Will Inhalable Insulin Reduce Medication Nonadherence With Insulin Among People With Diabetes?

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Before June 27, 2014, there were 2 classes of drugs that were approved by the US Food and Drug Administration (FDA) and being marketed for the treatment of type 1 diabetes and 12 classes of drugs approved and marketed for the treatment of type 2 diabetes (T2DM) in the United States. Approved insulins were administered as injections via the subcutaneous route, most times with multiple injections during the day, or with a pump that administers the drug subcutaneously. That landscape changed in a potentially significant way on June 27, as the FDA approved a new, inhalable insulin formulation and delivery device. Although the product (Afrezza® [MannKind Corporation, Valencia, California]) is new, the concept is not. As Drs. Santos-Cavaiola and Edelman write in this month's issue of *Clinical Therapeutics*,[1] inhalable insulin has been studied since the 1920s.[2] Since then, several manufacturers have developed different insulin drug-device systems, hoping to make the jump from conventionally delivered insulin to one that is easier for patients to self-administer and contributes to a faster bioavailability. These joint ventures include Nektar Therapeutics in collaboration with Pfizer, Inc; Aradigm Corporation with Novo Nordisk; and Alkermes with Eli Lilly.

Afrezza uses a unique, dry powder formulation that is predosed in cartridges, requiring patients to potentially use multiple cartridges to achieve a recommended dose. It is a rapid-acting insulin for use at the beginning of each meal. As a therapy that is not administered subcutaneously, an easy-to-use inhalable insulin has the potential for expanding the pool of insulin users beyond those typically considered to be good candidates for insulin, and thereby introducing significant positive public health and clinical outcomes. Key to achieving good population-level diabetes outcomes, however, will be getting it to those patients who are likely to have worse diabetes outcomes: low-income, uninsured minority patients with T2DM.

Patients with T2DM often balk at being switched up to insulin from oral antidiabetes medications for many reasons, but a fear of needles is usually high on the list of patient concerns. Other concerns include weight gain, episodes of hypoglycemia, guilt, and social stigma. Adherence to injectable insulin therapy ranges from 43% to 86%; the mean medication possession ratio (MPR) was $<80\%$ in a systematic review of 17 studies examining insulin adherence, indicating that the medication was on hand for $<80\%$ of a given period studied.[3] An MPR ≥ 0.80 is generally considered to be an inadequate rate of medication use. The **Table** provides an overview of reasons for medication nonadherence among patients with diabetes from a health care system perspective, as conceptualized by Odegard and Capoccia.[4]

Using conventional devices for administering insulin, including vial syringes and pens, patients often administer inappropriate insulin doses or neglect to use their prescribed insulin altogether. In a study of 3042 patients treated with basal insulin analogues, 38% reported a dosing irregularity in the previous 30-day period and 15% reported multiple dosing irregularities, including missing, mis-timing, or reducing doses.[5] Among patients who reduced their doses, 87% did so intentionally. Furthermore, a majority of those reporting that they had self-treated hypoglycemia episodes also admitted to intentionally misdosing their insulin. Similarly, Peyrot et al[6] found that 35% of 1530 insulin-treated adults reported 1 or more days of

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Table. Factors contributing to medication nonadherence among patients with diabetes from a health care system perspective.

Patient Factors	Medication Factors	Provider or System Factors
Fears: disease worsening, hypoglycemia, needles, social stigma, weight gain	Complexity of the regimen (ie, >1 diabetes mellitus drug), splitting tablets, drawing insulin	Fear that patient will not be able to use therapy
Knowledge and skill: education Self-efficacy	Dose frequency (ie, ≥2 doses daily) Cost	Knowledge: medications, use of insulin, monitoring, diabetes treatment
Health beliefs	Adverse effects	Skill: able to demonstrate proper use of devices
Depression		Inadequate educational support
Lack of confidence in immediate or future benefits of the medication		Inadequate follow-up resources
Remembering doses and refills		

insulin omission/nonadherence. A systematic review of adherence with diabetes medications reported 62% to 64% of patients with T2DM were insulin adherent.[7] Inadequate use of insulin as recommended can contribute to worse glycemic control,[8,9] higher inpatient costs,[10] and early mortality.[11]

A 2009 Cochrane Collaboration examined the effectiveness of interventions for improving adherence to treatment recommendations in patients with T2DM.[12] They categorized those interventions as follows: nurse interventions that usually consisted of telephone follow-up; educational materials or reminders that are mailed to patients' homes; diabetes educational programs; pharmacy-based interventions that typically consisted of pill counts, the Medication Event Monitoring System (microchip cap-equipped bottle) comprehensive care, treatment adjustments, or prescription refill reminders; and dosing and frequency models that consisted of calendar blister packs and changes in doses to reduce the daily frequency of medications. The authors concluded from their review that changes in glycosylated hemoglobin levels "floated around the zero line" and that, for the most part, changes identified as statistically significant were rarely clinically significant, leading them to assert that such interventions are unable to produce consistent and homogeneous effects given the complexity of diabetes, and that "diabetes management is indeed much more than taking medication alone." Nevertheless, one of the studies evaluated in the review compared use of oral chlorpropamide intake with insulin injections by using a randomized crossover design. The proportion of patients taking at least 80% of the prescribed medication was similar in both groups; however, patients preferred the orally administered therapy to injectable insulin.[13] Although use of chlorpropamide (a long-acting sulfonylurea) is no longer recommended, this study provides evidence that patients prefer a noninjectable alternative over subcutaneously delivered insulin, even when the alternative carries a risk of severe adverse effects, including long episodes of hypoglycemia.

From published data and anecdotal evidence collected through patient care, it is clear that an alternative means of administering exogenous insulin is needed that rapidly controls blood glucose levels, avoids the "hypoglycemic cliff," and contributes to a patient experience that is not unpleasant, painful, or considered putative. Before prescribing insulin, providers will consider patients' likelihood to use insulin therapy as recommended, basing their consideration on factors such as patient cognition and likelihood to understand dosing complexity, history of adherence with oral antidiabetes medications and other therapies, and patients' self-assessment regarding their likelihood to accept the recommendation to use insulin. A patient's financial capabilities should also be taken into consideration, including whether