Research design and methods

This study used a retrospective approach using administrative claims data. Two MarketScan[®] research databases from Thomson Reuters were used in this study: the Commercial Claims and Encounters (Commercial) and the Medicare Supplemental and Coordination of Benefits (Medicare Supplemental and COB) databases. The Commercial database contains the details of inpatient, outpatient, emergency room (ER), and outpatient prescription drug experience of several million individuals and their dependents (annually), who were covered under a variety of fee-for-service and capitated health plans, including exclusive provider organizations, preferred provider organizations, point of service plans, indemnity plans, and health maintenance organizations. The overall database includes individuals from over 100 self-insured large employers and health plans. The Medicare

Supplemental and COB database contains the healthcare experience of individuals with Medicare Supplemental insurance paid for by employers. Because it covers an older population than does the Commercial database, the Medicare Supplemental database is a key data source. Both the Medicare-covered portion of payment (represented as COB amount or COB) and the employer-paid portion are included in this database.

Inclusion criteria

Patients had to be new insulin initiators (basal or mixtures) between July 1, 2001, and December 31, 2006 (index date). Table 1 provides a list of insulins included in this study, which are classified by types: human vs analog and basal vs mixture. A 6-month preperiod was used to establish new insulin use, a diagnosis of type 2 diabetes (identified by ICD-9-CM codes), and the presence of stable diabetic therapy, as evidenced by having at least two prescriptions for exenatide (Byetta[®]) or an oral antidiabetic agent; the two oral antidiabetic agents could be for the same or different agents; patients were not required to use exenatide or oral antidiabetic agents in the postindex period. Subjects had to be enrolled in a qualified health plan with concurrent continuous pharmacy enrollment

Table 1 Insulin types and examples

Class	Generic name	Brand name	Type
Basal	Insulin human isophane (NPH)	Humulin N; Novolin N; Relion/Novolin N; Insulatard	Human
Basal	Insulin human zinc (Lente)	Humulin L; Novolin L	Human
Basal	Insulin human zinc, extended (Ultralente)	Humulin U	Human
Basal	Insulin detemir	Levemir	Analog
Basal	Insulin glargine, Recombinant	Lantus	Analog
Insulin mixtures	Insulin human isophane (NPH)/Insulin human regular	Humulin 50/50; Humulin 70/30	Human
Insulin mixtures	Insulin human isophane (NPH)/Insulin human regular	Novolin 70/30; Relion/Novolin 70/30	Human
Insulin mixtures	Insulin lispro/ Insulin lispro protamine	Humalog mix 50/50; Humalog mix 75/25	Analog
Insulin mixtures	Insulin aspart/ Insulin aspart protamine	Novolog mix 70/30	Analog
Mealtime	Insulin aspart, recombinant	Novolog	Analog
Mealtime	Insulin glulisine	Apidra	Analog
Mealtime	Insulin lispro, recombinant	Humalog; lispro-PFC	Analog
Mealtime	Insulin human regular	Humulin R; Novolin R; Relion/Novolin R	Human
Mealtime	Insulin human regular, buffered	Humulin BR; Velosulin BR	Human

for a 21-month period spanning the 6-month preindex period through the 15-month study period between January 1, 2001, and March 31, 2008. A moving target index data approach was used to maximize sample size and minimize the impact of seasonal effects (such as annual caps) on utilization.

Exclusion criteria

Patients were excluded if they had evidence of gestational diabetes (ICD-9-CM code of 648.8x), had evidence of type 1 diabetes (ICD-9-CM code of 250.x1 or 250.x3 or DRG 295), or used inhaled insulin or an insulin pump anytime in the observation period. In order to create a more homogenous patient population of insulin initiators, patients were also excluded if they used mealtime (short-acting) insulin or both basal and mixed insulins in the postindex period. Patients with only one insulin prescription claim were also excluded from this analysis.

Insulin use and variables of interest

Index insulin characteristics such as insulin type (human vs analog) and administration (pen vs vial and syringe) were noted.

Several study variables were used to describe insulin use. These include the following:

1. Number of prescription claims for index insulin at 3, 6, and 12 months
2. Average daily insulin supply calculated at 3, 6, and 12 months postindex date by calculating the total insulin supply in mL dispensed and dividing by the number of days in that period
3. Average time between refills of index insulin
4. Proportion that switched to a different insulin type or a different insulin administration.

Insulin persistence measures

Daily adherence to insulin, defined as, “the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen,” was of interest but could not be determined from a database of prescription claims.¹⁰ This study instead focused on evaluating persistence at 12 months, defined as the time from therapy initiation to discontinuation, including a limit on the days between fills.¹⁰ Persistence was evaluated at 12 months by the absence of gaps between refills (measure 1) or the number of refills within a prespecified period (measure 2). Under measure 1, patients were considered persistent at 3 months if they did not have a 90-day gap in index insulin prescriptions, which started prior to the end of the third month. Persistence at 6 and 12 months were defined

similarly but relative to the end of the sixth and twelfth months, respectively. Under measure 2, patients were considered persistent at 3 months if they had two index insulin prescriptions in the first 4 months. Patients were considered persistent at 6 months if they had at least three claims in the first 7 months, including at least one in 1–3 months and at least one claim in 4–6 months. Patients were considered persistent at 12 months if they had at least four insulin prescriptions in 12 months following their index prescription, with at least one index insulin prescription in each quarter. Measure 1 represents a standard definition of persistence,¹⁰ and measure 2 is a more lenient measure and hence was included as a sensitivity analysis. Nonpersistence, as determined by these measures, does not imply a permanent discontinuation from insulin and may be a marker for intermittent use.

Persistent and nonpersistent patients were compared using standard tests of statistical significance. Chi-square tests were used to evaluate the statistical significance of differences for categorical variables; however, two-tailed *t*-tests and analysis of variance were used for continuous variables. A series of logistic regression models were used to examine factors associated with being persistent with insulin therapy at 12 months. Factors included age, gender, location, type of insurance, insulin type, insulin administration mode, Deyo Charlson Comorbidity Index (described by Deyo et al¹¹), presence of hospitalization, presence of ER visit, presence of diabetes complications, presence of macrovascular complications, presence of mental health disorders, count of other diabetes medications, and average copayment per prescription of insulin. An alpha of 0.05 was used for all analyses. Due to the larger sample size, a power calculation was not performed.

Results

Of the 505,898 patients with a index prescription of basal or mixture insulins, 69,318 met the inclusion criteria, of which 17,987 patients also met the exclusion criteria and formed the final sample for this analysis. Nearly, 85% of these patients (N = 15,255) initiated insulin therapy with basal insulin using insulin analogs (88.1%) and vial and syringe (97%) (Table 2). Less than 1% of the basal insulin initiators switched to a different insulin type (analog or human) or different insulin administration mode in the 12 months following index insulin prescription. Conversely, in the insulin mixture cohort (N = 2,732), most patients initiated insulin using human insulin mixtures (62.5%) and vial and syringe (68.1%). Approximately, 7% of patients switched to a different insulin type and insulin administration mode in the 12 months following index insulin prescription.

Table 2 Insulin use

	Basal insulin (N = 15,255)			Insulin mixtures (N = 2,732)		
	Mean	Median	IQ range	Mean	Median	IQ range
No. of claims						
3 mo	2.07	2	(1, 3)	2.42	2	(1, 3)
6 mo	3.40	3	(2, 4)	3.97	4	(2, 5)
12 mo	5.99	5	(4, 8)	6.93	6	(4, 9)
Quantity per day (mL)						
3 mo	0.25	0.22	(0.17, 0.33)	0.31	0.33	(0.22, 0.33)
6 mo	0.20	0.17	(0.11, 0.25)	0.26	0.22	(0.17, 0.33)
12 mo	0.18	0.16	(0.11, 0.22)	0.22	0.19	(0.12, 0.30)
Time between refills (days)						
12 mo	80.11	67.40	(45.20, 95.67)	71.32	55.50	(27.92, 84.00)
Time until change in insulin administration (days): pen vs vial and syringe						
12 mo	192.80	189	(97, 286)	126.71	92.5	(22.5, 224.5)
Time until change in insulin type (days): human vs analog						
12 mo	164.03	159	(66, 257)	139.87	118	(49, 225)

Basal insulin initiators used an average of two other antidiabetic medications in the follow-up period compared with an average of 1.4 for insulin mixture initiators. Both basal and insulin mixture initiators had similar prevalence of diabetes complications (22% and 24%, respectively), macrovascular complications (49% and 51%, respectively), and mental health disorders (5% and 6.5%, respectively). Mean Deyo Charlson Comorbidity Index scores were also similar (1.9 for basal insulin initiators and 2.1 for insulin mixture initiators).

As shown in Table 2, the mean number of claims for basal and mixture insulins increased over time, but the average daily supply decreased. For eg, basal insulin index patients filled an average of 2.07 prescriptions in the first 3 months, 3.4 prescriptions in the first 6 months, and 5.99 in the whole year of the study, which corresponds to 0.69 prescription fills per month in the first 3 months and 0.57 and 0.50 prescription fills per month in the subsequent time periods. The average daily supply follows a similar, albeit less pronounced trend over the same time periods, dropping from 0.25 mL (25 IU) per day to 0.20 mL (20 IU) per day and eventually to 0.18 mL (18 IU) per day. The average time between refills over 12 months was slightly higher among basal index patients (mean: 80.1 days, median: 67.4 days) than mixture index patients (mean: 71.3 days, median: 55.5 days).

Using measure 1, persistence in the basal cohort was 50.6%, 38.5%, and 26.5%; and persistence in the mixture cohort was 58.5%, 47.6%, and 35.0% at 3, 6, and 12 months, respectively. In other words, almost three-quarters (73.5%) of the patients who initiated insulin therapy with basal insulin had a 90-day gap between prescriptions at some

point during the study period. Similarly, more than half of the mixture index patients (65.0%) had a 90-day gap between prescriptions. The start of a 90-day gap was, on average, 80 days and 90.6 days for basal insulin and insulin mixture initiators, respectively, after their index insulin prescription. Among basal insulin initiators, 38.4% had a 90-day gap immediately after their index prescription, and 6.7% had a 90-day gap that start within 30 days of their index prescription. Among insulin mixture initiators, 32.2% had a 90-day gap immediately after their index prescription, and 7.2% had a 90-day gap that start within 30 days of their index prescription. The majority of patients with a 90-day gap had another prescription following the period; 86.9% of basal index patients and 81.5% of mixture index patients restarted insulin following a 90-day gap. The time between the start of the 90-day gap and the next prescription was similar in both groups (basal index mean: 143.4 days, median: 120 days; mixture index mean: 145.9 days, median: 121 days).

Because measure 2 allowed for longer time between refills, more patients were likely to be classified as persistent with this measure. Using measure 2, persistence was 83.4%, 67.1%, and 55.8% among basal insulin initiators and 86.7%, 71.0%, and 59.1% among insulin mixture initiators at 3, 6, and 12 months, respectively. The agreement between measures 1 and 2 at 3, 6, and 12 months was 67%, 71%, and 71% among basal insulin initiators and 72%, 77%, and 76% among insulin mixture initiators, respectively. Agreement was measured as the number of concordant pairs divided by the number of discordant pairs.

Table 3 describes basal and mixture insulin initiators according to their persistence status determined by measure 2.

Table 3 Demographic and clinical characteristics

	Basal insulin initiators			Insulin mixture initiators				
	Persistent N = 8,515 Mean % (SD)	Nonpersistent N = 6,740 Mean % (SD)	P value	Total N = 15,255 Mean % (SD)	Persistent N = 1,615 Mean % (SD)	Nonpersistent N = 1,117 Mean % (SD)	P value	Total N = 2,732 Mean % (SD)
Gender: Female	43.43%	45.43%		44.31%	47.93%	50.13%		48.83%
Age (mean, SD)	59.44 (11.38)	60.01 (12.17)	0.003	59.69 (11.74)	60.67 (11.89)	59.87 (12.49)	0.093	60.34 (12.14)
Age group								
<18	0.07%	0.06%	<0.0001	0.07%	0.06%	0.00%	0.321	0.04%
18–34	1.12%	1.65%		1.35%	1.49%	1.97%		1.68%
35–44	7.00%	7.45%		7.20%	6.69%	7.97%		7.21%
45–54	25.01%	23.84%		24.50%	21.98%	24.26%		22.91%
55–64	37.49%	33.87%		35.89%	33.37%	31.87%		32.76%
65–74	18.27%	19.15%		18.66%	22.66%	20.14%		21.63%
≥75	11.04%	13.98%		12.34%	13.75%	13.79%		13.76%
Location								
Urban	77.79%	79.58%	0.026	78.58%	78.20%	77.08%	0.153	77.75%
Rural	21.90%	20.10%		21.11%	21.61%	22.29%		21.89%
Unknown	0.31%	0.31%		0.31%	0.19%	0.63%		0.37%
Index insulin type								
Human	10.43%	13.71%	<0.0001	11.88%	59.20%	67.23%	<0.0001	62.48%
Analog	89.57%	86.29%		88.12%	40.80%	32.77%		37.52%
Index insulin administration								
Vials and syringes	97.32%	96.51%	0.004	96.96%	67.99%	68.31%	0.860	68.12%
Pens	2.68%	3.49%		3.04%	32.01%	31.69%		31.88%
Change in index insulin								
Human vs analog change	2.50%	2.52%	0.935	0.25%	7.12%	6.09%	0.288	6.70%
Mean time to change	159.25 (105.94)	170.02 (112.85)	0.338	164.03 (109.05)	145.43 (104.95)	130.47 (106.70)	0.356	139.87 (105.56)
Pen vs vial and syringe change	0.73%	0.76%	0.838	0.74%	8.48%	6.00%	0.015	7.47%
Mean time to change	185.82 (106.88)	201.27 (106.99)	0.446	192.80 (106.73)	135.69 (115.19)	108.34 (103.73)	0.102	126.71 (112.04)
Insulin use: 12 months								
No. of index insulin claims	7.83 (3.08)	3.69 (1.52)	<0.0001	6.00 (3.25)	9.13 (3.63)	3.74 (1.88)	<0.0001	6.93 (4.03)
Index insulin quantity per day	0.23 (0.092)	0.11 (0.05)	<0.0001	0.18 (0.10)	0.30 (0.13)	0.12 (0.07)	<0.0001	0.22 (0.14)
Time between index insulin claims	57.95 (22.99)	108.11 (67.41)	<0.0001	80.11 (54.07)	49.32 (20.65)	103.12 (72.36)	<0.0001	71.32 (55.60)
Concomitant medications								
Diabetes medication count	2.00 (0.96)	2.12 (1.00)	<0.0001	2.05 (0.98)	1.27 (1.05)	1.66 (1.05)	<0.0001	1.43 (1.06)
Cardiovascular medication count	3.81 (2.21)	3.79 (2.32)	0.496	3.80 (2.26)	3.95 (2.38)	3.79 (2.42)	0.076	3.88 (2.40)
Copayment burden								
Total cost of prescriptions	\$5,278 (\$3,808)	\$4,612 (\$3,444)	<0.0001	\$4,984 (\$3,666)	\$5,075 (\$4,580)	\$4,362 (\$5,258)	<0.001	\$4,783 (\$4,881)
Copay per insulin prescription	\$18.63 (\$15.42)	\$20.10 (\$18.14)	<0.0001	\$19.28 (\$16.69)	\$17.28 (\$14.28)	\$18.72 (\$16.85)	0.017	\$17.87 (\$15.40)
Comorbidities								
Deyo Charlson Comorbidity index	1.86 (1.46)	1.96 (1.60)	<0.001	1.90 (1.52)	2.10 (1.72)	2.06 (1.74)	0.477	2.08 (1.73)

(Continued)

Table 3 (Continued)

	Basal insulin initiators			Insulin mixture initiators				
	Persistent N = 8,515	Nonpersistent N = 6,740	P value	Total N = 15,255	Persistent N = 1,615	Nonpersistent N = 1,117	P value	Total N = 2,732
	Mean % (SD)	Mean % (SD)		Mean % (SD)	Mean % (SD)		Mean % (SD)	
Diabetes complications	20.88%	23.09%	0.001	21.86%	24.21%	23.19%	0.537	23.79%
Macrovascular complications	48.40%	50.50%	0.010	49.33%	51.52%	50.94%	0.767	51.28%
Any mental health	4.67%	5.95%	<0.0001	5.24%	6.81%	6.00%	0.396	6.48%
Diabetes-related events								
Inpatient admissions	0.41%	0.89%	0.002	0.62%	0.99%	0.54%	0.416	0.81%
Mean length of stay	4.96 (3.63)	6.79 (6.81)	0.143	6.12 (5.89)	5.50 (6.27)	5.25 (3.79)	0.929	5.43 (5.62)
ER use	0.34%	0.42%	0.566	0.37%	0.43%	0.45%	0.956	0.44%
Cardiovascular-related events								
Inpatient admissions	3.35%	4.05%	0.233	3.66%	4.52%	4.92%	0.786	4.69%
Mean length of stay	3.28 (3.12)	3.83 (3.45)	0.050	3.55 (3.29)	3.44 (3.71)	4.74 (4.64)	0.082	4.00 (4.17)
ER use	1.54%	1.99%	0.035	1.74%	2.41%	2.15%	0.649	2.23%

Abbreviations: SD, standard deviation; ER, emergency room.

Across basal insulin and mixture insulin initiators, age, gender, use of human insulin, polypharmacy, and copayment burden were significantly associated with persistence status.

The average number of claims and the average quantity of insulin per day were higher for patients who were persistent. Among basal insulin initiators, patients who were persistent had an average of 9.7 claims compared with an average of 4.7 claims for nonpersistent patients (measure 1). Similarly, persistent patients averaged 0.28 mL (28 IU) of insulin per day compared with 0.14 mL of insulin per day for nonpersistent patients (data not shown in table). The same trends observed for measure 2, persistent patients had an average of 7.8 claims and 0.23 mL (23 IU) per day compared with an average of 3.7 claims and 0.11 mL (11 IU) per day for nonpersistent patients. Among insulin mixture initiators, the differences were more pronounced: patients without a 90-day gap had an average of 10.7 claims and 0.35 mL (35 IU) per day in the follow-up period compared with an average of 4.9 claims and 0.16 mL (16 IU) per day among patients with a 90-day gap during the follow-up period. The difference was also present for measure 2; persistent patients had an average of 9.1 claims and 0.30 mL (30 IU) per day compared with 3.7 claims and 0.12 mL (12 IU) per day for nonpersistent patients. The average quantity of insulin per prescription was similar for persistent and nonpersistent patients (basal insulin initiators: 10.8 mL vs 10.9 mL; insulin mixture initiators: 11.9 mL vs 11.8 mL).

The majority of insulin initiators had a 90-day prescription gap; 73.5% of basal insulin initiators and 64.0% of insulin mixture initiators had a 90-day gap in their first year of insulin use. Among these patients with a 90-day gap, the average time from index to the start of the 90-day gap was 80 days (SD = 49 days) for basal insulin initiators and 91 days (SD = 60 days) for insulin mixture initiators. The majority of insulin initiators with a 90-day gap had an insulin prescription following the gap (86.7% of basal initiators, 81.5% of insulin mixture initiators). Among these patients with a prescription following a 90-day gap, the average time between the start of the prescription gap and next prescription was 143 days (SD = 120 days) for basal insulin initiators and 146 days (SD = 121 days) for insulin mixture initiators.

Multivariate results: persistence at 12 months (Table 4)

Basal insulin initiators

By both persistence measures, women were slightly less likely to be persistent than men, with odds ratios (OR) of 0.94 (95% confidence interval [CI]: 0.87–1.01, $P = 0.074$) and 0.93 (95% CI: 0.87–0.99, $P = 0.022$), respectively. Patients younger than 35 years and those older than 65 years were less likely to be persistent at 12 months by both insulin persistence measures compared with patients aged 45–54 years. Rural location was positively associated with persistence

Table 4 Multivariate models predicting persistence

Sample size	Odds ratio (95 CI)			
	Basal cohort (N = 15,255)		Mixture cohort (N = 2,732)	
Variable	Persistence at 12 months measure 1	Persistence at 12 months measure 2	Persistence at 12 months measure 1	Persistence at 12 months measure 2
Female	0.94 (0.87, 1.01)	0.93 (0.87, 0.99) ^a	1.00 (0.85, 1.17)	0.93 (0.80, 1.09)
Age				
<35	0.63 (0.45, 0.88) ^a	0.66 (0.50, 0.87) ^b	0.76 (0.39, 1.46)	0.88 (0.48, 1.60)
35–44	0.98 (0.85, 1.14)	0.90 (0.78, 1.03)	0.96 (0.68, 1.35)	0.94 (0.68, 1.31)
55–64	0.92 (0.84, 1.01)	1.05 (0.96, 1.14)	0.97 (0.78, 1.21)	1.13 (0.91, 1.39)
65–74	0.69 (0.62, 0.78) ^c	0.91 (0.82, 1.01)	0.97 (0.76, 1.24)	1.21 (0.95, 1.54)
>74	0.69 (0.60, 0.79) ^c	0.77 (0.69, 0.87) ^c	0.80 (0.60, 1.07)	1.07 (0.82, 1.41)
Region				
North Central	0.98 (0.85, 1.14)	0.99 (0.87, 1.13)	0.85 (0.61, 1.20)	1.27 (0.91, 1.77)
South	1.07 (0.92, 1.24)	0.92 (0.81, 1.04)	0.84 (0.60, 1.17)	1.18 (0.85, 1.63)
West	1.17 (1.00, 1.38)	0.95 (0.82, 1.09)	0.88 (0.61, 1.27)	1.17 (0.82, 1.68)
Unknown	0.75 (0.36, 1.58)	0.99 (0.56, 1.77)	0.16 (0.02, 1.24)	0.60 (0.18, 1.99)
Rural	1.29 (1.18, 1.41) ^c	1.11 (1.03, 1.21) ^a	1.12 (0.91, 1.36)	0.98 (0.81, 1.19)
Capitated insurance	1.26 (1.14, 1.39) ^c	1.16 (1.06, 1.27) ^b	1.27 (1.01, 1.59) ^a	1.13 (0.91, 1.41)
Index				
human	0.73 (0.65, 0.83) ^c	0.70 (0.63, 0.77) ^c	0.68 (0.58, 0.81) ^c	0.69 (0.58, 0.81) ^c
pen	0.64 (0.50, 0.82) ^c	0.78 (0.65, 0.94) ^b	0.94 (0.79, 1.13)	0.99 (0.83, 1.17)
Deyo Charlson Comorbidity Index	0.99 (0.96, 1.02)	0.98 (0.96, 1.01)	0.98 (0.93, 1.04)	1.00 (0.95, 1.06)
ER admissions	0.86 (0.65, 1.15)	0.90 (0.71, 1.13)	0.79 (0.46, 1.34)	1.08 (0.66, 1.77)
Inpatient admissions	0.86 (0.69, 1.07)	0.79 (0.66, 0.95) ^a	0.79 (0.52, 1.19)	0.95 (0.64, 1.40)
Diabetes Complications	1.00 (0.90, 1.10)	0.94 (0.86, 1.02)	1.00 (0.81, 1.25)	1.03 (0.83, 1.27)
Count of OAD agents	1.02 (1.00, 1.04) ^a	1.02 (1.01, 1.04) ^b	1.02 (0.98, 1.06)	1.02 (0.98, 1.06)
Macrovascular complications	0.94 (0.87, 1.02)	0.93 (0.87, 1.00) ^a	1.02 (0.86, 1.22)	0.96 (0.81, 1.14)
Mental health disorders	0.81 (0.68, 0.96) ^a	0.79 (0.68, 0.91) ^b	0.99 (0.71, 1.37)	1.14 (0.83, 1.57)
Average copay for insulin	0.99 (0.99, 0.99) ^c	0.99 (0.99, 1.00) ^c	0.99 (0.99, 1.00) ^a	0.99 (0.99, 1.00) ^a

Note: Reference groups: age 45–54; Region: North East; Noncapitated Insurance; ^aDenotes $P < 0.05$; ^bDenotes $P < 0.01$; ^cDenotes $P < 0.001$.

Abbreviations: ER, emergency room; OAD, oral antidiabetic.

at 12 months, with an OR of 1.29 (95% CI: 1.18–1.41, $P < 0.001$) for measure 1 and 1.11 (95% CI: 1.03–1.21, $P = 0.01$) for measure 2.

The use of human insulin was significantly associated with poorer persistence (measure 1: OR = 0.73; 95% CI: 0.65–0.83, $P < 0.0001$; measure 2: OR = 0.70; 95% CI: 0.63–0.77, $P < 0.0001$). Use of insulin pen at index was also associated with poorer persistence by both measures (measure 1: OR = 0.64; 95% CI: 0.50–0.82, $P < 0.0001$; measure 2: OR = 0.78; 95% CI: 0.65–0.94, $P = 0.009$).

Of the clinical variables, the presence of a mental health disorder, which included a diagnosis of depression, was consistently associated with decreased persistence at 12 months by both measures (measure 1: OR = 0.81; 95% CI: 0.68–0.96, $P = 0.017$; measure 2: OR = 0.79; 95% CI: 0.68–0.91, $P = 0.002$). Increasing the count of oral antidiabetic agent classes was associated with a statistically significant increase in persistence by both

measures; however, this increase was modest with an OR of 1.02 for both measures (measure 1: 95% CI: 1.00–1.04, $P = 0.016$; measure 2: 95% CI: 1.01–1.04, $P = 0.004$). Similarly, increasing the average copayment for insulin by \$1 decreased the odds of being persistent at 12 months by 1% for both persistence measures ($P < 0.001$ for both measures). Regional location, comorbid burden measured by the Deyo Charlson Comorbidity Index, presence of ER or hospital admissions, and presence of diabetes or macrovascular complications were not statistically significantly associated with persistence.

Insulin mixture initiators

Among mixed insulin index patients, none of the demographic or clinical characteristics were statistically significantly associated with insulin persistence at 12 months.

The use of human insulin was associated with decreased persistence at 12 months by both measure 1 (OR = 0.68;

95% CI: 0.58–0.81, $P < 0.0001$) and measure 2 (OR = 0.69; 95% CI: 0.58–0.81, $P < 0.0001$). The use of a pen device was not statistically significantly associated with persistence at 12 months by both measures ($P > 0.5$).

Similar to the basal insulin patients, the average copayment for insulin was negatively associated with insulin persistence at 12 months, such that a \$1 increase in average copayment was associated with a 1% decrease in the odds of persistence at 12 months ($P = 0.012$ and $P = 0.022$, respectively).

Conclusions

Insulin use was much lower than expected in the first year following insulin initiation among insulin-naïve patients with type 2 diabetes. Furthermore, the proportion of patients who were persistent with insulin decreased over time, dropping from 83.4% at 3 months to 67.1% at 6 months and to 55.8% at 12 months among basal insulin initiators and dropping from 86.7% at 3 months to 71.0% at 6 months and to 59.1% at 12 months among insulin mixture initiators, as determined by the more lenient of the two measures utilized in this study (ie, measure 2). Using a more conservative gap-based persistence measure (ie, measure 1), 50.6%, 38.5%, and 26.5% of basal insulin initiators were persistent at 3, 6, and 12 months, respectively; 58.5%, 47.6%, and 35.0% of insulin mixture initiators were persistent over the same time periods. Although it is not a measure of discontinuation, the presence of a 90-day gap is an indication of poorer persistence with insulin, particularly, if that gap starts immediately after insulin initiation. Although the majority of patients had a 90-day gap sometime during their first year of insulin use, over one-third of all insulin initiators had a 90-day gap following their first insulin claim.

It is important to distinguish between persistence and permanent medication discontinuation. In this study, persistence was defined as a relatively short-term gap (90 days by persistence measure 1) in insulin prescription coverage over a relatively short time period (3, 6, or 12 months). According to Sikka et al,¹² once patients exceed the permissible gap in prescriptions (90 days in this study), they are no longer considered persistent, even if they have prescription fills following the permissible gap. Over 80% of patients with an insulin prescription gap of 90 days or greater had additional insulin prescription fills after the gap. Although these patients were nonpersistent by the study definitions, they did not completely discontinue insulin therapy and need further investigation. Persistence measure 2 was developed, in part, as a sensitivity analysis around the gap-based definition

of measure 1, allowing for substantially longer intervals between prescriptions to be considered persistent. Even by this lenient measure, only 55%–60% of insulin initiators were persistent at the end of first year.

There is no validated measure available to measure insulin adherence and persistence. The gap period is commonly used as a measure for persistence to oral antidiabetic medications and is well accepted in the literature. Similarly, an early formulation of persistence measure 2 incorporated the current number of claims structure and a requirement of 0.10 mL index insulin per day, on average. Descriptive analysis of the average daily supply of insulin did not provide a clear, clinically relevant cut off that did not appear arbitrary. Descriptive analysis also indicated that the number of claims requirement largely drove persistence determination. Both of these reasons support excluding insulin quantity per day from persistence determination.

It is possible that patients with prescription gaps of at least 90 days (nonpersistent by measure 1) were stockpiling insulin, potentially causing them to be misclassified as nonpersistent. This did not appear to be the case as patients with prescription gaps of 90 days had significantly lower average insulin supplies per day (0.14 mL vs 0.28 mL among basal insulin initiators).

In spite of these limitations, our results were consistent with other recent research. For example, Cooke et al¹³ found that 28.7% of new basal insulin initiators was persistent at 12 months. They also defined persistence as the time (in months) between the first and last insulin fill plus the days supply of the last insulin prescription. This current study was more conservative in that a 90-day gap constituted nonpersistence with insulin. Cooke et al also excluded patients who used any mealtime insulin in the postindex period, matching the exclusion criteria of this current study. Hertz et al¹⁴ also conducted a retrospective database analysis and reported that only 37.0% of new insulin initiators was persistent with insulin therapy at 12 months following index treatment. Similarly, in an evaluation of glargine vs exenatide, Fabunmi et al¹⁵ used a 90-day gap to evaluate persistence and determined that less than 60% of insulin glargine initiators were persistent at 12 months.

Nearly 2,779 insulin users were excluded from this analysis because they only had one prescription of their index insulin. These patients may have required insulin for acute, high hyperglycemia events (ie, they only needed one prescription for insulin, however unlikely that may be). These patients may have also discontinued insulin altogether after one prescription. Future research should examine this

subgroup of patients to better understand their reasons for discontinuation.

There is evidence that dislike of injections is related to the discontinuing of insulin use, suggesting that the use of insulin pens would be associated with better persistence or adherence than insulin vial and syringe.⁴ Other recent studies have found that insulin pens and vial and syringe have similar adherence profiles.¹⁶ This current study appears to support the latter standpoint; however, comparing vials and syringe vs insulin pens was not an explicit study objective. Furthermore, the availability of the products may have driven comparisons of insulin type or delivery system. Among basal insulin index patients, the findings regarding delivery system (pen vs vial and syringe) are likely due largely to the unequal distribution of products available; thus, for mixture insulin index patients, index insulin administration was not a significant predictor of persistence.

Multivariate analysis also indicated that human insulin was consistently associated with poorer persistence than analog insulin. This may be due to lower risk of hypoglycemia and greater flexibility in dosing associated with analog insulin. However, provider-related prescribing preferences for analog or human insulin may have also contributed to this finding.

The finding that higher counts of concomitant medications were positively associated with insulin persistence is inconsistent with existing literature.⁷ This association could be due, in part, to the fact that the prescription of additional classes of oral antidiabetic agents is a result of healthcare utilization and monitoring. On the other hand, the presence of comorbid conditions, such as macrovascular complications, was associated with poorer persistence.

While interpreting these results, it is also important to remember limitations of claim databases. Claim data studies are subject to incomplete recording of data or miscoding, particularly with variables that do not drive service payments. These recording errors are most likely to be random errors; therefore, the impact on study results is likely minimal, if any. Further, the data source only includes adjudicated claims, minimizing the risk of data errors and omissions. Similarly, free insulin samples, which are not captured in this dataset, may have caused this study to underestimate insulin use; however, there is no reliable way to estimate the magnitude of this limitation.

Little is known about physician behavior, such as potential channeling of patients to a particular therapy based on information not captured in the claims history. The absence of lab or medical record data further limits the ability of this

current study to understand physicians' decision making and prescribing practices. It also limits the ability to evaluate other lifestyle approaches to managing diabetes relative to insulin use and persistence. Furthermore, physician instructions to patients or individual dosing guidelines are unknown. This study only captures prescribed doses that a doctor writes and a patient fills. Finally, because glycemic control was not available in the dataset, we are limited in our ability to interpret results in relation to therapeutic needs of patients, eg, some patients may have discontinued insulin due to high risk of hypoglycemia. It is also possible that a patient may have been prescribed insulin in response to an acute glycemic event, making the patient appear nonpersistent with insulin following the acute insulin episode. Similarly, this current study does not capture how long a patient has had diabetes or the length of diabetes treatment, both of which may play a role in clinical decision making regarding the use of insulin and potentially impact persistence measures 1 and 2.

In conclusion, in a cohort of patients who were newly initiating insulin, its use was lower than expected in terms of quantity per day, number of claims, and persistence. Consistent predictors of poor persistence with insulin were: use of human insulin at index, age (elderly), presence of mental health disorders, increased average copayment for insulin (although impact was small), and polypharmacy. Although no formal comparisons were conducted, persistence appeared higher for patients starting on mixture insulin compared to basal insulin. Patients who were excluded because they filled only one insulin prescription or used mealtime insulin during the postindex period warrant further investigation.

Disclosures

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