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Challenges in Diabetes Management: Glycemic Control, Medication Adherence, and Healthcare Costs

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THE CURRENT STATE OF DIABETES MANAGEMENT: CHALLENGES AND UNMET NEEDS

The Growing Burden of Diabetes

Diabetes affects approximately 29.1 million Americans (9.3% of the US population), according to National Health and Nutrition Examination Survey (NHANES) data from 2012.[1] This number accounts for approximately 21.0 million diagnosed and 8.1 million undiagnosed individuals; in other words, 27.8% of people with diabetes in the United States have yet to be diagnosed.[1]

Healthcare costs associated with diabetes are high. In fact, the average cost of healthcare for patients with diabetes is 2.3 times higher than for patients without diabetes (based on 2012 estimates).[1] Direct healthcare expenditures associated with diabetes were estimated at $176 billion in 2012, with additional costs due to loss of productivity related to chronic disability and premature mortality representing an additional $69 billion, for a total of $245 billion in healthcare expenditures attributed to diabetes.[1,2]

At the 2017 Asembia Specialty Pharmacy Summit, a special presentation addressed key challenges in the current state of diabetes management and considered potential approaches to improve outcomes. Jay Skyler, MD, MACP, professor of medicine, pediatrics, and psychology in the Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, University of Miami Miller School of Medicine, led the discussion. He began by emphasizing the growing prevalence of diabetes: "In the United States, diabetes is projected to affect more than 40 million people by 2034." Skyler emphasized that complications associated with diabetes are related to poor metabolic control. He alo noted that the increasing prevalence of diabetes in America is "driven by obesity and a sedentary lifestyle."

Complications and the Importance of Glycemic Control in Diabetes

Diabetes is associated with many complications, notably macrovascular and microvascular diseases, which include cardiovascular disease (CVD) (eg, coronary artery disease, stroke, high levels of low-density lipoprotein cholesterol [LDL-C]) and peripheral vascular disease (PVD), which may lead to amputation.[1] Diabetes causes about 60% of nontraumatic lower-limb amputations for individuals 20 years or older.[1] Microvascular complications of diabetes also commonly include end-stage renal disease (ESRD) and retinopathy.[1] Diabetes was the primary cause of kidney failure in 44% of all new cases in 2011, and in 2005-2008, 4.4% of people with diabetes 40 years or older had advanced diabetic retinopathy, which could lead to severe vision loss.[1]

Given the prevalence and severity of complications associated with diabetes are associated with imbalanced blood glucose, achieving glycemic control is an important step in diabetes management. During this presentation, barriers to glycemic control and improvements for modifications diabetes management was a key topic of discussion. Glycemic control is typically measured by glycated hemoglo-

Table 1. Relationship Between Glycemic Control and Diabetes Complications[4]

Complication	Percentage decrease per 1% reduction in A1C (95% CI)	*P*
Any diabetes complication	21 (17-24)	<.0001
Diabetes-related mortality	21 (15-27)	<.0001
All-cause mortality	14 (9-19)	<.0001
Fatal and nonfatal MI	14 (8-21)	<.0001
Fatal and nonfatal stroke	12 (1-21)	.035
Microvascular disease	37 (33-41)	<.0001
Cataract extraction	19 (11-26)	<.0001
Amputation or death from PVD	43 (31-53)	<.0001
HF	16 (3-26)	.016

HF indicates heart failure; MI, myocardial infarction; PVD, peripheral vascular disease.
Adapted from Stratton IM, Adler AI, Neil HA, et al. *BMJ*. 2000;321(7258):405-412.

Table 2. Proportions of Commercially Insured Patients with Diabetes Achieving A1C Targets in 2015[8]

A1C target	Patients with HMO plans achieving target (%)	Patients with PPO plans achieving target (%)
<7%	36.7	32.6
<8%	55.3	46.6
>9%	33.8	44.3

HMO indicates health maintenance organization; PPO, preferred provider organization.
Adapted from the National Committee for Quality Assurance website. www.ncqa.org/report-cards/health-plans/state-of-health-care-quality/2016-table-of-contents/diabetes-care. Accessed June 2017.

bin (A1C) testing. A1C reflects glycemia over a period of approximately 3 months and has strong pre dictive value for diabetes-associated complications—in other words, increased levels of A1C are associated with higher risk of these complications in patients with diabetes.[3] As such, the American Diabetes Association (ADA) recommends that A1C testing be performed regularly, every 3 months, in patients with diabetes to determine whether glycemic targets have been reached and sufficiently maintained.[3]

The ADA-defined target goal for adult patients with diabetes is A1C of <7% (53 mmol/mol).[3] However, providers may suggest more stringent target goals (such as <6.5% [48 mmol/mol]) for select patients, such as those with short duration of diabetes, type 2 diabetes managed with lifestyle changes or metformin therapy only, long life expectancy, or no significant CVD.[3] In contrast, less stringent A1C goals (such as <8% [64 mmol/mol]) may be appropriate for patients with advanced complications, extensive comorbidities, or difficulty achieving A1C target levels despite appropriate diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents (eg, insulin).[3]

As mentioned, poor glycemic control in diabetes is strongly correlated with several potentially life-threatening complications, and with higher mortality as well. In a prospective observational study, diabetes-related mortality and all-cause mortality were both strongly associated with glycemia (*P* <.0001).[4] Furthermore, reductions in risk of diabetes complications were associated with a 1% reduction in A1C from baseline. There was a particular reduction in risk for microvascular endpoints, amputation, or death from PVD more so than for heart failure (HF), myocardial infarction (MI), or stroke (**Table 1**[4]).[4]

A meta-analysis of observational studies reported a moderate increase in cardiovascular risk with increasing A1C levels in people with diabetes. The pooled relative risk (RR) for total CVD in persons with type 2 diabetes was 1.18 (95% CI, 1.10-1.26) for each 1% increase in A1C. For the studies that examined A1C and stroke risk in people with diabetes, the pooled RR was 1.17 (95% CI, 1.09-1.25). The pooled RR for the studies of A1C and PVD in people with diabetes was 1.28 (95% CI, 1.18-1.39).[5]

In the United Kingdom Prospective Diabetes Study (UKPDS), an intensive approach was used to study glycemic control in patients with diabetes. Patients achieved median A1c reduction of 11% over the first 10 years, and the frequency of some clinical complications of type 2 diabetes decreased.[6] Patients assigned intensive treatment had a significant 25% risk reduction in microvascular end points (which included ESRD and retinopathy; *P* = .0099) compared with conventional treatment, most of which was due to fewer cases of retinopathy. The reduction in risk for MI was of borderline significance (*P* = .052).[6]

Achieving and maintaining glycemic control in patients with diabetes is of paramount importance to their overall health and survival. However, patients with diabetes often struggle to achieve glycemic control and recommended A1C targets. Among adults with diagnosed diabetes included in the NHANES 2007-2010 analysis, half (52.2%) of the study population had achieved the A1C goal of <7%. Even the proportion of patients achieving the less stringent goal of <8% was suboptimal (79.1% of the study population).[7] Real-world data from 2015 have also shown that patients with diabetes often fail to achieve glycemic control (**Table 2**[9]).[9] For example, less than 40% of commercially insured patients with diabetes achieved A1C targets of <7%.[8]

Skyler commented on the data presented above: "Regardless of commercial HMO [health maintenance organization] or Medicaid, 40% or less achieve an A1C goal of <7%. If you raise the target to 8% (which is not ideal, but used for assessment), <60% of patients are reaching the goal. Achievement rates are not changing over time despite these medications. That's the worry; people are doing something and yet nothing is happening."

While glycemic control is of great importance in patients with diabetes, Skyler noted that other measures carry significance as well. He stated that it is crucial to "not only consider A1C goals, but goals of blood pressure and LDL-C. We call these the ABC goals." Patients often struggle to meet these goals as well. According to NHANES 2007-2010 data, one-third to half of participants did not meet the targets for A1C level, blood pressure, or LDL-C level by 2010; only 14.3% of patients met the targets for all of these risk factors.[7] Said Skyler, "These are [key] contributors to the 4-fold increase in risk of heart disease among patients with diabetes compared with the general population."

Healthcare Costs Associated With Poor Glycemic Control

Diabetes-related healthcare costs are higher for patients with poor glycemic control compared with patients achieving and sustaining target A1C goals. A strong association between glycemic control and diabetes-related costs was found in an analysis of medical and pharmacy claims from a cohort of patients with diabetes (N = 6780).[9] Annual diabetes-related costs for patients with uncontrolled A1C levels (>7%) were 32% higher than for patients whose A1C levels were on target (≤7%).[9] Of course, diabetes-related complications are significant contributors to patient healthcare costs; an elevated risk of complications (eg, retinopathy, PVD) in patients whose A1C levels were not on target was observed.[9] In a longitudinal analysis, costs of direct medical care and prescription medications for patients with type 2 diabetes with controlled glycemia (A1C ≤7%) were significantly lower (P <.05) than in patients with poor glycemic control (A1C >9%).[10]

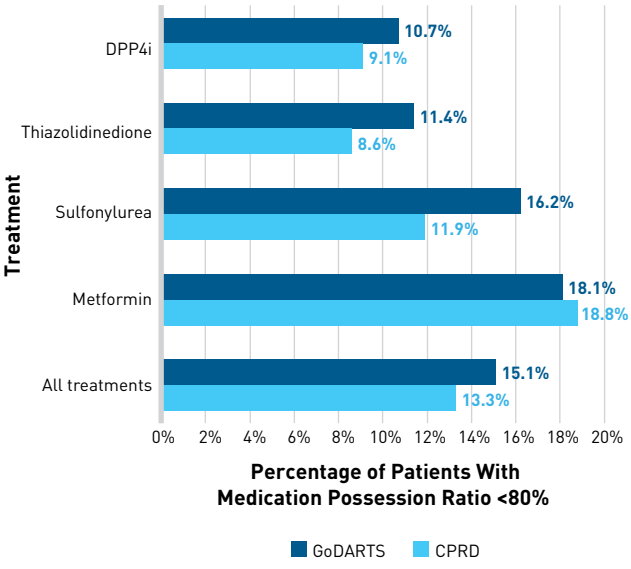
Key Challenges and Unmet Needs in Diabetes Management

Suboptimal A1C control rates persist despite the development of new therapies indicated for the treatment of diabetes. Skyler remarked, "[Over the] last 2 decades, as we try to tackle the disease, there have been more than 40 new diabetes treatment options approved by the US Food and Drug Administration; yet, despite that, there has been very little change in A1C and the proportion of patients who have achieved [glycemic] control." According to Skyler, key contributors to the lack of improvement in glycemic control include the complexity of diabetes treatment regimens and insufficient convenience of use for certain medications, which result in deficient patient adherence to medication.

Poor patient adherence to diabetes medications is a well-identified challenge to achieving glycemic control or lowering A1C. Skyler noted that "medication[s] may be filled, but it doesn't mean that the patient takes them." A retrospective cohort study using community-acquired clinical data from the UK reported that 13% to 15% of patients were adherent to all diabetes medications (**Figure 1**[11]).[11] Importantly, there was a clear association between adherence to glucose-lowering treatment and the corresponding decrease in A1C. The association was found to be consistent across all commonly used oral diabetes drugs, and the findings were consistent between the 2 data sets examined (the Clinical Practice Research Database and the Genetics of Diabetes and Audit Research Tayside Study database). Nonadherent patients, or patients taking on average less than 80% of the intended duration of prescription medication, did not achieve glycemic control; nonadherent patients had approximately half of the expected reduction in A1c compared with adherent patients.[11]

Another retrospective cohort study, which utilized the US MarketScan Commercial and Medicare Supplemental health insurance claims databases (2009-2012), compared adherence and persistence among patients with diabetes initiating dipeptidyl peptidase 4 inhibitors (DPP4is), sulfonylureas, and thiazolidinediones (TZDs) over 1- and 2-year follow-up periods.[12] During 1-year follow-up, 47.3% of DPP4i initiators, 41.2% of sulfonylurea initiators, and 36.7% of TZD initiators were medication-adherent. During 2-year follow-up, these percentages decreased to 40.5%, 34.6%, and 27.9% for DPP4i, sulfonylurea, and TZD initiators, respectively.[12] A proposed explanation for the greater adherence to DPP4is observed in this study was the better tolerability profile of DPP4is compared with both sulfonylureas and TZDs; however, more data are needed to confirm this hypothesis.[12]

Figure 1. Medication Adherence by Diabetes Treatment From Baseline to 1 Year[11]

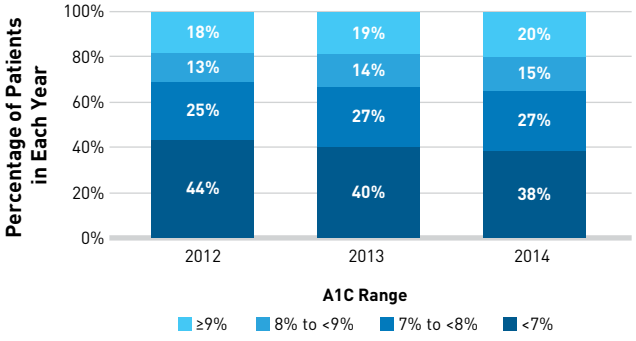


CPRD indicates Clinical Practice Research Database; DPP4i, dipeptidyl peptidase-4 inhibitors; GoDARTS, Genetics of Diabetes and Audit Research Tayside Study.

Additionally, a meta-analysis of published studies that examined adherence to prescribed oral antihyperglycemic agents in patients with type 2 diabetes found that the proportion of adherent patients ranged from 44.4% to 89.8%; the pooled mean proportion of adherent patients was 67.9% (95% CI, 59.6%-76.3%).[13] Furthermore, persistence estimates ranged from 41.0% to 81.1% with a mean of 56.2% (95% CI, 46.1%-66.3%), while discontinuation estimates ranged from 9.9% to 60.1%, with a mean of 31.4% (95% CI, 17.6%-45.3%).[13] Many different patient-, prescription-, and prescriber-related factors contribute to nonadherence to diabetes medications; these may include patient age, education, health beliefs, insurance coverage, out-of-pocket costs, prescription drug channel (mail vs retail), pill burden, regimen complexity and convenience, and prescriber specialty.[14-16] In any case, nonadherence places substantial health and economic burdens upon individuals and healthcare systems.

Skyler emphasized the costs and consequences associated with poor medication adherence and the resulting poor glycemic control. "Poor [medication] adherence and poor persistence translate to an increased risk of hospitalization, which tremendously adds to [direct medical] cost, [as well as] all-cause mortality rate, where there is a progressive increase of hospitalization with less adherence. Cost issues here are enormous," he said. In a recently published study of epidemiological and economic data for 184 countries, which Skyler highlighted during the presentation, the estimated global cost of diabetes

Figure 2. Patient Distribution by A1C Range, 2012-2014[a,14]



A1C indicates glycated hemoglobin.

[a]For patients with type 2 diabetes and A1c results in all 3 years.

Fitch K, Engel T, Pyenson B. Milliman website. www.milliman.com/uploadedFiles/insight/2017/Real-world-insights-Type-2-Diabetes.pdf. Published March 2017. Accessed May 2017.

for 2015 was $1.31 trillion (95% CI, $1.28-$1.36). Of note, indirect costs of diabetes (ie, labor-force dropout, absenteeism, presenteeism, and mortality) accounted for 34.7% (95% CI, 34.7%-35.0%) of the overall burden.[17] North America was the most affected region relative to gross domestic product as well as the largest contributor to global absolute costs; in other words, North America was found to have the highest absolute economic burden of diabetes.[17]

Numerous studies support Skyler's point. For example, in an analysis of claims data, Lau et al reported that patients nonadherent to oral diabetes medications in 2000 were at higher risk of hospitalization in 2001 (odds ratio [OR], 2.53; 95% CI, 1.38-4.64).[18] In a systematic review, 7 of 8 studies (87.5%) that evaluated hospitalization with respect to diabetes medication adherence showed a statistically significant association between higher levels of adherence and decreased hospitalizations. In fact, patients with <80% adherence may be at more than twice the risk for being hospitalized for a diabetes- or cardiovascular-disease–related event (OR, 2.53; 95% CI, 1.38-4.64); however, patients with ≥80% adherence ratios may be at a 29% decreased risk of hospitalization for any cause (OR, 0.71; 95% CI, 0.51-0.98) when adjusting for disease severity, demographics, and comorbidities.[19] A retrospective cohort study of patients in the Kaiser Permanente of Colorado diabetes registry determined that nonadherent patients had higher mean A1C, systolic and diastolic blood pressure, and LDL-C levels; higher all-cause hospitalization (P <.001); and higher all-cause mortality (P <.001) as compared with adherent patients with diabetes.[20]

As rising healthcare costs continue to be one of the biggest challenges facing our nation and the world, it is particularly important to identify areas where costs can be lowered and care improved for patients with chronic diseases like diabetes.[21] US medical claims data from 2005 -2008 suggest that improving and sustaining patient adherence to diabetes medications leads to a statistically significant estimated 13% decreased risk of hospitalization and emergency department (ED) visits (P <.001).[21] If nonadherent patients with diabetes became adherent to diabetes medication, it could save the United States an estimated $4.68 billion annually in healthcare expenditures ($3.95 billion in hospitalizations and $735 million in ED visits). On top of that, an added benefit of increasing the adherence would eliminate potential hospitalizations and ED visits and save an estimated $3.61 billion, for an a combined potential savings of $8.30 billion each year.[21]

ANALYSIS OF CHALLENGES IN DIABETES MANAGEMENT: REAL-WORLD INSIGHTS AND ECONOMIC CONSIDERATIONS

Analysis Overview: Objectives and Data Sources

Also at the 2017 Asembia Specialty Pharmacy Summit, Kathryn Fitch, RN, MEd, principal and healthcare management consultant for Milliman, Inc, led a discussion on the unmet needs in current diabetes management, and presented an analysis of key challenges in controlling glycemic targets and sustained A1C levels in patients with type 2 diabetes. This analysis, of which Fitch was lead investigator, offered real-world insights into the current state of glycemic control and diabetes medication adherence among commercially insured patients with type 2 diabetes.

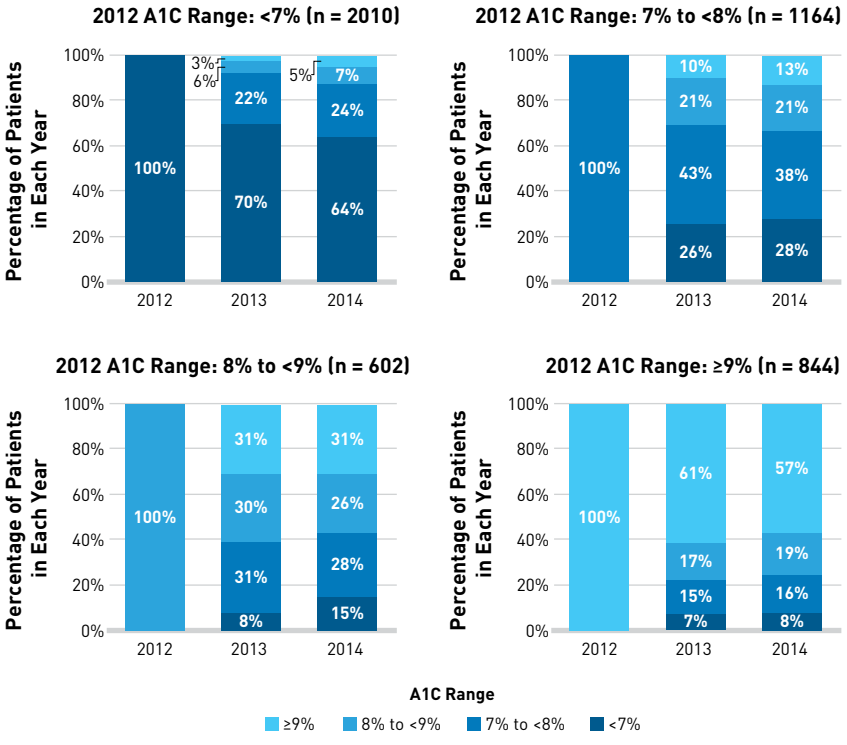
Fitch said, "The objective of this study was to understand the challenge of sustaining medication adherence. [We] collect[ed] 3 years of MarketScan A1C data linked to claims data in order to analyze trends in glycemic control and diabetes medication adherence." MarketScan Research Database medical and pharmacy claims data from 2012-2014 were analyzed for adult patients with type 2 diabetes.[14] This database contains paid claims from commercially insured patients with inpatient and outpatient healthcare services. These detailed patient claims allowed analysis of consistent patient information over time and enabled investigators to follow patients longitudinally as well as to observe treatment patterns. The data included MarketScan laboratory values of at least 1 A1C test annually during the 3-year analysis period.[14] Additionally, the investigators used the National Committee for Quality Assurance Healthcare Effectiveness Data and Information Set, which measures health plan quality outcome measures, including the following comprehensive diabetes care indicators: poor glycemic control defined as A1C >9.0%, glycemic control defined as A1C <8.0%, and glycemic control for selected populations (commercial and Medicaid) defined as A1C <7.0%.[14]

Trends in Glycemic Control in Patients With Diabetes

The first analysis showed that glycemic control was difficult to achieve and sustain over a 3-year period for patients with type 2 diabetes (**Figure 2**[14]).[14] Of 4620 eligible patients, 44% of patients with type 2 diabetes achieved glycemic control, meeting the target goal of A1C <7% in 2012. More patients failed to maintain target A1C levels during the following years, as the proportion of patients with target A1C at their annual measurement declined significantly to 40% in 2013 and 38% in 2014 (P <.001). In addition, the proportion of patients with uncontrolled A1C levels ≥7% increased significantly from 56% to 62% during the study period (P <.001).[14]

When the patient cohort was stratified by A1C range, investigators noted that patients with a higher A1C had greater difficulty achieving A1C control over time (**Figure 3**[14]).[14]For all patients with A1C levels <7% in 2012 (n = 2010), the proportion of patients able to sustain this control declined to 64% in 2014. Of the patients with uncontrolled A1C levels >7% in 2012, less than one-third of the patients in each cohort achieved glycemic control by 2014, indicating the challenge of achieving target A1C levels. This trended towards the least achievement among patients with highest glycemic index of ≥9% in 2012 (n = 844); the proportion of those patients meeting the target of <7% by 2014 was 8%. Similarly, of the patients with A1C measurements indicating moderate control between 7% to <8% (n = 1164) in 2012, 38% maintained the same level of control in 2014; only 28% of those patients achieved improvements in A1C levels in 2014.[14]As noted during the presentation, "A1C [that is] higher at the start [is] more difficult to control. [These data] show the challenge in achieving and sustaining [glycemic] control." Of the patient cohort in this analysis, 24% of patients had controlled A1C levels <7% in each of the 3 years compared with 42% of patients who never achieved A1C measures <7% (**Figure 4**[14]).[14]

Figure 3. Annual Changes in Patient Distribution According to the 2012 A1C Range[14]



A1C indicates glycated hemoglobin.

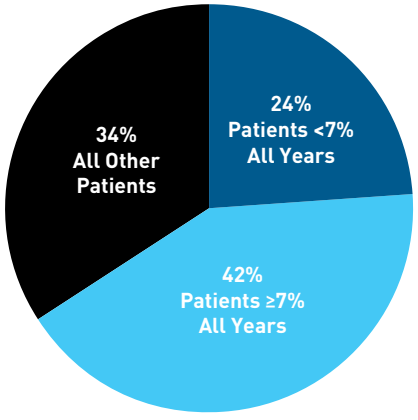
Fitch K, Engel T, Pyenson B. Milliman website. www.milliman.com/uploadedFiles/insight/2017/Real-world-insights-Type-2-Diabetes.pdf. Published March 2017. Accessed May 2017.

Trends in Diabetes Medication Adherence

From this study, investigators identified a subset of 4179 patients from the initial study population with type 2 diabetes with at least 1 annual measurement of A1C, and at least 1 claim for prescription diabetes medication annually, to assess medication adherence patterns and the influence of such patterns on trends in glycemic control across the 3-year study period.[14] Fitch pointed out that this analysis is unique because "the population of eligible patients had A1C levels measured all 3 years and used type 2 diabetes drugs [during this period], [enabling us] to observe [adherence] patterns over the full 3 years of data." Diabetes medication adherence rates were measured by the proportion of days covered (PDC) of the prescription claim, based on the prescription fill dates and number of days of medication supplied by the given prescription. This was calculated for each patient annually and stratified by agent class. The upper limit for adherence was established at PDC ≥80%, where <80% was considered nonadherent.[14]

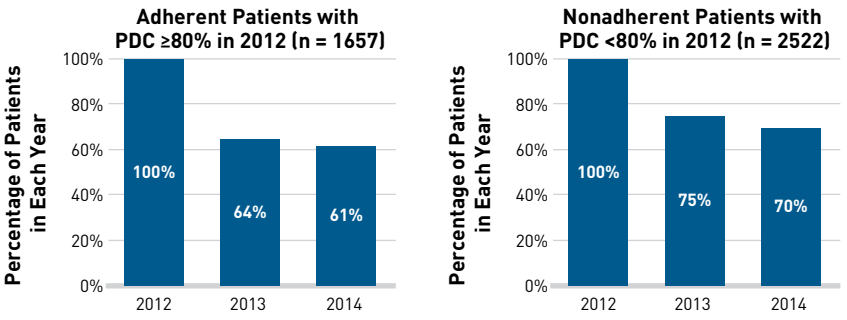
Similar to the difficulty in achieving and maintaining glycemic control, adherence to diabetes medication was a challenge in this patient population. The proportion of patients who were adherent to diabetes medications declined from 2012 to 2014 (**Figure 5**[14]).[14] Of the patients (n = 1657) who met the criteria for adherence (PDC ≥80%) in 2012,

Figure 4. Proportion of Patients with A1C <7%, 2012-2014[14]



A1C indicates glycated hemoglobin. Fitch K, Engel T, Pyenson B. Milliman website. www.milliman.com/uploadedFiles/insight/2017/Real-world-insights-Type-2-Diabetes.pdf. Published March 2017. Accessed May 2017.

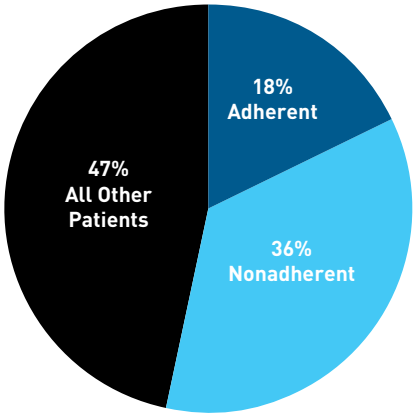
Figure 5. Annual Changes in Medication Adherence According to the 2012 Adherence Level[14]



PDC indicates proportion of days covered.

Fitch K, Engel T, Pyenson B. Milliman website. www.milliman.com/uploadedFiles/insight/2017/Real-world-insights-Type-2-Diabetes.pdf. Published March 2017. Accessed May 2017.

Figure 6. Proportion of Adherent Patients in All Years (2012-2014)[14]



Note: Numbers may not add up to 100% due to rounding.

Fitch K, Engel T, Pyenson B. Milliman website. www.milliman.com/uploadedFiles/insight/2017/Real-world-insights-Type-2-Diabetes.pdf. Published March 2017. Accessed May 2017.

64% and 61% maintained adherence in 2013 and 2014, respectively. Additionally, once patients were nonadherent, they were less likely to become adherent (Figure 4). Of the nonadherent patients (n = 2522), 75% and 70% remained nonadherent in 2013 and 2014, respectively.[3] In fact, only 18% of the study population was adherent to diabetes medication in every year of the analysis (**Figure 6**[14]).[14]

Trends in Healthcare and Pharmacy Costs Related to Diabetes

Healthcare costs related to diabetes were also evaluated. Fitch explained that the analysis "identified that patients with glycemic control had lower costs compared with those without glycemic control," supporting previous real-world and clinical investigations concluding that uncontrolled A1C influences healthcare costs in patients with type 2 diabetes.

Healthcare costs and A1C control were assessed in a population of adult patients (aged 18 to 64 years) with type 2 diabetes in 2014 (n = 36,233).[14] Investigators again used the MarketScan database to analyze medical and pharmacy claims data for diabetes-associated costs, and patients enrolled had at least 1 A1C laboratory assessment. Annual costs were evaluated per patient and were risk adjusted to account for differences in demographics and prevalence of chronic conditions associated with disease.[14] In 2014, healthcare costs were 8.1% higher for patients with A1C levels ≥7% ($17,428) compared with patients who had on-target A1C levels <7% ($16,119) ($P$ <.001).[14]

In addition, diabetes-related pharmacy costs for patients with inadequate glycemic control were higher than those for patients with on-target A1C levels. The annual costs per controlled or uncontrolled patient were similar across healthcare expenses; however, prescription drug costs for diabetes represented the largest difference between the cohorts. Claims from patients with A1C levels ≥7% were associated with a 120% higher diabetes-related pharmacy cost: $1490 in patients with controlled A1C <7% versus $3277 in patients with A1C ≥7%.[14] "What is interesting here is that the driver for difference in cost is diabetes prescription drugs; [we are] spending more on diabetes drugs for this cohort [with A1C] over 7% [who are] not achieving [glycemic] goals," Fitch emphasized.

Associations Between A1C Levels and Medication Adherence Patterns

The final analysis aimed to identify associations between A1C levels and medication adherence patterns in patients with type 2 diabetes. Using MarketScan claims and A1C laboratory data across the 3-year study period (2012-2014), the researchers analyzed a cohort of patients with type 2 diabetes (n = 79,933) and at least 1 claim for diabetes medication in the 6 months before having A1C measured. Investigators assigned each diabetes drug claim to 1 of the following drug classes: metformin, sodium-glucose cotransporter 2 inhibitor (SGLT2i), sulfonylurea and meglitinide, glucagon-like peptide-1 (GLP-1) receptor agonist, DPP4i, thiazolidinedione, and insulin.[14]

Investigators created the concept of "A1C episodes" (which were defined by the A1C measurement within a 6-month treatment period) to reflect the state of glycemic control and direct impact of medication adherence on A1C level. For this cohort, a total of 191,331 episodes of A1C measurements were analyzed. Additionally, investigators extended the review of medication use over 9 months (adding 3 months before the adherence period of measure) to assess prior use of a drug class and determine adherence.[14] Fitch stated that they "wanted to reflect, as close as possible, the adherence behavior in the time period measured by A1C measures."

Among all episodes, 40% (n = 75,823) were defined by A1C levels meeting the target of <7%, 66% of episodes had A1C levels <8% (n = 125,157), and 20% of episodes had A1C levels ≥9% (n = 38,524).[14] When listed by A1C level, patients with controlled A1C level episodes were found in episodes of adherence. Specifically, a total of 54% of episodes with A1C levels <7% met the criteria for adherence (PDC ≥80%); only 36% of episodes with A1C levels ≥9% met those criteria.[14]

Of the adherent episodes (PDC ≥80%; n = 93,880), 44% were associated with glycemic control (A1C <7%), while in comparison, 36% of the nonadherent episodes (PDC <80%; n = 97,451) were associated with this glycemic level (*P* <.001). Uncontrolled glycemic levels were more common in episodes of nonadherence, as 25% of the nonadherent episodes were associated with A1C ≥9% compared with a significantly smaller proportion (15%) at this A1C level in episodes with adherence (*P* <.001).[14] These comparisons are shown in **Figure 7**[14].

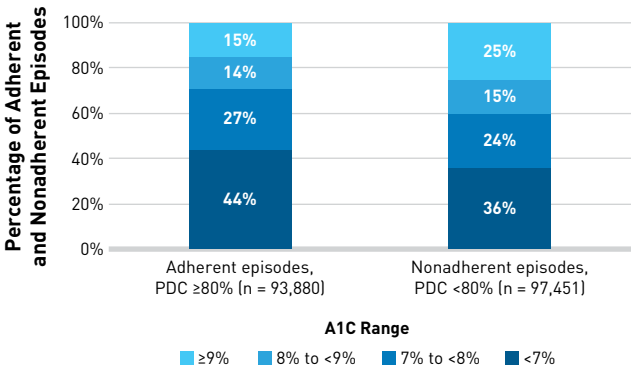
Mode of Administration and Medication Adherence Patterns

Episodes were further analyzed by the mode of administration of diabetes medication; 10% of episodes were associated with injectable therapy (GLP-1 receptor agonist and/or insulin), oral medication only was associated with 65% of episodes (metformin, SGLT2i, sulfonylurea and meglitinide, DPP4i, TZD), and oral plus injectable therapies were associated with 25% of episodes.[14] Importantly, the complexity of diabetes treatment regimen was found to contribute to lower rates of diabetes medication adherence.[14] Fitch stated, "When we looked at type of drug and association, we identified that more complex diabetes regimens were associated with higher nonadherence rates."

Compared with other diabetes medications, oral only episodes had significantly higher adherence (53%) versus injectable only episodes (43%) (*P* <.001). The combination of oral and injectable episodes, considered a more complex drug regimen, had the lowest adherence (40%) (**Figure 8**[14]).[14] These findings are consistent with the literature. In a retrospective analysis of 11 studies of patient adherence to oral diabetes therapy regimens, decreasing adherence was related to multiple daily dosing schedules and multiple therapies as compared with monotherapy regimens.[22] In other words, patients with diabetes were more adherent to monotherapy versus combination therapy, as a higher proportion of patients on monotherapy regimens achieved ≥90% adherence rates (defined as the proportion of doses taken as prescribed).[22] An analysis of cross-sectional survey data also found treatment complexity to be directly related to nonadherence to diabetes medications (*P* <.05).[23] In short, complex regimens are a barrier to patient adherence.

In an investigation of the relationship between these administration modes and adherence to medication, each 10% increase in PDC was found to result in an approximately 0.12% decrease in A1C level with the use of any diabetes therapy. Using the complex combination of oral and injectable therapy, each 10% increase in PDC was associated with a significant 0.17% decrease in A1C level (*P* <.001).[14] These real-world data support previously reported data that established correlations between diabetes medication adherence and improvement in A1C. Schectman et al reported that each 10% increase in adherence to diabetes medication improved glycemic control (by decreasing A1C level) by 0.16% (*P* <.0001).

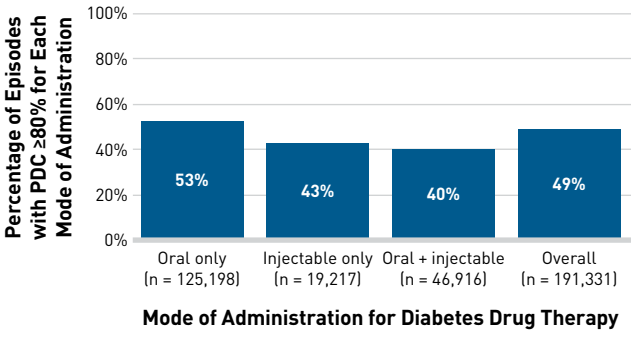
Figure 7. Comparison of A1C Levels Between Adherent and Nonadherent Episodes[14]



A1C indicates glycated hemoglobin; PDC, proportion of days covered.

Fitch K, Engel T, Pyenson B. Milliman website. www.milliman.com/uploadedFiles/insight/2017/Real-world-insights-Type-2-Diabetes.pdf. Published March 2017. Accessed May 2017.

Figure 8. Percent of Episodes Exhibiting Adherence (PDC ≥80%) by Mode of Administration for Diabetes Drug Therapy[14]



PDC indicates proportion of days covered.

Fitch K, Engel T, Pyenson B. Milliman website. www.milliman.com/uploadedFiles/insight/2017/Real-world-insights-Type-2-Diabetes.pdf. Published March 2017. Accessed May 2017.

For oral drugs specifically, each 10% increment in adherence resulted in 0.19% lower A1C levels (*P* <.0001). Also, more intensive therapy (ie, a larger number of oral agents and insulin use) was associated with higher A1C levels.[24] Similarly, Rozenfeld et al found that each 10% increase in adherence to oral diabetes medications was associated with a 0.1% decrease in A1C level (*P* = .0004).[25] An analysis of claims data revealed that a 10% increase in nonadherence to metformin and statins was associated with an increase of 0.14% in A1C in patients with diabetes.[26] A cohort study of American veterans with type 2 diabetes reported that mean A1C levels decreased by 0.24% for each 10% increase in medication possession ratio (95% CI, −0.27% to −0.21%; *P* <.001).[27]

As discussed earlier, higher risk of diabetes-related complications comes with poor glycemic control. As such, better adherence to diabetes medications and improvement in glycemic control will likely improve patient outcomes of diabetes complications.

CONCLUSION

Addressing the Challenges and Unmet Needs in Diabetes Management

In summary, the data from this real-world analysis highlighted the challenges and unmet needs in the current state of diabetes management. To conclude the special presentation given at the 2017 Asembia Specialty Pharmacy Summit, Fitch reiterated, "Glycemic control and diabetes medication adherence are suboptimal and difficult to sustain over time. Higher A1C levels are associated with higher [healthcare] costs." Thus, key questions include, "What can we do about this? Can we investigate other classes of drugs that will work in diabetes? What are the barriers to [glycemic] control and adherence?" She believes the findings of this real-world analysis present an opportunity to address outcomes, which continue to lag despite improvements in diagnosis and the increasing variety of treatment options.

One notable reason for the lack of adherence is the issue of complex multidrug regimens that hinder patients from taking diabetes medications as prescribed. Many factors affect poor glycemic control and poor diabetes medication adherence, which Skyler described as "lack of integrated care [and] clinical inertia among healthcare providers." Skyler pointed out, "One of the main issues here is that clinicians are not active in a prompt way. Type 2 diabetes patients remain in poor [glycemic] control for many years before intensification of therapy." He noted that regular follow-up in these patients is needed for appropriate management to ensure that treatment is of adequate intensity, and to develop a personalized, sustainable target goal for every individual. As healthcare continues to evolve, it is important to consider nontraditional approaches to diabetes management, perhaps in the form of disruptive therapies and technologies that revolutionize the way medications are delivered in order to improve patient outcomes. •

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