Proximal Predictors of Long-Term Discontinuance with Noninsulin Antihyperglycemic Agents

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ABSTRACT

BACKGROUND: Noninsulin antihyperglycemic agents (NAAs) are the mainstay of treatment for type 2 diabetes, yet persistence in NAA use is suboptimal in many diabetes patients. Most of the research on NAA discontinuance has focused on sociodemographic characteristics and general health status, but such factors are inherently limited in explaining dynamic events such as discontinuance.

OBJECTIVE: To assess the relative importance of static and proximal dynamic factors in explaining long-term NAA discontinuance among Medicare beneficiaries with diabetes.

METHODS: Two sets of probability models were estimated to predict NAA discontinuance as a function of static variables (age, sex, race, original reason for Medicare entitlement, low-income subsidy and dual Medicare/Medicaid eligibility status, and disease burden) and 21 dynamic factors capturing month-by-month changes in drug use, health status, and use of medical services leading up to discontinuance (defined as month 0) and the previous 4 months (designated months -1 to -4) among 71,619 patients with diabetes enrolled in Medicare Part D plans in 2006-2008.

RESULTS: Static variables explained just 1.2% of the variance in probability of NAA discontinuance compared with 14% for all variables combined. Key time-related predictors of NAA discontinuance included discontinuation with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs) and statins, hypoglycemia, NAA usage gaps, insulin use, and discharge from hospitals and skilled nursing facilities (SNFs). The strongest significant predictors ($P < 0.05$) of NAA discontinuance were discontinuation with statins and ACEIs/ARBs in month 0 (predicted probabilities of 37% and 34%, respectively). Other variables that significantly increased the probability of NAA discontinuance by 10% or more were hypoglycemia in month 0 (14%) and month -1 (17%), discontinuance with ACEIs/ARBs in months -1 (15%) and -2 (10%), discontinuance with statins in month -1 (13%), and insulin use in month 0 (12%). Experiencing a previous gap in NAA therapy was associated with higher likelihood of discontinuance if the gap occurred in month -2 (10%) or month -4 (6%), but a gap in therapy in month -1 actually reduced the likelihood of discontinuance by 13%. Discharge from a hospital or SNF was consistently associated with higher probabilities of NAA discontinuance ranging between 4% and 10%, with higher probabilities occurring closer to month 0.

CONCLUSIONS: A cascade of dynamic changes preceding discontinuance with NAA therapy among Medicare Part D enrollees with diabetes was observed between 2006 and 2008. Understanding that lack of persistence in drug use is a dynamic rather than a static phenomenon opens up new avenues for investigating and ultimately improving adherence behavior in the elderly.

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What is already known about this subject

- Discontinuation with noninsulin antihyperglycemic agents (NAA) is a common phenomenon among patients with type 2 diabetes mellitus.
- Known risk factors for NAA discontinuance include younger age, nonwhite race, low income, high comorbidity burden, and other non-time varying characteristics that cannot, in and of themselves, predict the timing of a dynamic event such as drug discontinuance.
- Certain dynamic factors associated with NAA discontinuance (hypoglycemia, hospitalization, and emergency department visits) have been studied but not in a time-to-event analytic framework.

What this study adds

- A month-to-discontinuation model was developed that identified timed factors hypothesized to predict long-term NAA discontinuance derived from Medicare enrollment and claims data.
- Dynamic factors proximal to discontinuation were shown to be far better predictors than static factors typically studied in the adherence literature.
- Analyzing medical as well as prescription drug claims data can help health plans and clinicians identify circumstances when patients are at elevated risk of drug discontinuation.

Noninsulin antihyperglycemic agents (NAAs) are the mainstay of treatment for type 2 diabetes mellitus (T2DM). Appropriate NAA treatment substantially reduces the risk of microvascular disease and other diabetes complications.¹⁻³ NAAs are prescribed to T2DM patients who are unable to control their glycemic levels through diet or exercise. Treatment typically begins with metformin or a sulfonylurea and may be augmented with a second NAA (alpha-glucosidase inhibitor, amylinomimetic, thiazolidinedione, meglitinide, dipeptidyl peptidase-4, or incretin mimetic) or insulin if the initial agent provides inadequate control. Treatment generally lasts a lifetime. Yet, persistence with NAAs is suboptimal in many diabetes patients with rates of discontinuance reaching 50% or more within 1.5 years of initiation.^{4,5} Reasons for poor persistence are not well understood. Most research in this area has focused on demographic characteristics

and general health status,⁵⁻¹³ but static factors alone cannot explain dynamic events such as discontinuation. A few studies have examined specific proximal factors associated with NAA discontinuation, such as medication experience,⁴ type of NAA prescribed,¹⁴ presence of hypoglycemic events,¹⁴⁻¹⁵ refill gaps,^{5,6} hemoglobin A1c measures,¹⁶ distribution channel,¹⁷ and medication cost.^{5,6,18} But to date, no comprehensive study has assessed how dynamic factors combine to explain NAA discontinuation, particularly for long-term discontinuers. As a result, clinicians are ill equipped to diagnose triggers for discontinuation and thus miss potentially important intervention opportunities. The objective of this study was to assess the relative importance of static and proximal dynamic factors in explaining long-term NAA discontinuation among diabetes patients enrolled in Medicare Part D plans in 2006-2008.

Methods

Data Source

Data were obtained from the Chronic Condition Data Warehouse (CCW) prepared by Buccaneer, a data contractor for the Centers for Medicare & Medicaid Services (CMS). The dataset comprised a random 5% sample of the Medicare population in 2006, which was then tracked through 2008. The data files included basic demographic and program enrollment information plus claims for inpatient and outpatient services as well as prescription drugs. The Part A and B claims include *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnostic codes used to identify diabetes and other diseases. The Part D claims files include National Drug Code (NDC) numbers that were used to identify drugs in classes of interest. The CCW files include a variable for first recorded diabetes diagnosis dating back to 1999.

Study Sample

The sample was selected based on the following inclusion criteria: (a) continuously enrolled in Medicare Part A, Part B, and Part D fee-for-service prescription drug plans from January 1, 2006, through December 31, 2008, or death; (b) diagnosed with T2DM before 2006 (ICD-9-CM codes 250.xx, 357.2, 362.01, 362.02, and 366.41 on any hospital claim or 2 outpatient or carrier claims); and (c) filled at least 2 NAA prescriptions during the study period.

From this base population, 2 cohorts were identified: long-term NAA discontinuers and continuing NAA users. Long-term discontinuers were identified by using a 2-step process. First, prescription records from the base population were reviewed to identify all NAA users with a minimum of 2 fills for one or more different NAAs in 2007 followed by an absence of any NAA use over the next 12 months. The last month with NAA days supply was defined as the index month (month 0). The 11 months previous to the index month were designated as the baseline period during which potential proximal factors associated with discontinuation were assessed. Second, beneficiaries who died

within 5 months of their index months were excluded. The rationale for this exclusion is that impending death was likely the proximal cause for discontinuation, which would typically be considered clinically appropriate for therapies with extended time to benefit such as NAAs. Individuals were retained who died 6 months or more after their index dates on the presumption that the proximal reasons for NAA discontinuation were factors other than impending death. The cutpoint of 6 months is admittedly arbitrary and is based on the predicted survival threshold used in the Medicare hospice benefit. In 2008, 40% of Medicare beneficiaries who died used hospice services,¹⁹ so it is reasonable to assume that physicians were familiar with the drug reduction regimens used in the program.

Next, a comparison cohort of continuing NAA users was identified. Continuing users were required to have a minimum of 2 NAA fills in their baseline and follow-up periods. We randomly assigned continuing users an index month through an algorithm that equated the distribution of index months for the 2 cohorts (this was designed to reduce any bias associated with seasonal factors that might influence drug discontinuation) and eliminated anyone who died in months 0 to 5. NAA users who fit neither the definition of a long-term discontinuer nor a continuing user were excluded.

Measures

We specified 28 variables from Medicare enrollment records and claims files that were hypothesized to influence persistence or discontinuation with NAA therapy. First were 7 static variables: age, gender, race, original reason for Medicare entitlement, low-income subsidy (LIS) status, dual eligibility, and annual counts of chronic conditions in the CMS risk adjuster known as RxHCC (prescription drug hierarchical chronic conditions), all measured in the baseline year of 2006. The original reason for Medicare entitlement included age 65, Social Security Disability Insurance (SSDI), and end-stage renal disease (ESRD). The SSDI and ESRD indicators captured beneficiaries with high disease burden and generally lower socioeconomic status. Dual Medicare/Medicaid eligibility and receipt of LIS captured the poorest Medicare beneficiaries. The RxHCC measure served as a Medicare-specific comorbidity index. We hypothesized that being older and nonwhite with lower socioeconomic status and higher disease burden would be associated with a greater probability of NAA discontinuation.

We specified 4 categories of potential dynamic predictors of NAA discontinuation: (1) drug use, (2) diabetes tests and preventive measures, (3) services indicating treatment for diabetes complications and comorbidities, and (4) Medicare use and spending. All variables were measured during the index month and for each of the preceding 4 months (in preliminary analyses, we evaluated events extending back 11 months previous to the index month, but because observations before month -4 were never consistently predictive of discontinuation, they are not reported here).

FIGURE 1 Study Cohort Selection Chart

NAA = noninsulin antihyperglycemic agents.

The NAA drugs included in the analysis were prescription fills for metformin, sulfonylureas, alpha-glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, meglitinides, and incretin mimetics. Antidiabetic drug predictor variables included first month of observed NAA use, NAA usage gaps defined as 30 days or more with no NAAs on hand bracketed by days with NAAs, monthly counts of different NAAs filled, any insulin fill, discontinuation with concomitant therapy for hypertension including angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), and discontinuation with concomitant therapy for treating hyperlipidemia (statins). We hypothesized that NAA usage gaps, insulin fills, and discontinuation with ACEIs/ARBs and statins would be positively associated with NAA discontinuation, while early NAA initiation and multiple NAAs would reduce the probability of NAA discontinuation.

Monthly indicators were created for the following diabetes tests and preventive measures: tests for A1c, fasting blood glucose, and diabetic eye exam. These variables were included for exploratory purposes without signed hypotheses (e.g., more frequent tests could indicate either worsening condition or good diabetes management).

The next set of variables was intended to capture differences in diabetes severity between the 2 study cohorts: uncontrolled diabetes (ICD-9-CM code 250.x2); short-term diabetes complications (ICD-9-CM codes 250.1x, 250.2x, and 250.3x); long-term diabetes complications (ICD-9-CM codes 250.4x, 250.5x, 250.6x, 250.7x, 250.8x, and 250.9x); hypoglycemia (ICD-9-CM code 251.2); ESRD (ICD-9-CM code 585.6); and cancer (ICD-9-CM codes 14.xx to 209.xx, excluding skin cancer). We hypothesized that hypoglycemia would increase the probability of NAA discontinuance. The other severity indicators were included as exploratory factors.

The final set of monthly variables included indicators for hospital discharge, skilled nursing facility (SNF) discharge, hospice admission, number of emergency department visits, number of physician visits, number of unique physicians seen in the month, and monthly values for Part A, B, and D spending. We hypothesized that all variables except Part D spending would be associated with increased likelihood of NAA discontinuance.

Statistical Analysis

Factors associated with long-term NAA discontinuance were estimated, using ordinary least squares (OLS) linear probability models and logistic regression models. Although OLS is not

TABLE 1 Baseline Characteristics of Study Cohorts

Characteristics	NAA Discontinuers (n = 6,436)	NAA Continuing Users (n = 65,183)	P Value
Age in years [SD]	71.3 [13.2]	70.5 [12.1]	<0.001
Sex, %			0.388
Male	33.6	34.2	
Female	66.4	65.8	
Race, %			<0.001
White	69.8	73.7	
Black	19.2	14.9	
Other and unknown	11.0	11.4	
Original reason for Medicare entitlement, %			<0.001
Old age	59.5	64.6	
SSDI/ESRD	40.5	35.4	
Low-income subsidy, %			<0.001
Yes	72.0	66.2	
No	28.1	33.8	
Dual eligibility status, %			<0.001
Yes	68.2	62.6	
No	31.8	37.4	
RxHCC counts [SD]	8.6 [3.8]	7.3 [3.3]	<0.001

ESRD = end-stage renal disease; NAA = noninsulin antihyperglycemic agents; RxHCC = Prescription Drug Hierarchical Condition Category; SD = standard deviation; SSDI = Social Security Disability Insurance.

traditionally used to estimate models with binary outcomes, it has several advantages in the context of this analysis. First, because we had no a priori knowledge of the true functional form of the relationships being investigated, we selected linear relationships as the simplest alternative. Second, we wished to provide a measure of how each variable contributed to explained variance and that is directly possible only with OLS (through partial and cumulative R^2 measures). Third, the results from such tests are far more intuitive—the OLS model coefficients are read as marginal probabilities—than those derived from standard logistic models. A final advantage of OLS over non-linear models is that parameter estimates are additive, thereby making it easy to identify combinations of effects that are most predictive of drug discontinuation. Two drawbacks to OLS models are that the predicted probabilities are not constrained to the unit interval, and the OLS errors are heteroskedastic. However, as Wooldridge (2013) notes in his classic econometrics text,²⁰ finding small numbers of predicted probabilities outside the unit interval is seldom problematic, and calculating robust standard errors controls for heteroscedasticity.

The initial OLS model estimated the probability that a study subject was classified as an NAA discontinuer as a function of the 7 static variables previously described. Next, a forward selection model was used that included static variables plus 5 monthly values for each dynamic factor. The variable with the

lowest P value was entered first, followed sequentially by the variable with next lowest P value, and so on, until no additional variable met the minimum criterion of $P < 0.05$. Results from otherwise identical models estimated using logistic regression are provided in Appendices A and B (available in online article).

Results

Sample Characteristics

Based on the study selection criteria (Figure 1), we identified 6,436 long-term NAA discontinuers and 65,183 continuing NAA users. It is worth noting that the exclusion criteria for impending death (died in months 0-5) had a much greater impact on delineating discontinuers compared with continuing users. As expected, NAA use is rare immediately preceding death. Baseline characteristics of the 2 cohorts are presented in Table 1. The distribution of age and gender was very similar, but discontinuers were less likely to be white (70% vs. 64.6%) and were more likely to have entered Medicare through SSDI or ESRD (40.5% vs. 35.4%). The discontinuer cohort also had higher proportions of LIS recipients and dual eligibles and carried a significantly heavier disease burden measured by RxHCC counts (8.6 vs. 7.3).

Dynamic characteristics of the 2 cohorts in the index month (0) and previous 4 months (-1 through -4) are summarized in Table 2. The first set of measures highlights differences in drug use. As hypothesized, NAA discontinuers exhibited much more volatile behavioral patterns compared with continuing users. In particular, discontinuers were more than twice as likely to experience gaps in NAA use before their index dates. They were less likely to use multiple NAAs but were much more likely to use insulin (e.g., 30.7% of discontinuers took insulin in month -4 rising to 39.2% in the index month, whereas insulin use among continuing users averaged just 15% with little change over time). Discontinuation with other ACEIs/ARBs and statins was relatively rare in both groups but spiked to nearly 5% among NAA discontinuers in the index month.

NAA discontinuers experienced strikingly higher rates of diabetes complications and comorbidities compared with continuing users. This was particularly apparent for ESRD, short-term diabetes complications, and hypoglycemia, albeit the prevalence of such complications was low in both groups. Similar patterns were evident for the Medicare use and spending variables shown in the bottom panel of Table 2. On a monthly basis, discontinuers had twice the number of emergency department visits and different physicians visited, 3 times the number of hospital discharges, and 4 times the number of SNF discharges. More contacts with the health system resulted in much higher spending on Medicare services by NAA discontinuers, with a marked spike in spending in the month immediately before discontinuation.

TABLE 2 Differences in Dynamic Characteristics by NAA Continuation Status and Month Previous to Index Month

Dynamic Variables	NAA Discontinuers (n = 6,436)				Index Month	NAA Continuing Users (n = 65,183)				Index Month
	Month Previous to Index Month					Month Previous to Index Month				
	-4	-3	-2	-1		0	-4	-3	-2	
Drug use variables										
NAA usage gap, %	15.89	15.78	17.22	4.36	–	6.39	6.39	5.97	3.95	–
Different NAAs filled, n	0.7	0.8	0.6	0.8	–	1.0	1.0	1.0	1.1	–
Any insulin use, %	30.73	31.40	32.78	35.90	39.21	15.33	15.53	15.68	15.97	16.21
Discontinuation of ACEIs/ARBs, %	0.61	0.65	1.04	1.54	4.93	0.27	0.31	0.33	0.33	0.43
Discontinuation of statins, %	0.36	0.62	0.73	1.09	4.81	0.28	0.26	0.29	0.31	0.35
Diabetes tests and other preventive measures, %										
A1c test	17.95	18.38	17.17	21.16	19.52	18.48	18.28	18.69	19.05	18.72
Fasting blood glucose test	3.70	3.89	4.36	4.76	4.81	3.73	3.72	3.73	3.93	3.73
Eye exam	6.68	6.24	6.02	5.95	6.27	6.96	6.94	6.89	7.05	6.98
Diabetes complications and comorbidities, ^a %										
Uncontrolled diabetes	9.76	10.13	11.10	13.22	11.80	8.38	8.39	8.52	8.73	9.02
Short-term diabetes complications	0.47	0.36	0.50	0.58	0.45	0.27	0.29	0.27	0.29	0.29
Long-term diabetes complications	7.08	7.50	7.46	9.57	8.50	5.43	5.32	5.57	5.47	5.77
Hypoglycemia	0.70	0.76	0.93	1.40	1.15	0.18	0.21	0.20	0.20	0.20
ESRD	3.27	3.44	3.55	3.70	3.89	1.04	1.05	1.07	1.10	1.11
Cancer	2.07	1.87	2.05	2.04	2.15	1.85	1.93	1.94	1.91	1.95
Medicare utilization and spending										
Hospital discharge, %	9.40	8.83	10.91	13.37	10.17	3.53	3.62	3.55	3.62	3.72
SNF discharge, %	2.01	2.26	2.26	3.39	2.16	0.50	0.52	0.55	0.48	0.50
Hospice admission, %	0.12	0.09	0.08	0.03	0.54	0.04	0.04	0.04	0.01	0.10
ED visits, n	0.2	0.2	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.1
Unique physicians seen, n	2.1	2.1	2.3	2.5	2.2	1.2	1.2	1.2	1.2	1.2
Part A & B spending, \$	2,225.51	2,403.83	2,603.14	3,007.58	2,240.41	934.02	939.62	924.26	921.49	922.47
Part D spending, \$	403.35	420.29	395.33	434.64	383.69	357.41	357.82	364.02	369.03	372.70

^aBased on the following ICD-9-CM codes: uncontrolled diabetes (250.x2); short-term diabetes complications (250.1x, 250.2x, 250.3x); long-term diabetes complications (250.4x, 250.5x, 250.6x, 250.7x, 250.8, 250.9x); hypoglycemia (251.2); ESRD (585.6); cancer (140.xx to 209.xx, excluding skin cancer).

A1c = hemoglobin A1c; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blockers; ED = emergency department; ESRD = end-stage renal disease; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; NAA = noninsulin antihyperglycemic agents; SNF = skilled nursing facility.

Multivariate Findings

Results from the OLS model predicting NAA discontinuation as a function of static variables only are shown in Table 3. All variables in this model except sex and other race were statistically significant predictors at $P < 0.05$, but the effects were small. The biggest difference was a 2.6% higher probability of discontinuation by blacks compared with whites. Beneficiaries whose Medicare entitlement was because of age were 1.5% less likely to discontinue NAAs, compared with those who entered the program through SSDI or ESRD. Being an LIS recipient increased risk of discontinuation by 0.9%, about the same amount as each additional RxHCC condition. Total explained variance attributable to all model variables was just 1.2%. Results from an identically specified logistic regression (see Appendix A, available in online article) were similar in direction and magnitude. The C statistic of 0.6 indicated that the combined predicted probability of NAA discontinuation was scarcely better than chance alone.

The multivariate OLS stepwise regression results are presented in Table 4. The variables are listed in the order in which they entered the model. The last column shows the cumulative R^2 through step 50, after which no variable was statistically significant at $P < 0.05$. The adjusted probabilities together with robust standard errors (which corrected for heteroscedasticity) are taken from the final 50-step equation. Findings from the logistic stepwise regression are shown in Appendix B (available in online article). These results are very similar to those generated by the OLS model in terms of parameter signs, significance levels, and relative order of magnitude, albeit the order in which variables entered the logistic model differed somewhat from the OLS version.

It is immediately apparent that dynamic characteristics explain far more of the total variance in the likelihood of discontinuation (14%), compared with static variables (1.2%). The strongest individual predictors of NAA discontinuation were discontinuation with statins and ACEIs/ARBs in the index month (predicted probabilities of 37% and 34%,

TABLE 3 Linear Probability Regression Results Predicting NAA Discontinuation with Static Variables Only

Static Variable	Adjusted Probability	Robust Standard Error	P Value
Age (per additional year)	0.0003	<0.001	0.031
Male (ref=female)	0.0044	0.002	0.058
Race (ref=white)			
Black	0.0264	0.003	<0.001
Other race	0.0001	0.004	0.974
Old age as original reason for entitlement (ref=SSDI or ESRD)	-0.0148	0.003	<0.001
LIS (ref=no LIS)	0.0093	0.004	0.035
Dual eligible (ref=not dual eligible)	-0.0007	0.004	0.870
RxHCC (per additional RxHCC)	0.0085	<0.001	<0.001
R ²	0.0120		

ESRD = end-stage renal disease; LIS = low-income subsidy; NAA = noninsulin antihyperglycemic agents; ref = reference; RxHCC = Prescription Drug Hierarchical Condition Category; SSDI = Social Security Disability Insurance.

respectively). Other variables that increased the probability of NAA discontinuation by 10% or more were hypoglycemia in month 0 (14%) and month -1 (17%), discontinuation with ACEIs/ARBs in month -1 (15%) and month -2 (10%), discontinuation with statins in month -1 (13%), and insulin use in the index month (12%). Experiencing a previous gap in NAA therapy was associated with higher likelihood of discontinuation if the gap occurred in month -2 (10%) or month -4 (4%), but a gap in therapy in month -1 actually reduced the likelihood of discontinuation by 13%. Discharge from a hospital or SNF was consistently associated with higher probabilities of NAA discontinuation ranging between 4% and 10%, with higher probabilities occurring in months closer to the index month. The model contained numerous other statistically significant predictors of long-term NAA discontinuation, but the effects were generally small and occasionally inconsistent in signs.

Two points should be kept in mind when interpreting these results. First, the unadjusted probability of long-term NAA discontinuation in this study sample was just 9%, so even the largest estimated marginal effects increased the absolute probability of discontinuation by just a few percentage points. Second, although parameter estimates in OLS equations are technically additive, some variable combinations are ruled out by definition (e.g., it is only possible to discontinue ACEIs/ARBs or statins once, and gaps in NAA therapy cannot occur in contiguous months). Nonetheless, there are several combinations of predictive factors, such as discontinuation with ACEIs/ARBs and statins, hypoglycemia, and institutional transitions, that together more than double the likelihood of long-term discontinuation.

Discussion

Several aspects of the results warrant discussion. First, as hypothesized, a model containing only static predictors explained very little of the total variance in long-term NAA discontinuation in a nationally representative sample of diabetes patients enrolled in Medicare Part D plans ($R^2=0.012$), compared with a model that included time-dependent proximal predictors ($R^2=0.14$). The earliest a static variable entered the stepwise model was step 19 (LIS). “Black” entered the equation at step 33. Although being an LIS recipient or black may (slightly) increase the risk of long-term drug discontinuation, the vast majority of NAA users who shared these characteristics were not discontinuers, and those who were must logically have responded to some time-related stimulus (or lack thereof) that influenced when they stopped taking their medications. This is not to suggest that clinicians and policymakers should forgo focusing on individual characteristics associated with higher risk of drug discontinuation, just that the focus should be combined with information on dynamic circumstances for which the chances of discontinuation are highest.

Second, relatively few dynamic variables accounted for almost all of the variance in long-term NAA discontinuation. The first 5 variables in the stepwise regression accounted for over 70% of the total explained variance, and 5 of the first 7 variables had coefficient values (adjusted probabilities) exceeding 10 percentage points. Key time-related predictors of NAA discontinuation in the model included discontinuation with ACEIs/ARBs and statins, hypoglycemia, NAA usage gaps, insulin use, and discharge from hospitals and SNFs.

Third, the time to estimated effect was short. We originally estimated the effect of 21 dynamic variables up to 11 months before the index month but found that values more than 5 months before the index month had little or no predictive power. But, even when the analysis was restricted to a shorter time horizon, the strongest effects were observed either in the index month itself or the 2 months immediately preceding it. This observation suggests that prognostic tools designed to identify circumstances under which high-risk patients are most likely to have difficulty remaining on their medications should focus on short-run targets.

Limitations

This study has a number of important limitations that suggest avenues for future research, with potentially high returns in improving medication adherence among older people with serious chronic disease. Perhaps the most important limitation is that this model is deterministic rather than prognostic. We compared known discontinuers with known continuing users for the expressed purpose of being able to go back in time to identify not only which circumstances were most strongly associated with discontinuation but how that association changed as the discontinuation decision neared.

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TABLE 4 Stepwise Linear Probability Regression Results Predicting NAA Discontinuation as a Function of Static and Dynamic Variables

Step	Variable	Parameter Estimate	Robust Standard Error	Model R ²
1	Number of NAAs filled month -2	-0.02	<0.01	0.02
2	Insulin use month 0	0.12	0.01	0.05
3	Number of unique physicians seen month -1	0.00	<0.01	0.06
4	Discontinuation of statins month 0	0.37	0.02	0.08
5	Discontinuation of ACEIs/ARBs month 0	0.34	0.02	0.10
6	NAA usage gap month -2	0.10	0.01	0.10
7	NAA usage gap month -1	-0.13	0.01	0.11
8	Number of NAAs filled month -1	-0.02	<0.01	0.11
9	Parts A & B spending [per \$100] month -2	0.00	<0.01	0.11
10	NAA usage gap month -4	0.06	0.01	0.12
11	Number of unique physicians seen month 0	0.01	<0.01	0.12
12	Hospital discharge month -1	0.05	0.01	0.12
13	Hospital discharge month -4	0.04	0.01	0.12
14	Part D spending [per \$100] month 0	-0.00	<0.01	0.12
15	Part D spending [per \$100] month -3	0.00	<0.01	0.12
16	Hypoglycemia month -1	0.17	0.03	0.13
17	Discontinuation of ACEIs/ARBs month -1	0.15	0.02	0.13
18	Parts A & B spending [per \$100] month -3	0.00	<0.01	0.13
19	LIS (1: yes, 0: no)	0.01	<0.01	0.13
20	Discontinuation of statins month -1	0.13	0.02	0.13
21	SNF discharge month -1	0.10	0.02	0.13
22	Discontinuation of ACEIs/ARBs month -2	0.10	0.02	0.13
23	Hypoglycemia month 0	0.14	0.03	0.13
24	Count of ED visits month -2	0.02	<0.01	0.13
25	Eye exam month -1	-0.01	<0.01	0.13
26	ESRD month 0	0.05	0.01	0.13
27	Uncontrolled diabetes month -1	0.02	<0.01	0.13
28	SNF discharge month -4	0.06	0.02	0.13
29	Discontinuation of statins month -2	0.08	0.02	0.13
30	Eye exam month 0	-0.01	<0.01	0.13
31	Insulin use month -3	-0.02	0.01	0.13
32	RxHCC count	0.00	<0.01	0.13
33	Black race	0.01	<0.01	0.13
34	Other race	-0.00	<0.01	0.13
34	Cancer month -3	-0.02	0.01	0.13
35	Parts A & B spending [per \$100] month -1	0.00	<0.01	0.14
36	Eye exam month -2	-0.01	<0.01	0.14
37	SNF discharge month -3	0.05	0.02	0.14
38	Hypoglycemia month -2	0.08	0.03	0.14
39	A1c test month -2	-0.01	<0.01	0.14
40	Uncontrolled diabetes month -4	-0.01	<0.01	0.14
41	Part D spending [per \$100] month -4	0.00	<0.01	0.14
42	Discontinuation of statins month -3	0.07	0.03	0.14
43	SNF discharge month 0	0.05	0.02	0.14
44	Number of NAAs filled month -4	-0.00	<0.01	0.14
45	Number of NAAs filled month -3	0.00	<0.01	0.14
46	Long-term complications month -1	0.01	0.01	0.14
47	Hypoglycemia month -4	0.07	0.03	0.14
48	Eye exam month -3	-0.01	<0.01	0.14
49	Glucose test month -4	-0.01	0.01	0.14
50	Hospice admission month 0	0.09	0.04	0.14

Note: Variables entered sequentially based on lowest P value among remaining variables until no remaining variable was statistically significant at P<0.05. Coefficient values shown are from the final model iteration.

A1c=hemoglobin A1c; ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blockers; ED=emergency department; ESRD=end-stage renal disease; LIS=low-income subsidy; NAA=noninsulin antihyperglycemic agents; SNF=skilled nursing facility.

Obviously, this approach does not work going forward, when it is unknown if or when a person will discontinue therapy. For example, we found that discontinuing statins raised the probability of NAA discontinuance by 37% in the index month, 13% in month -1, 8% in month -2, and 7% in month -3%. A clinician looking forward in time would thus not know whether a patient observed to discontinue statins had a 7% or a 37% chance of NAA discontinuation in the next month.

One approach to address this issue would be to establish contemporary correlates with each timed measure of statin discontinuance (and by extension other proximal predictor variables) to characterize the particular collection of factors uniquely associated with each pre-index month and then prospectively test the sensitivity and specificity of the results in predicting drug discontinuance in another dataset. Such an exercise is beyond the scope of this study but offers promise as a tool for prospectively assessing medication persistence.

A good prognostic tool will require an expanded set of predictor variables. Even though we have shown that dynamic variables are much more predictive of medication discontinuance than static factors, the fact remains that we only explained 14% of the variance. Like most adherence studies that rely on claims data, we did not directly observe important patient behaviors that could trigger drug discontinuance. There is voluminous literature on patient beliefs and behaviors that could theoretically be brought to bear on this subject with the right data.^{5-7,10,13} It is equally important to identify drug discontinuation initiated by prescribers, but without direct information on prescription orders (original prescriptions, refills, and stop orders), this is impossible to achieve. Eventually, when claims data are routinely combined with electronic medical records, it will become possible to examine a more expansive set of proximal reasons for drug discontinuation, including patient intolerance, side effects, and lack of drug effectiveness.

Another limitation of our approach is that we focused exclusively on long-term NAA discontinuers (12+ months with no observed use) with the assumption that individuals meeting this criterion had ceased taking this class of diabetes medications altogether, as opposed to those taking a drug holiday or otherwise experiencing short gaps in therapy. However, we discovered that, among study subjects whom we could track up to 24 months after discontinuation, approximately a quarter resumed NAA use (results not shown) with unobserved future resumption rates presumably higher still. This suggests that adherence studies focused on persistence with chronic medications are mostly about short and long gaps in adherence rather than outright discontinuance, even if that goes unrecognized in studies of short duration. What our research adds to this line of reasoning is that different proximal factors may be associated with short and long gaps and that what we have been able

to deduce about predictors of long-term gaps may or may not hold for shorter gaps.

A final limitation is that we focused on diabetics taking a single class of medications and cannot generalize the findings to other chronic diseases or other evidence-based drugs. Filling this knowledge gap should be given high priority in future medication adherence studies.

Conclusions

In this study, a cascade of dynamic changes in drug use, disease severity, and institutional episodes have been observed preceding discontinuance with NAA therapy among Medicare Part D enrollees with diabetes between 2006 and 2008. Understanding that lack of persistence in drug use is a dynamic rather than a static phenomenon opens up new avenues for investigating and ultimately improving adherence behavior among older adults.

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DISCLOSURES

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Study concept and design were primarily contributed by Stuart, Quinn, and Brandt, along with Shen, Roberto, Hendrick, Huang, and Rajpathak. Shen, Loh, Hendrick, and Kim collected the data, and data interpretation was performed primarily by Stuart, Shen, and Roberto, assisted by Quinn, Brandt, Hendrick, Huang, and Rajpathak. The manuscript was written primarily by Stuart, with assistance from the other authors, and revised by Huang, Rajpathak, and Stuart, with assistance from the other authors.

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APPENDIX A Logistic Regression Results Predicting NAA Discontinuation with Static Variables Only

Static Variable	Odds Ratio	95% CI
Age (per additional year)	1.0036	(1.0008-1.0065)
Male (ref=female)	1.0512	(0.9938-1.1120)
Race (ref=white)		
Black	1.3413	(1.2511-1.4379)
Other race	0.9955	(0.9121-1.0866)
Old age as original reason for entitlement (ref=SSDI or ESRD)	0.8358	(0.777-0.8992)
LIS (ref=no LIS)	1.1370	(1.0148-1.274)
Dual eligible (ref=not dual eligible)	0.9896	(0.8876-1.1032)
RxHCC (per additional RxHCC)	1.0995	(1.0914-1.1076)
C-statistic		0.6003

CI=confidence interval; ESRD=end-stage renal disease; LIS=low-income subsidy; NAA=noninsulin antihyperglycemic agents; ref=reference; RxHCC=Prescription Drug Hierarchical Condition Category; SSDI=Social Security Disability Insurance.

APPENDIX B Stepwise Logistic Regression Results Predicting NAA Discontinuation as a Function of Static and Dynamic Variables

Step	Variable	Odds Ratio	95% CI
1	Insulin use in month 0	2.9870	(2.807-3.177)
2	Discontinuance of statins in month 0	9.7680	(7.971-11.97)
3	Number of NAAs filled in month -2	0.6640	(0.633-0.696)
4	Number of unique physicians seen in month -1	1.0300	(1.017-1.044)
5	Discontinuance of ACEIs/ARBs in month 0	8.7520	(7.242-10.576)
6	Parts A & B spending [per \$100] in month -2	1.0010	(1-1.002)
7	NAA usage gap in month -4	1.5960	(1.45-1.757)
8	NAA usage gap in month -1	0.2310	(0.197-0.272)
9	Number of NAAs filled in month -1	0.7040	(0.671-0.738)
10	NAA usage gap in month -2	2.1510	(1.944-2.381)
11	Number of unique physicians seen in month 0	1.0500	(1.04-1.061)
12	Hospital discharge in month -1	1.4980	(1.294-1.733)
13	Discontinuance of ACEIs/ARBs in month -1	3.1740	(2.399-4.2)
14	Hospital discharge in month -4	1.3610	(1.211-1.531)
15	Hypoglycemia in month -1	2.8450	(2.051-3.947)
16	Discontinuance of statins in month -1	2.9940	(2.187-4.098)
17	Part D spending [per \$100] in month 0	0.9450	(0.937-0.953)
18	Part D spending [per \$100] in month -3	1.0230	(1.015-1.031)
19	RxHCC count	1.0260	(1.017-1.036)
20	LIS (1: yes, 0: no)	1.1680	(1.087-1.255)
21	Discontinuance of ACEIs/ARBs in month -2	2.4040	(1.763-3.278)
22	Hypoglycemia in month 0	2.4600	(1.732-3.493)
23	Parts A & B spending [per \$100] in month -3	1.0010	(1-1.001)
24	Count of ED visits in month -2	1.1220	(1.044-1.207)
25	Discontinuance of statins in month -2	2.1470	(1.502-3.069)
26	Number of NAAs filled in month -4	0.8910	(0.849-0.935)
27	Part D spending [per \$100] in month -4	1.0130	(1.005-1.021)
28	SNF discharge in month 0	1.5280	(1.199-1.948)
29	SNF discharge in month -1	1.3940	(1.121-1.734)
30	ESRD in month 0	1.3810	(1.154-1.652)
31	Uncontrolled diabetes in month -1	1.2160	(1.11-1.331)
32	Eye exam in month -1	0.8350	(0.743-0.94)
33	Discontinuance of statins in month -3	1.8750	(1.278-2.752)
34	Hypoglycemia in month -4	1.7230	(1.146-2.589)
35	Black race	1.1210	(1.038-1.211)
	Other race	0.9470	(0.861-1.041)
36	SNF discharge in month -4	1.4000	(1.084-1.809)
37	Eye exam in month -2	0.8560	(0.762-0.962)
38	Hospital discharge in month -2	1.2090	(1.038-1.408)
39	Eye exam in month 0	0.8570	(0.765-0.962)
40	Uncontrolled diabetes in month -4	0.8770	(0.793-0.971)
41	A1c test in month -2	0.9040	(0.84-0.974)
42	Hypoglycemia in month -2	1.6290	(1.12-2.37)
43	SNF discharge in month -3	1.3050	(1.02-1.669)
44	Cancer in month -3	0.7680	(0.622-0.947)
45	Hospice admission in month 0	1.7790	(1.066-2.971)
46	Parts A & B spending [per \$100] in month -1	1.0010	(1-1.002)
47	Eye exam in month -3	0.8800	(0.784-0.988)
48	Age	1.0050	(1.002-1.008)
49	Old age as original reason for Medicare entitlement	0.9190	(0.848-0.995)
50	Part D spending [per \$100] in month -1	1.0080	(1-1.016)

A1c=hemoglobin A1c; ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blockers; CI=confidence interval; ED=emergency department; ESRD=end-stage renal disease; LIS=low-income subsidy; NAA=noninsulin antihyperglycemic agents; RxHCC=Prescription Drug Hierarchical Condition Category; SNF=skilled nursing facility.