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A Comparison of Data Driven-based Measures of Adherence to Oral Hypoglycemic Agents in Medicaid Patients

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Abstract

Objective: Using observational clinical data from our local operational health information exchange, we evaluated different methods for measuring adherence to Oral Antihyperglycemic Agents (OHA) in patients with Type 2 diabetes. The primary objective is to compare different OHA adherence measures based on their associations with glycated hemoglobin A1c (HbA1c) levels. The secondary objective is to examine the relationship between patient demographic and clinical characteristics and HbA1c level.

Methods: An observational sample of 831 Medicaid patients with Type 2 diabetes who had HbA1c test results recorded between January 1, 2001 and December 31, 2005 was identified in the Indiana Network of Patient Care (INPC). OHA adherence was measured by medication possession ratio (MPR), proportion of days covered (PDC), and the number of gaps (GAP) for 3, 6, and 12-month intervals prior to the HbA1c test date. The associations between these nine OHA adherence measures and HbA1c levels were examined and compared using mixed effects generalized linear models. Patient age, gender, race, duration of OHA treatment, number of concurrent OHAs, and OHA class were used to control the possible confounders in the analyses.

Results: All three OHA adherence definitions showed consistent and significant association with HbA1c control. Unadjusted coefficients ranged -0.98 to -1.07 for PDC, -0.90 to -0.92 for MPR, and 0.25 to 0.19 for GAP. The 6-month PDC showed the strongest association with HbA1c levels in both unadjusted (-1.07, $p<0.0001$) and adjusted (-1.12, $p<0.0001$) models.

Conclusion: Better OHA adherence is significantly associated with lower HbA1c level in Medicaid patients with Type 2 diabetes. The 6-month PDC is more highly correlated with the outcome than other OHA adherence measurements.

Keywords: Adherence measures; Oral hypoglycemic agents; Glycemic control; Type 2 diabetes; Claim database; Medicaid; Health information exchange

What is Already Known about this Subject?

- Medication adherence can be objectively estimated by medication possession ratio (MPR), proportion of days covered (PDC), and gap (GAP).
- Different time frames (3-month, 6-month, or 12-month) are commonly used to measure adherence.
- Adherence to Oral hypoglycemic Agents (OHA) is correlated with glycemic control in patients with Type 2 diabetes.

What this Study Adds?

- This study documents the strength of association between HbA1c levels and nine OHA adherences using three different adherence definitions (PDC, MPR, and GAP) across three time intervals (3, 6, and 12 months) by utilizing longitudinal real-world data from an operational Health Information Exchange.
- The 6-month PDC is most highly correlated with the HbA1c levels. Among patient factors, age, African-Americans ethnicity, number of concurrent OHA medications, and Sulfonylurea treatment were all significantly correlated with HbA1c level.

Background

Medication non-adherence is a major problem in health care, especially among patients with chronic conditions like diabetes, which has estimated non-adherence rates between 36%- and 87% [1]. Non-adherence to prescribed oral antihyperglycemic agents (OHA) can cause serious consequences to diabetic patients, with higher rates of micro- and macro-vascular complications, increased emergency medical events and a higher mortality rate [2]. In addition, the costs of poor medication adherence for all conditions are estimated at hundreds of billions of US dollars per year [3]. Despite the known consequences, one study reported that the medication adherence rate for patients with diabetes has not improved for over 30 years [4].

Although an effective adherence intervention may have a greater effect on population health than many other medical treatment improvements [5], information about patients' adherence is usually not available to health care professionals. Patient self-reported medication adherence is sometimes used to estimate patient medication taking behavior, but they are subject to recall bias and do not correlate well

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with other methods of assessing adherence [6,7]. While successful interventions have combined convenient care, information, reminders, self-monitoring, and counseling [8], studies also suggest that developing a data-driven approach to better measure adherence and initiating interventions in clinical practice can potentially improve both adherence and clinical outcomes [9], An accurate assessment of OHA adherence and understanding its association with glycated hemoglobin A1C (HbA1c level), which is one of the objective measures of glycemic control for diabetic patients, is the first step towards improving OHA adherence.

The definition of adherence varies, and there is no consensus on the best method of measurement. The medication possession ratio (MPR) reflects the patient's overall accordance with the prescribed dosing regimen and disregards the timeliness of particular refills. On the other hand, both the proportion of days covered (PDC) and the gap (GAP) focus on duration or continuation of prescribed treatment, and they both take the timeliness of each refill into account [10]. In addition, different time frames are used to measure adherence; the most frequently used is 12-months [11]. However, some studies showed significant improvement in health outcomes if patients have good medication adherence in 3-month or 6-month intervals. In order to identify the most helpful feedback to physicians, the adherence measures that are best correlated with the HbA1c level, PDC, MPR, and GAP across different intervals should be analyzed and compared.

Previous studies have demonstrated the significant association between OHA adherence and HbA1c level in clinical trials or specific diabetes management programs [12-14]. However, the subjects of these studies were followed for short periods of time or they were informed that their medication use was being monitored. The extent to which these design features affect the validity of study findings remains unclear. As a result, conclusions drawn from these studies provide somewhat limited insight into the long-term effectiveness of drugs in real-world populations and settings.

In order to identify the measure of patient adherence best suited for providing feedback to physicians, we undertook a study using data from a population-based health information exchange (HIE). We calculated OHA adherence using three different measures (PDC, MPR, and GAP) across three time intervals (3, 6, and 12 months) utilizing longitudinal HIE data. We also analyzed and compared the effects of these objective adherence measurements and patient factors on HbA1c level based on laboratory test results from our local, operational HIE.

Methods

Data sources and settings

We extracted patient information from Indiana Medicaid data which contained demographic (race, gender and age), diagnosis, and treatment information over time. The OHA prescription claims records include refill dates, days of supply, dose, and frequency. HbA1c test results were retrieved from the Indiana Network of Patient Care (INPC). The INPC is an operational regional clinical informatics network that has served Indianapolis for more than fifteen years (and now includes more than 90 Indiana hospitals and more than 22,000 physicians among its members). This system delivers medical record information from hospitals, laboratories, imaging centers, pharmacies, and physician offices, including registration records, laboratory tests, radiology reports, diagnosis and administrative data [15]. The claims-based medication dispensing data was linked to the INPC laboratory data by medical record number. The medical record number is assigned to patients once they visit any facility in the INPC institutions, such as hospitals, laboratories, and clinics. This study was approved by the Institutional Review Board of Indiana University and the INPC Management Committee.

Eligibility criteria

The study sample was limited to patients with Medicaid coverage who were prescribed an OHA and who had HbA1c data in the INPC. Inclusion criteria were established as follows for the study period January 1, 2001 through December 31, 2005:

1: 18-64 years old in Indiana Medicaid data during the study period.

2: Have at least one *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD_9_CM) code for Type 2 diabetes (250.X0 or 250.X2) in Medicaid claims for either inpatient or outpatient encounters.

3: Have at least one First Databank *Standard Therapeutic Code* (STC: 71) for OHAs: Biguanides, Sulfonylurea (SU), Thiazolidinedione (TZD) and other OHAs (Meglitinides and α-glucosidase) in Medicaid medication claims.

4: Does not take fixed-combination OHA regimens.

5: Does not take insulin (STC: 0177).

6: Have a medical record number in the INPC from one of the major hospital systems in Central Indiana.

7: Have at least one HbA1c test result from the INPC during the study period.

8: Have at least one OHA prescription prior to HbA1c test date.

Measurements

The independent variable, medication adherence, was measured by calculating PDC, MPR, and GAP. PDC is defined as the total number of medication-covered days divided by the number of days in a certain time period. PDC can be calculated if a subject has even one fill and has been used increasingly to measure patient medication adherence for quality assurance [16]. MPR is commonly calculated as the total number of days supplied by all refills divided by the number of days between the first and last refill, and it usually requires at least two refills date to be calculated [17] Both PDC and MPR range from 0 to 1. GAP assesses any lapse in medication therapy. GAP is measured in days with various lengths where 30 days is considered significant enough to cause suboptimal clinical outcomes [16]. Both MPR and GAP need at least two refill dates to be calculated.

The dependent variable was the patient HbA1c level based on the INPC laboratory test results. To dynamically and accurately reflect the effect of OHA adherence on HbA1c level, we defined the HbA1c test date as the index date, and then traced back the patient medication adherence prior to this index date. For each patient, MPR, PDC, and GAP were calculated for 3-month, 6-month, and 12-month intervals prior to each HbA1c test date. For patients who were taking multiple OHAs, the average adherence was counted to reflect the overall medication taking behavior.

In order to control for possible confounders which may influence patient HbA1c levels, [18,19] we analyzed age, gender, race, duration of OHA treatment, and number of concurrent OHAs. The prescribed OHA drug classes included Biguanides, Sulfonylurea, Thiazolidinedione, other OHAs, and multiple classes.

Statistical analysis

Levels of patients' medication adherence were assessed through three different metrics: PDC, MPR, and GAP, measured over 3, 6, and 12-month intervals. Average HbA1c values were calculated and reported. We examined the associations between HbA1c level and various adherence metrics using mixed effect generalized linear regression models. Random subject effects were used in these models to accommodate the potential association among observations contributed by the same study subjects. All analyses were implemented using SAS 9.1 (*SAS Institute, Gary, North Carolina*). p values less than 0.05 were considered significant.

Results

Demographic and clinical characteristics

A total of 831 subjects met all inclusion and exclusion criteria. Patient characteristics are outlined in Table 1. The average entry age of study subjects was 48 years. Female subjects accounted for 68.7% of the sample. The average HbA1c level of the study population was 7.60% (95% CI: 7.58%-7.71%). The average duration of OHA treatment was 2.09 years. The average number of HbA1c tests was 3.5 per patient. The majority of the study sample (61.0%) was taking one medication: 27.0% were prescribed Biguanides, 25.8 % SUs, 3.0% TZDs and 5.3% other drugs. More than one OHA was being taken by 39.0% of patients; such patients had a slightly lower HbA1c level than patients who were treated by SU only.

	Number of Subjects (Percentage)		HbA1c (%)	
	(n=831)		Mean	(95% CI)
Demographics				
Age (year)				
18-30	71	(8.54%)	7.98	(7.64-8.31)
31-40	150	(18.05%)	7.87	(7.66-8.07)
41-50	295	(35.49%)	7.62	(7.52-7.73)
51-64	314	(37.78%)	7.53	(7.44-7.63)
Gender				
Female	570	(68.69%)	7.66	(7.57-7.73)
Male	261	(31.31%)	7.62	(7.51-7.73)
Race				
African-American	371	(44.64%)	7.88	(7.79-7.98)
Hispanic	7	(0.80%)	7.78	(6.90-8.63)
Asian	4	(0.48%)	6.55	(6.20-6.90)
Other	11	(1.30%)	6.98	(6.45-7.50)
White	438	(52.70%)	7.42	(7.33-7.51)
Diabetes Severity				
Duration of OHA Treatment (Year)				
0-3	514	(61.85%)	7.60	(7.51-7.69)
3-6	241	(29.00%)	7.61	(7.49-7.72)
6-9	76	(9.15%)	7.97	(7.77-8.17)
Number of concurrent OHAs				
1	507	(61.01%)	7.29	(7.18-7.41)
2	253	(30.44%)	7.87	(7.75-7.99)
>=3	71	(8.55%)	7.98	(7.75-8.22)
OHA Classes				
Biguanides Only	224	(26.96%)	7.54	(7.42-7.67)
Sulfonylurea Only	214	(25.75%)	7.80	(7.69-7.97)
Thiazolidinedione Only	25	(3.00%)	7.66	(7.45-7.87)
Other	44	(5.29%)	6.81	(6.08-7.53)

Table 1: Summary of selected characteristics of subjects and their hemoglobin A1c.

Adherence	3-months		6-months		12-months	
	Mean (95 CI)	Freq	Mean (95 CI)	Freq	Mean (95 CI)	Freq
PDC	0.60 (0.59-0.61)	2,795	0.51 (0.49-0.52)	2,838	0.39 (0.38-0.41)	2,934
MPR	0.85 (0.84-0.86)	1,721	0.82 (0.81-0.83)	2,117	0.79 (0.78-0.80)	2,336
GAP	0.13 (0.12-0.14)	1,721	0.18 (0.16-0.20)	2,117	0.25 (0.24-0.28)	2,336

PDC: Proportion of Days Covered; MPR: Medication Possession Ratio
Freq =Frequency
PDC and MPR ranged from 0 to 1, and GAP ranged from 0 to 5

Table 2: Patient adherence measures mean value and the 95% confidence interval across three time intervals.

Adherence	3-months		6-months		12-months	
Unadjusted estimate						
PDC	-0.98	(-1.20, -0.76)	-1.07	(-1.28, -0.87)	-1.01	(-1.21, -0.81)
MPR	-0.51	(-0.94, 0.07) †	-0.92	(-1.29, -0.56)	-0.90	(-1.20, -0.59)
GAP	--	--	0.25	(0.12, 0.38)	0.19	(0.11, 0.29)
Adjusted estimate						
PDC	-0.89	(-1.12, -0.67)	-1.12	(-1.35, -0.91)	-1.20	(-1.42, -0.96)
MPR	-0.29	(-0.72, 0.14) †	-0.68	(-1.06, -0.32)	-0.87	(-1.19, -0.55)
GAP	0.19	(-0.002, 0.39) †	0.05	(-0.10, 0.20) †	0.05	(-0.06, 0.17) †

PDC: Proportion of Days Covered; MPR: Medication Possession Ratio
-- data did not converge
† *p*-value is greater than 0.05. *p*-value for any other unadjusted coefficients is smaller than 0.05

Table 3: Unadjusted and adjusted coefficients and 95% confident intervals between OHA adherence and HbA1c control.

OHA adherence, other covariates, and their association with hba1c control

From January 1, 2001 to December 31, 2005, a total of 1,721 to 2,934 observations of OHA adherence and HbA1c results were formed for 831 subjects. Table 2 summarizes frequency and average value of adherence (PDC, MPR and GAP) at time intervals of 3, 6, and 12-months. The average adherence ranged from 39% to 85%. In unadjusted analyses, all three OHA adherence measurements for 6 or 12 months showed consistent and significant associations with HbA1c control. In adjusted analyses, PDC and MPR measured for 6 or 12 months were significantly correlated with HbA1c. The 6-month PDC showed the greatest association with HbA1c control in both unadjusted and adjusted analyses (Table 3).

We additionally estimated the effects of patient characteristics and treatment status on HbA1c levels. Among patient factors, increased age was correlated with better HbA1c control ($p<0.0001$). African-Americans had a higher average HbA1c level as compared with Whites ($p<0.0001$). The associations between number of medications and HbA1c level were about 0.41 ($p<0.0001$). Compared with patients treated with multiple OHA classes, patients treated with SU had slightly higher HbA1c levels ($p<0.0001$). Gender and duration of OHA treatment had no effect on HbA1c level.

Discussion

We have two main findings from this study. First, increased PDC and MPR are strongly correlated with lower HbA1c level while increased GAP relates to higher HbA1c level. Second, across different adherence measures and different time frames, 6-month PDC is more correlated with HbA1c level than other measures in both unadjusted and adjusted models.

The primary goal for this study is to analyze and compare associations between measurements of OHA adherence and HbA1c level among patients with Type 2 diabetes using real-world clinical data. In most cases (except in the 3-month models), PDC and MPR produced significant negative coefficients with HbA1c level, meaning that increased PDC or MPR is related to decreased HbA1c level. On the other hand, GAP produced positive coefficients, which means that increased GAP is associated with increased HbA1c level. The coefficients in the unadjusted model indicated that a 10% increase in PDC/MPR is related to a 0.09-0.10% reduction in HbA1c. In contrast, an increase in GAP of one is correlated with a 0.19-0.25% increase in HbA1c level. The adjusted model demonstrated similar results except that GAP is not significantly correlated with HbA1c These findings are consistent with results from previous studies that OHA adherence was independently associated with HbA1c control: HbA1c decreases 0.10% to 0.16% for each 10% increment in OHA adherence [20].

All three measures of adherence, PDC, MPR, and GAP, were significantly correlated with HbA1c control but in different degrees. PDC had the biggest coefficient values in both adjusted and unadjusted models which indicated that PDC was most correlated with HbA1c level (Tables 3 and 4). These results are consistent with how PDC, MPR and GAP are calculated. MPR is calculated by adding the days' supply for all medications and then dividing over a certain period of time [17]. It assumes that all drugs eventually get used within the time period, which may overestimate the actual adherence if patients refill their medication before the last date of the preceding prescription. In contrast to MPR, PDC looks at each day to determine if the patient has one or more dispensed drugs and then determines the proportion of days that a patient has a drug available in a study interval [16]. Theoretically, PDC more accurately reflects patient adherence behavior, and it more effectively handles drug switching and prescription overlaps. GAP is simply measured by calculating the number of medication lapses greater than 30 days, [16] and it can be used as a reference to confirm the pattern of PDC or MPR (Figure 1).

Predictors	PDC		MPR		GAP	
Intercept	7.30	± 0.44††	7.08	± 0.58††	7.13	± 0.21††
6-Month Adherence	-1.12	± 0.10††	-0.68	± 0.18††	0.26	± 0.06 ††
Age*	-0.09	± 0.03††	-0.11	± 0.04††	-0.16	± 0.04††
Gender						
Female	0.10	± 0.6	0.16	± 0.7	0.15	± 0.7
Male	--		--		--	
Race						
African-American	0.28	± 0.06††	0.24	± 0.07††	0.30	± 0.06††
Hispanic	-0.10	± 0.30	-0.34	± 0.32	-0.26	± 0.30
Asian	-0.45	± 0.69	-0.11	± 0.71	-0.36	± 0.70
Other	-0.30	± 0.35	-0.36	± 0.36	-0.38	± 0.36
White	--		--		--	
Duration of OHA Treatment	0.20	± 0.10†	0.24	± 0.11	-0.08	± 0.13
Number of Medications	0.38	± 0.04††	0.41	± 0.05††	0.42	± 0.05††
OHA Class						
Biguanides Only	1.04	± 0.35	0.86	± 0.53	0.77	± 0.36
Sulfonylurea Only	1.46	± 0.35†	1.23	± 0.53†	1.18	± 0.36†
Thiazolidinedione Only	0.94	± 0.36	0.67	± 0.53	0.71	± 0.37
Other	-0.03	± 0.48	-0.37	± 0.62	-0.34	± 0.48
Multiple Classes	--		--		--	

PDC: Proportion of Days Covered; MPR: Medication Possession Ratio
Age* units in 10 years
† *p*-value is greater than 0.0001 and smaller than 0.05
†† *p*-value is smaller than 0.0001
-- =reference

Table 4: Adjusted coefficients between adherence and HbA1c level at 6-month interval.

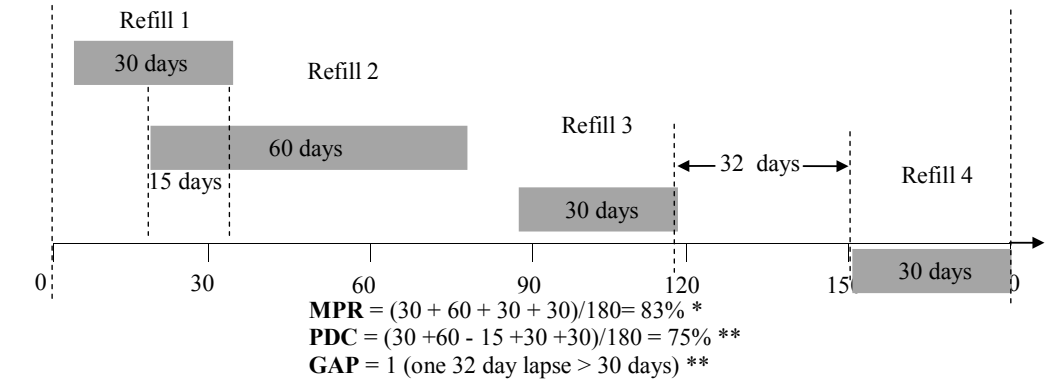
This study also compared OHA adherence with HbA1c control across three time intervals. In the unadjusted model, significance disappeared for both MPR and GAP in the 3-month interval. Further investigation showed that 11% of refills were prescribed with a 90-day supply, resulting in insufficient information to calculate the MPR and GAP since they both would need at least two refill dates during the 3-month interval. The coefficients were close for PDC, MPR, and GAP across the 6-month and 12-month intervals. However, from a clinical perspective, the 6-month interval can provide patient adherence information in a more timely fashion. In summary, the 6-month PDC most accurately reflects OHA adherence and is the measure most closely associated with HbA1c level for patients with Type 2 diabetes in our study.

It is well-known that race is one predictor of suboptimal HbA1c control [20]. In our study, compared with Whites, African-Americans had a significantly higher HbA1c level (by 0.28-0.30%, $p<0.0001$). Sociodemographic, behavioral, genetic, or biological factors may independently or partially affect HbA1c level [21-23] Our study also found that increased age is related to better HbA1c control, which is generally consistent with the notion that young patients are less likely to benefit from OHA therapy [24]. We additionally observed positive associations between number of concurrent OHAs and HbA1c levels. Patients were prescribed one additional OHA when their HbA1c level increased by 0.4%. A plausible explanation might be that patient may have been prescribed additional OHAs because they were not responding to one [25].

The main findings from this study provided evidence and knowledge to establish intervention in medication adherence to improve health outcomes for patients with Type 2 diabetes. Challenges of medication adherence in diabetes are at patient, medication and provider levels, and a multi-dimensional approach is required to establish efficient interventions. Health information technology (HIT) and health information exchange (HIE) offer great potential to establish such a system. First, objective and data-driven approaches can be programmatically established through an HIE. These objective adherence measures enable accurate assessment of patient medication taking behaviors, which is the essential for physicians to estimate the effectiveness of treatment. This study provides specific information on which to base a choice for which adherence measures to use in clinical practice. Second, a clinical decision support system may deliver patient adherence information and generate relevant recommendations in routine clinical practice. In addition, a well-established HIE/HIT supports patient-centric and team-based care that better engaged patients, providers and health care systems for improving medication adherence.

Limitations

Certain limitations should be recognized. First, the study population was Indiana Medicaid members younger than 65, with relatively low socioeconomic status and with at least one HbA1c laboratory result in the INPC which covers the central Indiana region most closely. Therefore, the findings from this study may lack generalizability to all patients with Type 2 diabetes, including those who had no HbA1c results recorded in the INPC. Second, dispensing claim-based measures may not be equivalent to measures of the actual ingestion of medication. Nevertheless, filling a prescription is usually consistent with taking medication [26]. It also should be noted that it is



PDC: Proportion of Days Covered; MPR: Medication Possession Ratio

*MPR calculation was based on the reference 17

**PDC and GAP calculation were based on the reference 16

Figure 1: An example of calculating MPR, PDC and GAP.

possible we did not capture dispensing information about free samples or free medications offered by providers or pharmacies. Third, the average HbA1c levels of this study population were elevated (>7.0%) even though the average OHA treatment duration was 2.09 years. Provider inertia may be playing a role in inadequate glycemic control apart from patient adherence. However, we lack the necessary data to further analyze if providers have failed to adequately intensify OHAs, or to initiate insulin or HbA1c tests [27]. Similarly, the comparisons of different OHA adherence measures mainly rely on their effects on HbA1c levels, and we did not study pharmacodynamics/kinetics contributions, which may also affect patient HbA1c levels. Fourth, we excluded patients using insulin. However, insulin is commonly administered to patients with Type 2 diabetes whose HbA1c is poorly controlled. One study suggested that insulin use may affect adherence rates to oral medications [28]. Whether there is a significant association between insulin use and OHA adherence is an area for further study.

Conclusion

By evaluating real-world clinical data from the INPC and Medicaid claims data, this study confirmed the strong association between OHA adherence measured by PDC/MPR and HbA1c level among Medicaid patients with Type 2 diabetes. The 6-month PDC is the best measure of OHA adherence in this population. This study also suggested that linking HIE laboratory data with claims data is a helpful approach for comparing medication adherence and clinical phenomena.

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References

1. Lee WC, Balu S, Cobden D, Joshi AV, Pashos CL (2006) Prevalence and economic consequences of medication adherence in diabetes: a systematic literature review. Manag Care Interface 19: 31-41.
2. Ho PM, Bryson CL, Rumsfeld JS (2009) Medication adherence: its importance in cardiovascular outcomes. Circulation 119: 3028-3035.
3. Egede LE, Gebregziabher M, Dismuke CE, Lynch CP, Axon RN, et al. (2012) Medication nonadherence in diabetes: longitudinal effects on costs and potential cost savings from improvement. Diabetes Care 35: 2533-2539.
4. Rubin RR (2005) Adherence to pharmacologic therapy in patients with type 2 diabetes mellitus. Am J Med 118 Suppl 5A: 27S-34S.
5. Burkhart PV, Sabati E (2003) Adherence to long-term therapies: evidence for action. J Nurs Scholarsh 35: 207.
6. Cook CL, Wade WE, Martin BC, Perri M 3rd (2005) Concordance among three self-reported measures of medication adherence and pharmacy refill records. J Am Pharm Assoc (2003) 45: 151-159.
7. Hansen RA, Kim MM, Song L, Tu W, Wu J, et al. (2009) Comparison of methods to assess medication adherence and classify nonadherence. Ann Pharmacother 43: 413-422.
8. Osterberg L, Blaschke T (2005) Adherence to medication. N Engl J Med 353: 487-497.
9. Cohen HW, Shmukler C, Ullman R, Rivera CM, Walker EA (2010) Measurements of medication adherence in diabetic patients with poorly controlled HbA(1c). Diabet Med 27: 210-216.
10. Vink NM, Klungel OH, Stolk RP, Denig P (2009) Comparison of various measures for assessing medication refill adherence using prescription data. Pharmacoepidemiol Drug Saf 18: 159-165.
11. Caetano PA, Lam JM, Morgan SG (2006) Toward a standard definition and measurement of persistence with drug therapy: Examples from research on statin and antihypertensive utilization. Clin Ther 28: 1411-1424.
12. Rozenfeld Y, Hunt JS, Plauschinat C, Wong KS (2008) Oral antidiabetic medication adherence and glycemic control in managed care. Am J Manag Care 14: 71-75.
13. Krapek K, King K, Warren SS, George KG, Caputo DA, et al. (2004) Medication adherence and associated hemoglobin A1c in type 2 diabetes. Ann Pharmacother 38: 1357-1362.
14. Lawrence DB, Ragucci KR, Long LB, Parris BS, Helfer LA (2006) Relationship of oral antihyperglycemic (sulfonylurea or metformin) medication adherence and hemoglobin A1c goal attainment for HMO patients enrolled in a diabetes disease management program. J Manag Care Pharm 12: 466-471.
15. McDonald CJ, Overhage JM, Barnes M, Schadow G, Blevins L, et al. (2005) he Indiana network for patient care: a working local health information infrastructure. An example of a working infrastructure collaboration that links data from five health systems and hundreds of millions of entries. Health Aff (Millwood). 24: 1214-1220.
16. National Committee for Quality Assurance. (2008) Pharmacy Quality Alliance (PQA) Demonstration Project.
17. Warren J, Warren D, Yang HY, Mabotuwana T, Kennelly J, et al. (2011)

Prescribing history to identify candidates for chronic condition medication adherence promotion. Stud Health Technol Inform 169: 634-638.

18. Yang Y, Thumula V, Pace PF, Banahan BF 3rd, Wilkin NE, et al. (2009) Predictors of medication nonadherence among patients with diabetes in Medicare Part D programs: a retrospective cohort study. Clin Ther 31: 2178-2188.

19. Curkendall SM, Thomas N, Bell KF, Juneau PL, Weiss AJ (2013) Predictors of medication adherence in patients with type 2 diabetes mellitus. Curr Med Res Opin 29: 1275-1286.

20. Schectman JM, Nadkarni MM, Voss JD (2002) The association between diabetes metabolic control and drug adherence in an indigent population. Diabetes Care 25: 1015-1021.

21. Sequist TD, Fitzmaurice GM, Marshall R, Shaykevich S, Safran DG, et al. (2008) Physician performance and racial disparities in diabetes mellitus care. Arch Intern Med 168: 1145-1151.

22. Selvin E, Steffes MW, Ballantyne CM, Hoogeveen RC, Coresh J, et al. (2011) Racial differences in glycemic markers: a cross-sectional analysis of community-based data. Ann Intern Med 154: 303-309.

23. Chandalia M, Grundy SM, Adams-Huet B, Abate N (2007) Ethnic differences in the frequency of ENPP1/PC1 121Q genetic variant in the Dallas Heart Study cohort. J Diabetes Complications 21: 143-148.

24. Odegard PS, Capoccia K (2007) Medication taking and diabetes: a systematic review of the literature. Diabetes Educ 33: 1014-1029.

25. Yurgin N, Secnik K, Lage MJ (2007) Antidiabetic prescriptions and glycemic control in German patients with type 2 diabetes mellitus: a retrospective database study. Clin Ther 29: 316-325.

26. Steiner JF, Prochazka AV (1997) The assessment of refill compliance using pharmacy records: methods, validity, and applications. J Clin Epidemiol 50: 105-116.

27. Vinik A (2007) Advancing therapy in type 2 diabetes mellitus with early, comprehensive progression from oral agents to insulin therapy. Clin Ther 29: 1236-1253.

28. Reach G, Le Pautremat V, Gupta S (2013) Determinants and consequences of insulin initiation for type 2 diabetes in France: analysis of the National Health and Wellness Survey. Patient Prefer Adherence 7: 1007-1023.