The Burden of "Serial Non-adherence" in Patients With Type 2 Diabetes

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BACKGROUND

- Diabetes is one of the leading causes of death in the world, affecting 382 million individuals across all age, gender, income, social groups, and countries. Over 90% of diabetes is Type 2 (T2DM).[1,2] The number of patients with diabetes is expected to increase by 55% by 2035.[2]
- Despite significant recent innovation in diabetes drug development, less than half of patients with diabetes achieve or maintain glycemic control (e.g., HbA1c<7%).
- Non-adherence to therapy is recognized as a major reason for this lack of control, reflected in health care quality measures (e.g. such as HEDIS in the U.S).
- Better understanding of the drivers and impact of non-adherence is needed to guide efforts by the healthcare community to improve glycemic control.
  - Existing research on available predictors of non-adherence remains limited.
  - Notably, little is known about "serial non-adherence" in diabetes, i.e. where patients are repeatedly non-adherent to multiple medications (both anti-diabetic and non-diabetes) over time.
  - The impact of non-adherence on poor glycemic control can be challenging for physicians to evaluate (given the limited reliable information on patient behavior outside the office).[3]

STUDY OBJECTIVES

The objectives of the study were to:

- Characterize the prevalence of non-adherence, and of "serial non-adherence" in particular, in a broad cohort of US patients with diabetes.
- Identify key predictors of non-adherence to anti-diabetes therapy.
- Characterize the burden of illness associated with non-adherence with anti-diabetes therapy (e.g., hypoglycemia, health care costs).

The analyses focused on patients receiving second-line anti-diabetic therapy (defined as patients who initiate another diabetes therapy following their first initiation of metformin or a metformin containing anti-diabetic medication). This represents a large population that is both i) attempting to manage their diabetes with sequential pharmacotherapy (therefore ideal to evaluate serial non-adherence) and ii) relatively homogenous in terms of their position on the treatment algorithm (thus addressing an important confounding factor).

PATIENTS AND METHODS

Data Source

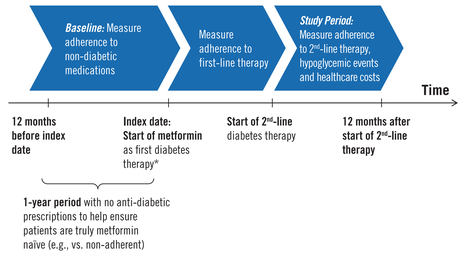
- Truven Health MarketScan® Commercial Claims and Encounters database, one of the largest claims-based databases in the U.S., was used for the study. The data include individual-level medical and drug information of enrollees (employees and their dependents) in health plans offered by U.S. employers.
- About 4 million T2DM patients in the U.S. are included in the data (2008Q1 – 2012Q4).

Study Design & Population

- The study used retrospective data from a cohort of treatment-naïve patients with T2DM who initiated first-line anti-diabetic therapy containing metformin and subsequently initiated a second-line therapy. Requirements included:
  - A 12-month period where no anti-diabetic drugs were used prior to first metformin prescription
  - The date of the first metformin prescription was defined as the index date
  - A minimum of 12 months of continued enrollment post–second-line therapy initiation (study period) (**Figure 1**)

http://www.easdvirtualmeeting.org/resources/14869

Figure 1. Study Time Periods



*Either monotherapy or combination therapy

- Patients with T2DM were selected based on the following criteria:
  - ≥ 1 claim for T2DM (International Classification of Diseases ICD-9-CM codes 250.x0 or 250.x2)
  - ≥ 1 claim for metformin with no prior claims for anti-diabetic therapy in the previous 12 months
  - ≥ 1 claim for a new (non-biguanide) anti-diabetes agent following metformin initiation (index date)
  - Continuous enrollment in both medical and prescription plans for ≥12 months prior to the index date (baseline) and after the initiation of second-line therapy (study period)
  - At least 18 years of age as of the index date
- Patients with claims for type 1 diabetes (T1DM) (ICD-9 CM 250.x1, 250.x3) and/or secondary diabetes (ICD-9 CM 249.xx) were excluded from the study.

Study Variables

Baseline Patient Characteristics

- Demographic and clinical characteristics including age, gender, geographic region, type of insurance plan, co-morbidities, pharmacy costs, and medical care costs were collected at baseline.

Medication Adherence

- Medication adherence was measured using the proportion of days covered (PDC), calculated as the total number of non-overlapping days of supply of medication one year following therapy initiation divided by 365 days.
  - Non-adherence was defined as PDC<80%.
- Adherence was measured for non-diabetes medications at baseline (lipid-lowering drugs, anti-hypertensives, anti-depressants, anti-asthmatics, and proton-pump inhibitors), first-line anti-diabetic therapy during the first year after the index date and second-line anti-diabetic medications during the study period (year after the start of second-line therapy) (**Figure 1**).
  - This metric accounts for both compliance during a line of therapy (captures failure to take all prescribed doses on time) and for gaps between lines of therapy if a new line is initiated subsequent to the date at which all doses of the prior line should have been taken.

Burden of Non-Adherence

- The burden of non-adherence was measured during the 12 months after initiation of second-line diabetes therapy and included medical care costs (inpatient, outpatient, and emergency department visits) and visits for hypoglycemia.
- Medical care costs were measured using allowed charges which include expected payments from third party payers and the patient, after negotiated discounts. All costs were inflation adjusted to 2012 dollars using the Medical Care Price Index.[4]
- Hypoglycemia was defined as a visit (inpatient or outpatient) associated with the following ICD-9 CM codes: 251.0-251.2 or 250.8 and no co-diagnosis of an alternative diabetic event (e.g., 259.8, 272.7, 681.xx, 682.xx, 686.9x, 707.1-707.9, 709.3, 730.0-730.2, 731.8). Severe hypoglycemia was defined as an inpatient stay or emergency room visit with one or more hypoglycemia codes.

Statistical Analysis

- Baseline characteristics of patients who were and were not adherent to second-line anti-diabetic therapy were compared and differences between patient groups were assessed using standardized differences, which is useful in large samples where *P*-values may detect small statistically significant differences. Standardized differences can help identify larger and more meaningful difference. Differences greater than 10% were considered to be clinically meaningful.[5]
- Logistic regression models were estimated to identify predictors of non-adherence to second-line anti-diabetic therapy. Potential predictors considered included baseline demographic and clinical characteristics, baseline healthcare costs, time to second-line therapy, metformin regimen (monotherapy vs. combination therapy), and previous medication adherence. *P*-values and 95% confidence intervals (CIs) assessing statistical significance of odds ratio (OR) are reported.
- The incremental costs associated with non-adherence to second-line anti-diabetic therapies was estimated using a GLM model (log-link and normal distribution) that included controls for the following (all measured at baseline): age, gender, region, type of insurance plan, comorbidities (cardiovascular disease, dyslipidemia, hypertension, chronic pulmonary disease, depression, osteoarthritis, and sleep disorder), Charlson Comorbidity Index[6-7], pharmacy costs, and medical costs. Year of metformin initiation and time to second-line therapy were also included as controls.

RESULTS

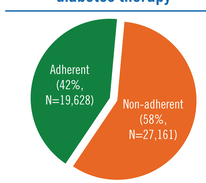
- A total of 46,789 patients who initiated second-line anti-diabetic therapy with at least 12 months of follow-up met criteria for inclusion into the study.

Patient Characteristics

- Patients not adherent to second-line therapy were on average 4 years younger (54 vs. 58, standard difference ≥10%), more likely to be female, and residents of the southern US. They were more likely to have been non-adherent to first-line anti-diabetic therapy and to baseline non-diabetic medications.

MEDICATION NON-ADHERENCE PATTERNS

Figure 2: Adherence to 2nd-line diabetes therapy*



- A majority of patients (58%, N=27,161) were non-adherent to anti-diabetic therapy during the first year after initiating second-line therapy (**Figure 2**).

Figure 3. Prior Adherence Among Patients Not Adherent to 2nd-line Diabetes Therapy

		%	N
Not adherent to 1st-line diabetes therapy (80%, N=21,632)	Not adherent to non-diabetes therapy (serial non-adherence†)	27	7,448
	Adherent to non-diabetes therapy	24	6,495
	Other‡	28	7,689
Adherent to 1st-line diabetes therapy (20%, N=5,529)	Not adherent to non-diabetes therapy	4	1,035
	Adherent to non-diabetes therapy	11	3,088
	Other‡	5	1,406
	Total	100	27,161

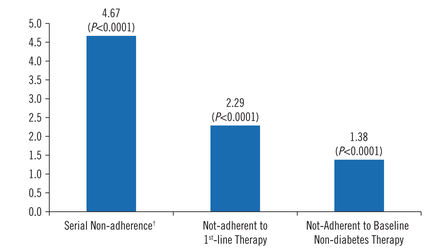
- Among patients not adherent to second-line therapy, non-adherence to first-line metformin was very common (80%, N=21,632). Among patients non-adherent to first line metformin, 27% (N=7,448) were non-adherent to non-diabetic therapy (serial non-adherence) (**Figure 3**).
- Sixty-nine percent of patients who were non-adherent to first-line anti-diabetic therapy were not adherent to second-line. Conversely, two-thirds of patients adherent to first-line therapy were adherent to second-line.

*Adherence is defined as Proportion of Days Covered (PDC)≥80%. PDC is calculated as the total number of non-overlapping days of supply of medication one year following therapy initiation divided by 365 days.
†Serial non-adherence is defined as non-adherence to second-line diabetes therapy, non-adherence to first line diabetes therapy and non-adherence to baseline non-diabetes therapy.
‡Other groups include patients with no prescription fill for non-diabetes medications observed during the baseline period.

PREDICTORS OF NON-ADHERENCE

- Among factors observed prior to the start of second-line therapy, serial non-adherence had the greatest association with second-line non-adherence (OR: 4.67; 95% CI: 4.37 – 5.00; *P*<0.0001) and accounted for a large fraction of the explained variance (65%), followed by first-line (metformin) non-adherence (OR: 2.29; 95% CI: 2.13 – 2.47; *P*<0.0001) and non-adherence to non-diabetic medication (OR: 1.38; 95% CI: 1.28 – 1.50; *P*<0.0001) (**Figure 4**).

Figure 4. Odds Ratio On Predictors of Non-Adherence to 2nd-Line Diabetes Therapy‡

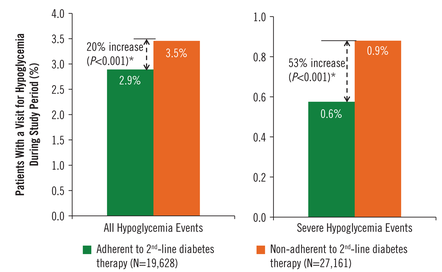


*Adherence is defined as PDC>80%, not-adherence defined as PDC <80%.
†Serial non-adherence is defined as non-adherence to second line diabetes therapy, non-adherence to first line diabetes therapy and non-adherence to at least one of the baseline non-diabetes therapy.
‡Patients who were adherent to non-diabetic medication and to metformin are in the reference group.

THE BURDEN OF NON-ADHERENCE

- Non-adherence to second-line therapy was associated with a 20% increase in the rate of observed visits for hypoglycemia (2.9% vs. 3.5%; *P*<0.001). Non-adherence was further associated with a 53% increase in the rate of observed severe hypoglycemic events (0.6% vs. 0.9%, *P*<0.001) (**Figure 5**).

Figure 5. Percent of Patients With a Visit for Hypoglycemia After Start of 2nd-Line Diabetes Therapy (study period)



- During the 12 months following initiation of second-line therapy, non-adherence to a second-line diabetes regimen was associated with a significant medical cost burden after controlling for baseline differences in patients (**Table 1**).
  - Average annual medical costs were 30% ($2,432) higher for non-adherent patients than adherent patients, driven largely by 70% ($1,678) higher hospitalization costs for non-adherent patients compared to adherent patients (*P*<0.0001 for both).

Table 1. Medical Care Costs for the First Year After the Initiation of Second-line Diabetes Therapy, Stratified by Adherence to Second-line Therapy

	First-Year Costs, $			
Cost Component	Adherent to 2nd-Line Diabetes Therapy (N=19,628)	Not Adherent to 2nd-Line Diabetes Therapy (N=27,161)	Adjusted Cost Difference, $	*P*-value
Hospitalizations	2,409	4,087	-1,678	<.0001*
ER visits	216	311	-96	<.0001*
Outpatient visits	4,960	5,467	-507	0.0001*
Other visits	602	753	-151	0.0004*
Total Medical Care	8,187	10,618	-2,432	<.0001*

Regression adjusted to control for baseline differences between patients

LIMITATIONS

- The study data include a subset of U.S. patients with employer-sponsored health insurance who are younger and likely healthier than the general U.S. T2DM population.
- Administrative claims data do not include key clinical characteristics that can impact treatment decisions and outcomes. In particular, the absence of HbA1c values prevents controlling for potentially important differences between patients.
- Medication adherence can be overestimated in claims, as claims only measure filled prescriptions and not all medications dispensed are taken by the patient. Notably our PDC measure (which is based on prescription fill date) is likely to overestimate the duration of medication therapy as patients may delay starting to take the medication or discontinue their medication prior to the end of their medication supply.
- The burden of non-adherence was examined during the first year after initiation of second-line therapy and thus likely underestimates the long-term impact of non-adherence.

CONCLUSIONS

- Based on real-world data, this study showed that more than half of patients initiating second-line anti-diabetic therapy are not adherent to therapy, and that serial non-adherence is present in over a quarter of these patients.
- Burden of non-adherence in T2DM appears to be significant, with "serially non-adherent" being a good predictor of patients at particularly high risk of future non-adherence. Consistent with previous literature[8-12], non-adherence was found to be associated with higher risk of hypoglycemia and with higher medical care costs.
- Since prior non-adherence is observable and appears to be highly predictive of later non-adherence, intervention strategies that can curb non-adherence early in their treatment may be particularly effective in improving the care of diabetes patients.
- Future research should seek to address some of the limitations of this study (e.g., lack of HbA1c information) and extend the analyses beyond second-line therapy.

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