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ORIGINAL ARTICLE

Trend Analyses of Insulin Delivery Systems in the United States

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Abstract

Background:

Despite potential advantages in insulin pen delivery systems (IPDSs), the percentage of patients using an IPDS is relatively low in the United States.

Objective:

Our aim was to investigate the trend of initiating IPDSs among patients with type 2 diabetes mellitus (T2DM) who newly initiated insulin therapy.

Methods:

A retrospective analysis was conducted using a U.S. database from January 1, 2004, to December 31, 2008. Patients with T2DM who initiated a new insulin type and delivery system were included. The Cochran–Armitage test was used to assess the significance of the trend of initiating an insulin delivery system, including vial/syringe, IPDS overall, reusable pen delivery systems (RPDSs), and prefilled pen delivery systems (PPDSs). Different types of insulin (e.g., basal analog, prandial analog) were examined separately.

Results:

Patients initiating an IPDS increased from 10.6% in 2004 to 48.5% in 2008 ($p < .001$), most notably in basal analog and prandial analog insulin therapies. Although the percentage of patients using a PPDS increased by 36.2 percentage points (from 9.2% in 2004 to 45.4% in 2008; $p < .001$), use of a RPDS increased only by 1.7 percentage points (from 1.4% in 2004 to 3.1% in 2008; $p < .001$).

Conclusion:

There was an overall increase in the use of IPDSs in the United States among patients with T2DM who newly initiated insulin from July 1, 2004, to December 31, 2008. This increase was driven by the use of PPDSs for basal analog and prandial analog insulin therapies. Despite the increasing use of IPDS over time, approximately 50% of patients still initiated insulin using a vial/syringe in 2008.

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Abbreviations: (ICD-9-CM) International Classification of Disease, Ninth Edition, Clinical Modification, (IPDS) insulin pen delivery system, (NPH) neutral protamine Hagedorn, (PPDS) prefilled pen delivery system, (RPDS) reusable pen delivery system, (SEM) standard error of the mean, (T2DM) type 2 diabetes mellitus

Keywords: insulin, pen, type 2 diabetes, vial

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Introduction

Since the first insulin pen delivery system (IPDS) was launched in the mid 1980s, manufacturers have developed various IPDSs for improved portability and convenience. The IPDS is reported to have better treatment satisfaction, medication adherence, and/or outcomes for patients with diabetes than the traditional vial/syringe.[1–7] However, the percentage of patients using the IPDS in the United States is low compared with other countries. In 2002, Da Costa and colleagues[8] reported that IPDS use in the United Kingdom was three times higher than in the United States, with U.S. use at <10%. Differences in health care systems and coverage by health care payers were hypothesized to be contributing to the different rates of IPDS use in the United States and the United Kingdom. Several papers investigated factors associated with the use of IPDSs.[6,9,10] The physician's role in introducing and educating a patient played an essential part in the use of an IPDS,[11] and the mere presentation and encouragement by a physician were associated with a substantial increase in its use.[12] According to a comprehensive literature review by Molife and associates[6] that included 41 studies, multiple patient-reported outcomes were more favorable with an IPDS versus a vial/syringe, including preference, acceptability, ease of use, and convenience.

Patient lifestyle and a better administration experience were considered when improving the design of the IPDS. Studies by Graff and McClanahan[12] as well as Rubin and Peyrot[13] showed an improved attitude toward insulin therapy and an increase in quality of life when patients used an IPDS versus a vial/syringe, but whether these findings have translated into an increase in use has not been investigated. The perception among health care providers and manufacturers of IPDSs is that the adoption of IPDSs among patients is slow, but technological advances may have increased their prevalence. This study investigated the trend of initiating different insulin delivery systems over time among patients with type 2 diabetes mellitus (T2DM) who initiated a new type of insulin in the United States.

Methods

Data Source and Sample Selection

This retrospective database analysis was conducted using the MarketScan® claims database from Thomson Reuters Healthcare (Ann Arbor, MI). The dataset contained medical and pharmacy claims of >20 million U.S. residents who were insured with a variety of commercial health plans, including Medicare supplemental plans.

The study period for this analysis was from January 1, 2004, to December 31, 2008. Using a previously validated algorithm,[14] patients with T2DM were identified by first isolating those with at least two diagnoses of diabetes using International Classification of Disease, Ninth Edition, Clinical Modification (ICD-9-CM) diagnosis codes of 250.xx and then excluding those with type 1 diabetes mellitus (ICD-9-CM codes 250.x1 or 250.x3). The index insulin and delivery system were defined by the first insulin prescription claim in one of the nine 6-month periods that stratified the time from July 2004 to December 2008. The initiation of the index insulin and delivery system required no prescription of the same type of insulin or delivery system in the preceding 6-month period. Index insulin was classified in the following six categories: basal analog, basal human [more specifically, Neutral Protamine Hagedorn (NPH)], prandial analog, prandial human, premixed analog, and premixed human. The types of insulin delivery system considered included vial/syringe, reusable pen delivery system (RPDS), and prefilled pen delivery system (PPDS).

Patients with the following criteria were excluded from the study: less than 18 years of age at the index date, without continuous medical and pharmacy enrollment of at least 6 months prior to and after the index date, or evidence of pregnancy (ICD-9-CM codes 761.5x, V22.xx, V72.40, V2.32, and V23.86) or gestational diabetes (ICD-9-CM codes 648.0x or 648.8x) during the entire study period.

Outcome and Analysis

From July 2004 to December 2008, nine 6-month periods were used to demonstrate the trend of initiating vials/syringes or IPDSs overall, as well as RPDS and PPDS subcategories, among patients with T2DM who initiated a new type of insulin. The significance of the trends was assessed by the Cochran–Armitage test at the significance level of 0.05. This study also investigated the trends in the six different subgroups of insulin therapy: basal analog, NPH, prandial analog, prandial human, premixed analog, and premixed human. All data processing and statistical analyses were conducted using SAS (version 9.1; SAS Institute Inc., Cary, NC).

Baseline characteristics were determined within the 6-month period before the index date. Previous studies[10,15] were used to identify baseline characteristics that are most likely to impact the use of insulin and delivery systems. Baseline characteristics included age, gender, geographic region, provider type, insurance type, general health status (measured by the Charlson comorbidity index score),[15] microvascular complications, macrovascular complications, use of oral antihyperglycemic agents, and frequency of hemoglobin A1c tests. To focus on the trend of insulin delivery system initiation, statistical significance tests were not conducted to compare patient baseline characteristics across different insulin delivery systems at each time period or over time for each insulin delivery system. Summary statistics of baseline characteristics were only reported for the first 6-month period in 2004 and the first 6-month period in 2008 for patients using a vial/syringe, RPDS, or PPDS, separately.

Results

There were 2,514,105 patients diagnosed with T2DM from January 2004 to December 2008. Among these patients, 193,448 initiated a new type of insulin and delivery system in at least 1 of the 6-month periods from July 2004 to December 2008. The final sample included 112,895 adult patients who were not pregnant and had continuous enrollment 6 months before and after the index date. Baseline patient characteristics are summarized in **Table 1**. Mean ages of patients initiating PPDSs and RPDSs were 56 years [standard error of the mean (SEM): 0.4] and 57 years (SEM: 1.0), respectively, in 2004 and 58 years (SEM: 0.1) and 60 years (SEM: 0.5), respectively, in 2008. Mean age of those initiating vials/syringes was 60 years in both years (SEM: 0.2 in 2004 and 0.1 in 2008). In all types of insulin delivery system initiation, the proportion of males increased slightly from 2004 to 2008 (range: 45.8–49.0% in 2004 versus 51.1–54.6% in 2008). A higher percentage of patients initiating a PPDS had an endocrinologist as their health care provider for insulin delivery systems in both years than those initiating a vial/syringe (14.2% PPDS versus 5.3% vial/syringe in 2004; 12.4% versus 4.1% in 2008).

For all newly initiated insulin, the percentage of patients initiating the traditional vial/syringe system decreased over time, from 89.4% in 2004 to 51.5% in 2008 ($p < .001$), while the percentage initiating any IPDS increased from 10.6% in 2004 to 48.5% in 2008 ($p < .001$; **Table 2** and **Figure 1**). The significantly increasing trend of IPDS use was observed among two specific types of newly initiated insulin: basal analog (from 0% in 2004 to 57.8% in 2008; $p < .001$; **Table 2** and **Figure 2**) and prandial analog (from 31.3% in 2004 to 53.2% in 2008; $p < .001$; **Table 2** and **Figure 3**). Basal human, prandial human, and premixed analog exhibited slight, albeit statistically significant, reductions in vial/syringe use compared with corresponding slight increases in IPDS use, with a maximum reduction in vial/syringe use of 10.9 percentage points for premixed analog (**Table 2**). Trends were

Table 1.
Patient Baseline Characteristics in 2004 and 2008: All Insulin Types Combined

Variables	2004						2008					
	Vial/syringe		Reusable pen		Prefilled pen		Vial/syringe		Reusable pen		Prefilled pen	
	Mean or %	SEM	Mean or %	SEM	Mean or %	SEM	Mean or %	SEM	Mean or %	SEM	Mean or %	SEM
Age (years)	60.2	0.2	57.2	1.0	55.8	0.4	60.0	0.1	59.5	0.5	57.7	0.1
Gender												
Male	48.5%	0.0	49.0%	0.0	45.8%	0.0	51.1%	0.0	54.6%	0.0	52.6%	0.0
Female	51.5%	0.0	51.0%	0.0	54.2%	0.0	48.9%	0.0	45.4%	0.0	47.4%	0.0
Geographic region												
North Central	25.5%	0.0	22.9%	0.0	31.1%	0.0	27.5%	0.0	33.2%	0.0	34.5%	0.0
South	38.1%	0.0	29.9%	0.0	44.1%	0.0	42.3%	0.0	37.8%	0.0	42.9%	0.0
West	30.1%	0.0	39.5%	0.0	14.0%	0.0	23.7%	0.0	19.9%	0.0	12.8%	0.0
Other	6.2%	0.0	7.6%	0.0	10.8%	0.0	6.4%	0.0	9.1%	0.0	9.8%	0.0

Continued →

Table 1. Continued

Variables	2004						2008					
	Vial/syringe		Reusable pen		Prefilled pen		Vial/syringe		Reusable pen		Prefilled pen	
	Mean or %	SEM	Mean or %	SEM	Mean or %	SEM	Mean or %	SEM	Mean or %	SEM	Mean or %	SEM
Population density												
Rural	17.8%	0.0	11.5%	0.0	18.1%	0.0	17.5%	0.0	19.7%	0.0	16.8%	0.0
Other	82.2%	0.0	88.5%	0.0	81.9%	0.0	82.5%	0.0	80.3%	0.0	83.2%	0.0
Provider for insulin delivery system												
Primary care physician	36.4%	0.0	21.7%	0.0	33.1%	0.0	37.9%	0.0	46.0%	0.0	46.7%	0.0
Endocrinologists	5.3%	0.0	4.5%	0.0	14.2%	0.0	4.1%	0.0	3.0%	0.0	12.4%	0.0
Other	58.3%	0.0	73.9%	0.0	52.7%	0.0	58.0%	0.0	51.0%	0.0	40.9%	0.0
Copayment for the insulin delivery system (2009 U.S. dollars)	23.7	0.2	24.7	2.0	26.5	0.8	19.4	0.2	29.2	1.3	27.4	0.3
Deductible for the insulin delivery system (2009 U.S. dollars)	0.4	0.1	1.2	0.7	0.7	0.3	1.4	0.1	4.4	1.5	1.5	0.2
Plan source												
Commercial	61.8%	0.0	73.9%	0.0	74.9%	0.0	63.5%	0.0	67.0%	0.0	72.1%	0.0
Medicare	38.2%	0.0	26.1%	0.0	25.1%	0.0	36.5%	0.0	33.0%	0.0	27.9%	0.0
Plan type												
Indemnity plan	25.8%	0.0	16.6%	0.0	27.9%	0.0	16.8%	0.0	18.3%	0.0	14.5%	0.0
Other plan type	74.2%	0.0	83.4%	0.0	72.1%	0.0	83.2%	0.0	81.7%	0.0	85.5%	0.0
Charlson comorbidity index	2.0	0.0	1.5	0.1	1.9	0.1	2.1	0.0	1.7	0.1	1.9	0.0
Microvascular complications	28.3%	0.0	28.0%	0.0	27.9%	0.0	33.1%	0.0	31.9%	0.0	28.0%	0.0
Neuropathy	15.4%	0.0	16.6%	0.0	14.3%	0.0	18.5%	0.0	18.4%	0.0	15.7%	0.0
Nephropathy	10.9%	0.0	8.3%	0.0	8.8%	0.0	14.6%	0.0	12.5%	0.0	10.7%	0.0
Retinopathy	6.9%	0.0	9.6%	0.0	8.6%	0.0	6.4%	0.0	7.5%	0.0	6.3%	0.0
Macrovascular complications	31.2%	0.0	19.7%	0.0	26.2%	0.0	31.4%	0.0	22.4%	0.0	24.2%	0.0
Cardiovascular disease	28.6%	0.0	17.2%	0.0	24.0%	0.0	28.4%	0.0	19.6%	0.0	21.6%	0.0
Peripheral circulatory diseases	6.8%	0.0	3.2%	0.0	4.5%	0.0	7.8%	0.0	5.8%	0.0	6.0%	0.0
Use of OHAs												
No OHA use	27.0%	0.0	27.4%	0.0	29.0%	0.0	30.4%	0.0	22.9%	0.0	17.7%	0.0
Use 1 OHA	28.1%	0.0	27.4%	0.0	28.9%	0.0	31.4%	0.0	30.4%	0.0	28.8%	0.0
Use >1 OHA	45.0%	0.0	45.2%	0.0	42.0%	0.0	38.2%	0.0	46.6%	0.0	53.5%	0.0
Total number of hemoglobin A1c tests	0.9	0.0	1.2	0.1	1.0	0.1	0.6	0.0	0.6	0.0	0.6	0.0
Total number of self-monitoring of blood glucose	0.6	0.0	0.6	0.1	0.7	0.0	0.6	0.0	0.7	0.0	0.9	0.0

OHA, oral anti-hyperglycemic agent.

Table 2.
Use of Insulin Delivery Systems by Insulin Type in 2004 versus 2008

	2004		2008			
	n	%	*n*	%	Difference	*P* value[a]
1. All insulin						
Vial/syringe	10,155	89.4	10,425	51.5	-37.9	<0.001
All pen	1201	10.6	9800	48.5	+37.9	<0.001
Reusable pen	157	1.4	624	3.1	+1.7	<0.001
Prefilled pen	1044	9.2	9176	45.4	+36.2	<0.001
2. Basal analog						
Vial/syringe	4545	100.0	5000	42.2	-57.8	<0.001
All pen	0	0.0	6861	57.8	+57.8	<0.001
Reusable pen	0	0.0	442	3.7	+3.7	<0.001
Prefilled pen	0	0.0	6419	54.1	+54.1	<0.001
3. Basal human						
Vial/syringe	1684	90.7	1364	88.1	-2.6	<0.001
All pen	173	9.3	185	11.9	-2.6	<0.001
Reusable pen	37	2.0	26	1.7	-0.3	0.411
Prefilled pen	136	7.3	159	10.3	+3.0	<0.001
4. Prandial analog						
Vial/syringe	831	68.7	1530	46.8	-21.9	<0.001
All pen	379	31.3	1740	53.2	+21.9	<0.001
Reusable pen	38	3.1	114	3.5	+0.4	0.350
Prefilled pen	341	28.2	1626	49.7	+21.5	<0.001
5. Prandial human						
Vial/syringe	1883	97.8	1506	97.4	-0.4	0.029
All pen	43	2.2	40	2.6	+0.4	0.029
Reusable pen	24	1.2	19	1.2	0	0.590
Prefilled pen	19	1.0	21	1.4	+0.4	0.008
6. Premixed analog						
Vial/syringe	318	40.9	375	30.0	-10.9	<0.001
All pen	460	59.1	876	70.0	+10.9	<0.001
Reusable pen	13	1.7	1	0.1	-1.6	<0.001
Prefilled pen	447	57.5	875	69.9	+12.4	<0.001
7. Premixed human						
Vial/syringe	893	85.9	650	86.9	+1.0	0.380
All pen	146	14.1	98	13.1	-1.0	0.380
Reusable pen	45	4.3	22	2.9	-1.4	0.751
Prefilled pen	101	9.7	76	10.2	+0.5	0.215

[a] *P* value based on Cochran–Armitage test.

not statistically significant among patients initiating premixed human insulin. Basal analog and prandial analog can be considered the primary drivers of the trend for overall newly initiated insulin.

Although the percentage of patients using IPDSs increased over time, trends were different for RPDS and PPDS use. For all newly initiated insulin, the percentage of patients using a PPDS increased by 36.2 percentage points (from 9.2% in 2004 to 45.4% in 2008; $p < .001$), while the use of a RPDS increased only by 1.7 percentage points (from 1.4% in 2004 to 3.1% in 2008; $p < .001$; **Table 2** and **Figure 1**). The pattern of increasing trends also differed across the two IPDSs. For all newly initiated insulin, the percentage of patients using a PPDS became much larger after the first 6-month period in 2007, but the percentage of patients using a RPDS decreased over the same time period (**Figure 1**). The increase in overall IPDS use was mostly driven by the increased use of PPDSs for basal analog (from 0% in 2004 to 54.1% in 2008; $p < .001$) and prandial analog insulin (from 28.2% in 2004 to 49.7% in 2008; $p < .001$; **Table 2** and **Figures 2** and **3**). The percentage of RPDS use decreased for basal analog insulin after the first 6-month period in 2007 (**Figure 2**) and remained steady for prandial analog insulin over time (**Figure 3**).

Discussion

The current study results demonstrated that there was a trend of increased use of IPDSs when patients with T2DM newly initiated insulin. The increasing trend was more substantial with PPDSs than RPDSs, and the trend was driven by patients who initiated basal analog or prandial analog insulin therapies. Although the overall rate of RPDS use in 2008 versus 2004 showed a slight increase, the actual trend over time was not linear. There was a substantial increase in RPDS use for basal analog insulin (and all insulin types driven by basal analog) from 2004 to 2006, but most of these gains were lost in the following 2 years (**Figures 1** and **2**), and the trend from 2006 to 2008 showed a decrease in RPDS use. The trend of the low rate of RPDS use for prandial analog insulin was stable over the entire study period (**Figure 3**). The cause of directional change in RPDS and PPDS use from 2004–2006 versus after 2006 was not determined in the current study. Further examination in future studies of health care system or insurance plan changes around 2006 may elucidate potential causes.

Similar increasing trends of IPDS use were observed in a study by Shaghouli and Shah[10] in Ontario, Canada.

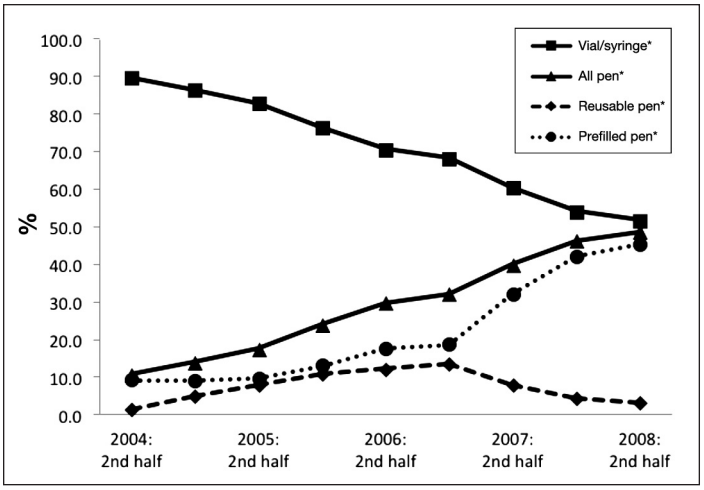

Figure 1. Trend in the use of insulin delivery systems for all insulin types combined. The asterisks represent significant trend ($p < .05$) based on Cochran–Armitage test.

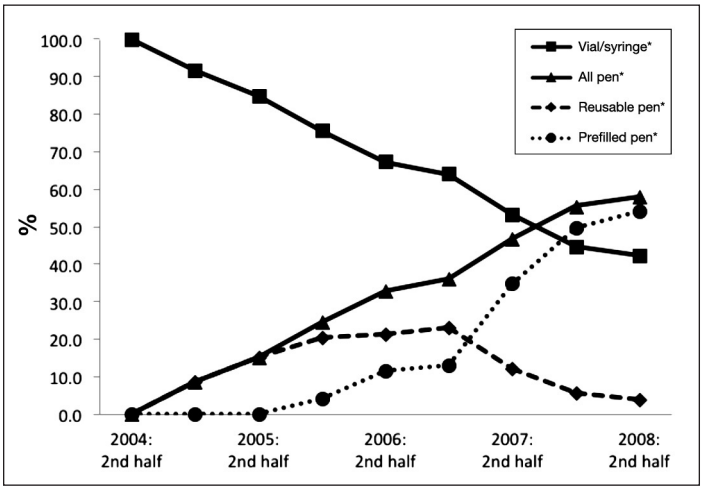

Figure 2. Trend in the use of insulin delivery systems for basal analog insulin. The asterisks represent significant trend ($p < .05$) based on Cochran–Armitage test.

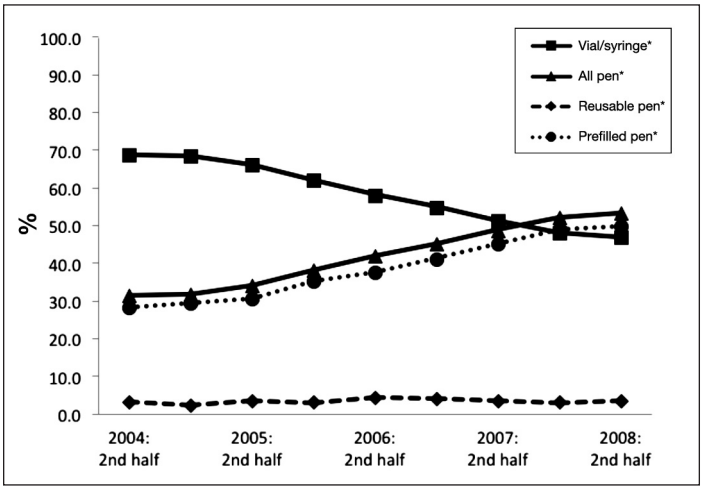

Figure 3. Trend in the use of insulin delivery systems for prandial analog insulin. The asterisks represent significant trend ($p < .05$) based on Cochran–Armitage test.

In the study by Shaghouli and Shah,[10] the percentage of patients using a vial/syringe system dropped from 54% to 14% in 8 years (from 1998 to 2006), and the percentage of patients using an IPDS increased from 46% to 86% among patients with diabetes who were aged 66 years and older. In reviewing patient characteristics (**Table 1**), there seemed to be an increasing trend of starting a RPDS for patients who lived in rural areas and who received their diabetes care from a primary care physician and an increasing trend of both RPDS and PPDS use for those patients on more than one oral antihyperglycemic agent. However, more research needs to be done to prove these trends so IPDSs can be targeted to patient populations whose unmet medical needs can be addressed more effectively.

There are no studies that examine potential reasons for the increasing trend of using IPDSs rather than vial/syringes in the United States over time. However, authors of the present study hypothesize several potential reasons. First, studies supporting better patient-reported and economic outcomes of IPDS versus vial/syringe use are increasing in the literature.[1,3,5–7] According to a systematic literature review by Molife and associates,[6] IPDS use was associated with less injection pain and better treatment satisfaction, handling, convenience, dosing, ease of use, preference, and acceptability than vial/syringe use. Medication adherence was better with an IPDS than with a vial/syringe in studies by Lee and coworkers,[5] Cobden and colleagues,[3] and Baser and associates[1] and among pen-naïve patients in a study by Pawaskar and coworkers.[7] Use of an IPDS was also associated with greater reduction in health care expenditures than vial/syringe use in studies by Lee and coworkers,[5] Cobden and colleagues,[3] and Pawaskar and coworkers.[7] Increased sharing of positive outcomes data associated with IPDS use may have impacted formulary modifications and/or increased education for both patients and health care providers on the advantages of using an IPDS.

Second, the increasing use of IPDSs and the decreasing use of vials/syringes may be due to the choice of insulin regimen and insulin-initiation training. For example, the trend could be associated with increasing use of basal analog with a rapid-acting prandial analog. The trend may also be due to the ease of learning how to use a pen versus a vial/syringe for a subgroup of patients who have never used insulin therapy. Third, there has been continual progress in IPDS technology. Various features ofIPDSs, including ease of dose dialing, injection force, thumb reach, and confirmation of dose administration, have been improved for different types of IPDSs over time.

In this study, the vial/syringe continued to be a significant delivery system when newly initiating insulin. The authors hypothesize that there may be more anxiety about using an IPDS within the patient population using NPH and prandial human insulin, because these patients can mix these insulin therapies in one syringe, but they need to double their injections (one per insulin type) if switching to an IPDS. If an IPDS can be developed that will give a patient the ability to manually combine insulin types, some of the barriers that previously existed with needle anxiety (multiple shots) would be minimized.

There are limitations to this study. First, no statistical tests were conducted to compare patient baseline characteristics. The tests were not necessary in this study because the purpose of looking at baseline characteristics was to describe patient profiles and, if possible, identify potential factors associated with the trend of insulin delivery system initiation. Given the large sample size and small SEM (range: 0.0 to 2.0), the tests will not provide useful information. Multivariate regression would be a better approach to analyze the impact of patient baseline characteristics, which is beyond the scope of this study. Also, only comparing data from 2004 and 2008 would not provide complete information. An alternative is to apply statistical tests to compare baseline characteristics across different insulin delivery systems at each time period from 2004 to 2008, but such analyses would distract from the main objective of analyzing trends of insulin delivery system initiation. Some other researchers also did not apply statistical tests to compare baseline characteristics in a trend analysis, such as the study by Mokdad and colleagues[16] that examined the trend of diabetes in the United States from 1990 to 1998. Second, the MarketScan database used in this study represents medical and pharmacy claims from employer-based health plans and some Medicare supplemental claims. The database is underrepresentative of the elderly population in the United States as well as patients who are uninsured or covered by other health plans such as Medicaid. The MarketScan database, however, is more representative than many other standard claims databases available at this time, due to the inclusion of Medicare supplemental claims. Finally, this study was conducted using medical and pharmacy claims data only, without verification of actual diagnosis of T2DM. Claims diagnoses represent justifications for billing and may not always accurately reflect patients' medical conditions, although this study had the ability to modify patient selection and attribution criteria to best classify all patients. Health care received outside of the health insurance plan, such as over-the-

counter medications, would not appear in the claims data and hence could not be examined in this study.

Conclusion

There was a significant increase of 37.9 percentage points in the initiation of IPDSs among patients with T2DM who started a new type of insulin in the United States from 2004 to 2008. Increasing use of PPDSs when initiating basal analog or prandial analog insulin therapy was the most important contributor to this trend. Despite increasing use of IPDS over time, approximately 50% of patients still initiated insulin using a vial/syringe in 2008.

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Disclosures:

Lauren J. Lee is an employee and a stock owner of Eli Lilly and Company. Qian Li, Matthew W. Reynolds, and William Engelman are employees of United BioSource Corporation. Eli Lilly and Company contracted with United BioSource Corporation for the analysis of this study.

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