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Effect of Adherence and Insulin Delivery System on Clinical and Economic Outcomes among Patients with Type 2 Diabetes Initiating Insulin Treatment

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ABSTRACT

Background: Adherence to insulin affects real-world health outcomes and may itself be affected by the choice of insulin delivery device (pen or vial/syringe). The choice of insulin delivery device may also have direct effects on effectiveness. **Objective:** This study aimed to estimate the effects of insulin adherence and delivery device on real-world health outcomes. **Methods:** This study included adults with type 2 diabetes mellitus initiating insulin, with continuous health plan insurance for 6 or more months before initiation (baseline) and 1 or more year after. Measured outcomes included glycosylated hemoglobin (Hb A_{1c}) reduction, hospitalization rate, total health care costs, and pharmacy costs over 1 year of follow-up. *Adherence* (defined as having insulin fills sufficient for the entire quarter), pen or vial/syringe use, and disease-related patient characteristics were assessed in each quarter. To account for the time-varying relationship between adherence, patient characteristics, and outcomes, marginal structural generalized linear models were used to estimate the effect of adherence and device use. Mean outcomes were predicted for different combinations of adherence and device choice. **Results:** Among the 13,428 patients (mean age 54 years; 46% women; baseline Hb A_{1c} 9.3%), adherent pen users had greater reductions in Hb A_{1c} (−0.35%; $P = 0.045$), lower hospitalization rates (−0.36; $P < 0.01$), and higher pharmacy costs ($2923; $P < 0.01$) than did nonadherent vial users, and similar total health care costs ($3906 lower; $P = 0.1$). Pen use and adherent vial use decreased hospitalization rate and increased pharmacy but not total costs. **Conclusions:** Adherence and pen use have beneficial effects on patients' real-world outcomes, with the most favorable effects attributable to adherent pen use.

Keywords: adherence, health care costs, insulin, type 2 diabetes mellitus.

Introduction

Diabetes mellitus is a chronic metabolic disease that affects approximately 26 million people in the United States [1]. Its incidence was estimated at 1.9 million cases in the United States in 2011, and this number is expected to increase rapidly over the next few decades [1]. Nearly 90% of all cases of diabetes are classified as type 2 diabetes mellitus (T2DM) [2]. Current treatment guidelines for T2DM recommend a stepwise approach to disease treatment, starting with metformin therapy combined with lifestyle interventions [3,4]. Insulin therapy is usually recommended for patients who fail to achieve or to maintain their blood glucose level target (as measured by glycosylated hemoglobin [Hb A_{1c}] levels) during the first 3 to 6 months after the start of initial treatment, or for those who have markedly elevated blood glucose levels [5].

A significant limiting factor of the real-world effectiveness of insulin therapy is nonadherence, with more than one third of the patients with T2DM being poorly adherent [6]. Adherence can be challenging for patients with T2DM on insulin therapy because these patients often do not experience immediate consequences when skipping insulin injections [7]. Other factors influencing adherence include lack of time, travel, or public embarrassment [8]. Nonadherence, however, has been shown to result in serious clinical and economic consequences [6,7,9].

The choice of insulin delivery system used by patients, such as syringe/vial or insulin pen, may play an important role in maintaining insulin adherence, and influences the clinical and economic outcomes of insulin treatment. Compared with the traditional syringe/vial, an insulin pen offers a number of practical advantages, including greater ease of use, superior accuracy in dosing, greater social acceptability, and less pain at administration [10]. Consequently, patients frequently report greater satisfaction and develop treatment preference for pen devices [10–12]. Beyond patient satisfaction, pen devices may help improve clinical outcomes, including improvements in insulin adherence [7,10,13,14] and reductions in Hb A_{1c} levels and hypoglycemic events [13,14].

Conflict of interest: Chunshen Pan is a consultant for and receives research support from Sanofi-Aventis. Wenhui Wei is an employee of Sanofi-Aventis and may own stock/stock options. Rajeev Ayyagari, David Cheng (former employee), James Signorovitch, and Eric Q. Wu are employees of Analysis Group, Inc., which has received consultancy fees from Sanofi-Aventis.

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Although pen devices have higher unit costs than do syringe/vial options, reductions in hospitalizations and other health care costs may potentially offset or even lead to decreases in total health care utilization and costs [7,13–15].

Such improvements in clinical and economic outcomes may be attributed at least in part to improvements in adherence to insulin treatment administered with pen devices. Adherence, however, involves multiple components itself, and pen devices may also confer advantages beyond improving adherence. In particular, insulin administration via pen devices may result in more timely use of insulin, consistent dosing, elimination of errors associated with incorrect injection techniques, and prevention of other medication errors associated with syringe and vial [16]. All these effects may also affect the patients' clinical and economic outcomes.

This study aimed to estimate the causal effect of adherence—on the basis of prescription refill data—and the effect of using pen devices versus syringe/vial on annual % Hb A_{1c} changes, hospitalization rates, pharmacy costs, and total health care costs in patients with T2DM. To estimate these effects, the following approaches were adopted.

First, this study assesses treatment types, adherence, and outcomes longitudinally because they may change over time. Previous studies have used an intent-to-treat approach, with pen use or adherence determined during a baseline period and carried forward through the observation period. This approach will not capture the impact of real-world treatment decisions, which are known to change over time in response to patient outcomes. To account for these changes over time, and to adjust for time-dependent confounding of the effect of pen use and adherence on outcomes by patient characteristics, this study uses marginal structural models (MSMs) [17]. In the longitudinal setting, the choice of insulin administration device and adherence are affected by disease indicators and other patient characteristics at previous time points, which, in turn, affect patient characteristics at later time points. In this setting, traditional regression adjustment for baseline characteristics may not yield causally meaningful estimates. When the appropriate assumptions are satisfied, however, MSMs provide reasonable estimates of the causal effects of time-varying treatments [17–20]. In this article, we focus on the effect of fixed sequences of adherence and treatment choices. MSMs, however, have also been used to assess the impact of dynamic intervention regimes in diabetes, in which the effect of treatment strategies is evaluated on the basis of patients' health status [21,22], and to study mediators in the development of diabetes [23].

Second, previous studies have separately examined the associations between administration with pen and various outcomes, whereas this study focuses on the effect of both pen use and adherence. This allows for finer distinctions of estimates of the effect of pen device treatment and adherence to treatment to be drawn than by studying the effect of pen use or of adherence alone. For example, the model can be used to estimate the effect of pen use for patients who are not likely to be regular with treatment.

Finally, this study uses a measure of adherence that estimates the number of days' worth of insulin recorded in a prescription fill rather than using the reported days of supply filed in medical claims [7,24]. Because insulin dosages vary widely between patients, measuring adherence on the basis of days of supply reported in claims data may be biased. The measure used in this article is believed to better reflect actual adherence.

Methods

Data and Study Sample

This study was a retrospective analysis of administrative medical claims data from the IMPACT national managed care database, supplemented with laboratory measurements. The database includes health insurance claims from more than 45 private and government-sponsored health plans throughout the United States, and covers claims from January 2001 to December 2010. The study sample included patients who were diagnosed with T2DM (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] code 250.x0 or 250.x2) and who had at least one claim for basal insulin (glargine, detemir, or Neutral Protamine Hagedorn insulin). Patients were required to have continuous insurance eligibility for 6 months (baseline period) before the date of the first claim for basal insulin (index date) and for 12 months after the index date (follow-up period). Patients were also required to have no claims for insulin during the baseline period, to have at least one claim for an oral antidiabetic drug (OAD) or glucagon-like peptide 1 (GLP1) agonist in the baseline period (to ensure that only patients with T2DM were selected for analysis), and to have at least one recorded measurement of Hb A_{1c} in the baseline period. Baseline characteristics were examined using data recorded within 6 months before the index date. These variables included age at the index date, sex, region, types of insurance coverage, Hb A_{1c} level, comorbidities (identified via *ICD-9-CM* codes; Charlson comorbidity index [25], microvascular diseases, hypertension, hyperlipidemia, obesity, and mental illness [defined by the *ICD-9-CM* codes 290.xx–311.xx]), number of OADs, GLP-1 agonist use, concomitant medications, and total and diabetes-related health care utilization and costs. Baseline Hb A_{1c} data originated from Hb A_{1c} test levels measured between 6 months before the index date and 15 days after. If patients had multiple Hb A_{1c} results during this period, the value dated closest to the index date was used as the baseline value.

Data on each patient's insulin adherence and insulin device usage were summarized in four consecutive, nonoverlapping 90-day intervals (i.e., annual quarters) during the follow-up period. When defining adherence, using the stated days' supply on a prescription fill claim can be problematic with insulin because dosage depends on various factors, including body weight and diabetes progression [7]. To account for differences between stated and actual days of supply, the following data-driven approach to the estimation of days' supply of insulin was adopted. The effective duration of insulin supply for a particular type of insulin package was determined by examining the interfill times associated with that type of insulin package. Specifically, the effective days' supply associated with each claim was calculated as the 90th percentile of all interfill times reported for claims with the same metric quantity and insulin product [24]. A dichotomous variable for insulin adherence was defined in each quarter for each insulin type on the basis of whether the patient had insulin supply for all days in that quarter. Availability for all days in a quarter was determined by totaling the effective days' supply for all fills in that quarter. Patients were defined as adherent in a quarter if they were adherent to at least one type of insulin. Pen use versus vial and syringe use in each quarter was determined on the basis of whether the patient exclusively had claims for insulin pen or for insulin in vial and syringe delivery format. If the patient had claims for both pen and vial delivery in a quarter, device use in that quarter was classified according to the first quarter in a patient's treatment history in which he or she did not use both pen and vial and syringe.

The outcomes studied were change in Hb A_{1c} levels, number of hospitalization events, pharmacy costs, and total health care costs accumulated over the follow-up period. The change in Hb A_{1c} levels was calculated as the last measurement of Hb A_{1c} available in the fourth quarter subtracted from the last available Hb A_{1c} measurement recorded in the baseline period. Patients who did not have a measurement of Hb A_{1c} available in the fourth quarter were excluded from the analysis of this outcome, with inverse probability of censoring weights applied to account