Use of an Early Disease-Modifying Drug Adherence Measure to Predict Future Adherence in Patients with Multiple Sclerosis

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ABSTRACT

BACKGROUND: Patients with multiple sclerosis (MS) who are adherent to their treatment regimens are less likely to experience relapses and the cost associated with relapse. Pharmacists whose practice involves these specialty pharmaceuticals used to treat MS are striving for ways to improve outcomes by achieving treatment adherence in their patients. Specialty pharmacies have reported higher adherence rates than traditional pharmacies, which may translate to improved outcomes. Identifying patients who warrant increased adherence intervention is critical. Models using administrative health care claims to predict adherence have typically included demographic characteristics, comorbidities, and/or previous consumption of health care resources. Addition of a measure of early adherence may improve the ability to predict future adherence outcomes.

OBJECTIVE: To evaluate early adherence with disease-modifying drugs (DMDs) as a predictor of future adherence in patients with MS.

METHODS: The first DMD claim (i.e., index event) for adult MS patients (aged ≥18 years and aged ≤65 years) who received self-injected DMDs between January 1, 2006, and May 31, 2010, was identified in a national U.S. managed care database. Patients were required to have continuous eligibility for 12 months pre- and 24 months post-index. Multiple regression models were used to predict future adherence as measured by the proportion of days covered (PDC). The base model included age, gender, a medication intensity measure, presence of a non–MS-related hospitalization pre-index, and markers for physical difficulty, forgetfulness, or depression/stress. Models adding early DMD adherence as a covariate were analyzed using incrementing 30-day periods predicting the subsequent 360 days.

RESULTS: There were 4,606 patients included with an average age of 46.0 (SD 9.4) years, and 78.7% were female. Average PDC in the first 360 days post-index was 80.0% (SD 26.0). Using the first 60 days of early adherence as the only predictor in the model showed an R^2 of 20.6%. The base model (i.e., no early adherence measure but other covariates included) yielded an adjusted R^2 of only 2.3%. As the time period of early adherence is increased (from 60 to 360 days), the explained variance as measured by adjusted R^2 values increased from 20.6% to 53.5% (early adherence-only models). Addition of the covariates, other than early adherence, increased the R^2 by 1% to 2%.

CONCLUSIONS: Statistical predictive models that include early adherence with DMDs were able to explain the variance in future adherence outcomes to a greater extent than models based solely on baseline characteristics. The efficiency of an adherence intervention in reaching its intended target can be improved by using models such as these with enhanced specificity and selectivity.

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What is already known about this subject

- Multiple sclerosis (MS) patients with greater adherence to disease-modifying drug therapy have fewer relapses and increased quality of life, compared with nonadherent patients.
- Predictive models using patient characteristics are not very accurate in identifying which patients are likely to be nonadherent.
- Adherence to MS therapy has been shown to decrease costs and improve outcomes.

What this study adds

- Models that include a measure for early adherence are better predictors of future adherence than models that only include baseline characteristics.
- Adding other covariates (e.g., age, gender, a medication intensity measure, presence of a non–MS-related hospitalization pre-index, and markers for physical difficulty, forgetfulness, or depression/stress) to a predictive model using early adherence data to predict future adherence has only a small incremental effect on the model's predictive value.
- Models with early adherence data may be useful in simplifying the identification of target populations that may benefit from adherence interventions.

Multiple sclerosis (MS) patients adherent to disease-modifying drugs (DMD) have been shown to be associated with a decreased likelihood of experiencing relapse, emergency room (ER) visits, severe relapse, hospitalizations, neuropsychological issues, higher costs, and increased likelihood of higher quality of life compared with nonadherent patients.[1-4] An observational, multicenter, multinational phase 4 study of over 2,000 patients with an average treatment duration of 31 months found that the most common reason for medication nonadherence was forgetting to take the injection (50.2%).[3] Twenty-five percent of the patients in this analysis were nonadherent (i.e., missed at least 1 dose). Adherent patients reported a higher quality of life and less neuropsychological impairment.[3] In an analysis of 648 patients from an employer-based database, over a 2-year period, patients that were adherent to their DMDs had a 12.4% rate of severe relapse (i.e., hospitalization or ER visit) versus 19.9% for the nonadherent patients ($P = 0.013$).[4] Another 12-month analysis of an administrative claims database that used 2,446 subjects

evaluated the effect of adherence on MS-related outcomes while controlling for baseline demographic and clinical characteristics.[1] This analysis found that 59.6% were adherent, and compared with the nonadherent group, adherent patients were less likely to have MS-related inpatient hospitalization (odds ratio [OR] = 0.63, 95% confidence interval [CI] = 0.47-0.83) or an MS relapse (i.e., hospitalization or MS-related outpatient visit with steroid use within 7 days; OR = 0.71, 95% CI = 0.59-0.85).[1] A 3-year retrospective cohort analysis of a pharmacy and medical claims database found a lower risk of relapse (i.e., claims-based algorithm) for adherent patients (risk ratio [RR] 0.89; 95% CI 0.81, 0.97) compared with nonadherent patients during the baseline year. Relapse rates were not significantly different for the other study years. Patients that were adherent over the entire study period had a 3% lower risk of relapse ($P < 0.05$) over the 3-year study period.[2]

Physicians and pharmacists who care for patients using specialty products strive to improve adherence in an effort to improve outcomes and lower morbidity and its associated costs. In a comparison of immunosuppressive specialty products, patients receiving services and specialty medication from specialty pharmacies had improved adherence rates (87% vs. 83%) compared with patients receiving the same medications in traditional retail pharmacies.[5] A 5% improvement in adherence in a patient population may have significant consequences, especially if the improvement is in a subset of the patients; for example, if adherence efforts are focused on only 10% of the patients, these patients would have to improve their adherence by 50 percentage points (e.g., from 30% to 80%, or a significant consequence) for the population mean to improve by 5 percentage points. To achieve higher average adherence rates in a population, pharmacists may benefit from having tools and metrics that predict which patients are most likely to be nonadherent and may therefore be at an increased risk of experiencing an MS relapse. Interventions can be targeted at these individuals if they can be identified.

The efficiency of adherence improvement programs might be enhanced with the availability of simple methods with good predictive ability for identifying patients who might benefit from increased intervention. Conceptual frameworks have identified dozens of variables that could affect adherence.[6,7] Only a subset of these variables is available in administrative databases. A large national pharmacy benefit management company has developed a predictive model that employs 400 variables available in its database, including adherence to other medications and the adherence behavior of a spouse, but it did not describe its predictive validity nor indicate if early adherence behavior is included in the model.[8] Inclusion of a variable that estimates MS patient DMD medication compliance behavior (i.e., early adherence) may add predictive ability to the traditional variables available in administrative database adherence analyses. It is important to note that models using early adherence will have to be applied after the patient has been on therapy.

The purpose of this analysis was to evaluate a measure for early adherence with DMDs as a predictor of future adherence in patients with MS.

Methods

This analysis was designed as a descriptive, exploratory, retrospective analysis of pharmacy and medical claims data. Patients with third-party payer coverage were selected from the IMS Life Link Health Plans Database, which is an anonymous patient-centric, HIPAA (Health Insurance Portability and Accountability Act)-compliant, national managed care database that represented approximately 70 million enrollees from more than 65 health plans. Because the data are blinded and designed for research purposes, no institutional review board approval was necessary.

Patients were included in the analysis if they met the following 3 criteria: (1) had a DMD (interferon beta-1a intramuscular, interferon beta-1a subcutaneous, interferon beta-1b, or glatiramer acetate) billed using a National Drug Code (NDC) between January 1, 2006, and May 31, 2010; (2) had continuous insurance eligibility for medical and pharmacy services for 12 months before and 24 months after their first DMD claim date (i.e., index date) occurring between January 1, 2006, and May 31, 2010 (inclusive); and (3) were aged ≥ 18 years and aged ≤ 63 years.

Patients were excluded from the analysis if they met any of the following 5 criteria: (1) had any DMD claims reimbursed as a medical benefit (to ensure retention of only self-injectors); (2) had claims for more than 1 DMD at index; (3) had any claims for natalizumab (not self-injected) or fingolimod (very low counts because of the U.S. Food and Drug Administration approval date relative to the study analysis dates); (4) had missing, zero, or negative values for the days' supply variables required for calculation of adherence; or (5) had an unknown gender.

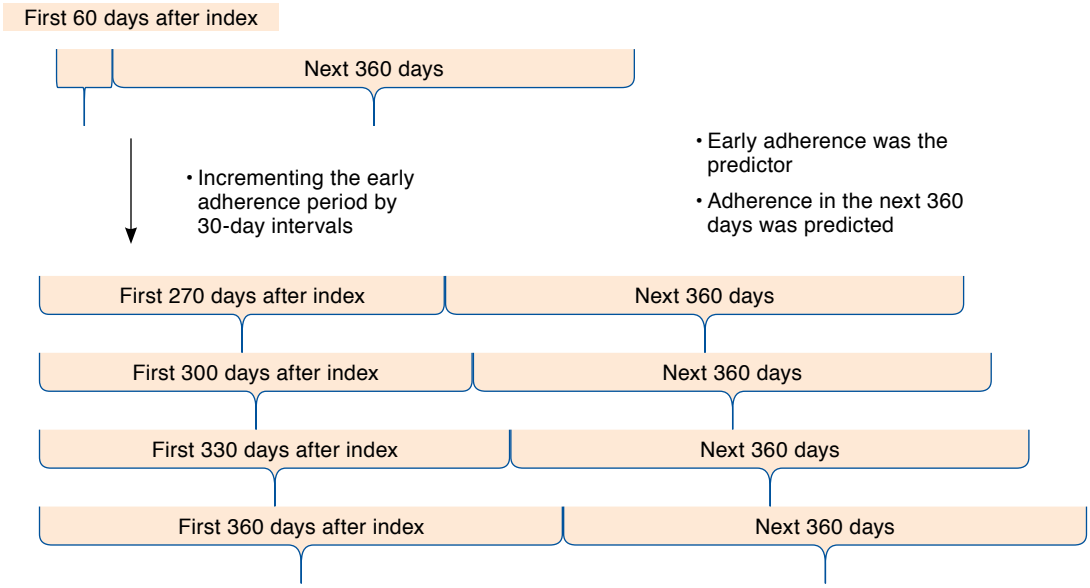
Adherence

Adherence was estimated across all DMD therapies by calculating the proportion of days covered (PDC) based on dispensing dates and number of days of medication supply. If the days' supply overlapped (i.e., patients had a prescription for the same product filled early), then it was assumed that the product was used sequentially, and the dates of use were extended. If days' supply overlapped across DMDs, then it was assumed that only 1 product was used, and overlapping dates were counted only once. The calculation of PDC was performed as follows:

PDC = (Number of days DMDs available during observation period) / (Number of days in the observation period)

Because there is not an accepted definition of early adherence, this analysis defined early adherence starting with a small interval (i.e., 60 days), and this time period was incremented in 30-day intervals (Figure 1). A period of 60 days was selected as a minimum value, since prescriptions are typically

FIGURE 1 Time Periods for Predicting Adherence



dispensed in 30-day supplies, and time for at least 2 prescriptions would be needed for a patient to have the opportunity to demonstrate nonadherence. The periods that were used for early adherence were 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, and 360 days. Adherence was evaluated for 3 cohorts: (1) all patients meeting analysis criteria (All); (2) the new patient cohort, defined as no DMD therapy for at least 180 days prior to index (New); and (3) the existing patient cohort, defined as presence of a DMD within 180 days prior to index (Existing).

Analyses

Linear multiple regression analysis was used to predict adherence as a continuous measure. R^2 was used to evaluate the percentage of variance explained by each model. The predicted values were also dichotomized to ≥80% or <80%, to assign patients to adherent or nonadherent groups, respectively. The dichotomized values were used in an analysis of sensitivity and specificity of the models predictive ability. SAS version 9.3 for Windows (SAS Institute, Inc., Cary, NC) was used for all analyses.

The following 3 models were evaluated:

1. *Covariates only without a measure of early adherence:* A base model predicting adherence in the 360 days post-index using the following static or pre-index variables (without the early adherence measure): age in years; gender; sum of the days' supply of all medications in the 180 days pre-index as a measure of prescription burden; an indicator for whether the patients had a non-MS hospitalization (anything other than *International Classification of Diseases, Ninth Revision, Clinical Modification* code 340.XX) in the 360 days pre-index; a dichotomous indicator for presence of diagnoses in the 360-day pre-index period that may create physical difficulty with medication adherence (rheumatoid arthritis, hand osteoarthritis, ataxia, optic neuritis, macular degeneration, blindness, tremor, or balance disorders); a dichotomous indicator for a diagnosis that may cause forgetfulness in the 360 days pre-index (Alzheimer's disease, dementias, alcohol dementia, unspecified brain damage, persistent unclassified mental disorders, mild cognitive impairment, or altered mental state); and a dichotomous indicator for a diagnosis for depression/stress in the 360 days pre-index (depression, anxiety, or bipolar disorder). Diagnosis codes used for assignment are available in Appendix A (available in online article).
2. *Early adherence measure models without covariates:* A model using only the early adherence measure predicting the subsequent 360 days. This model was repeated for the 60- through 360-day measures predicting the subsequent 360 days as shown in Figure 1, incrementing the early adherence period by 30-day intervals.
3. *Early adherence measure models with covariates:* A model using the covariates plus the early adherence measure predicting the subsequent 360 days. This model was repeated for the 60- through 360-day measures predicting the subsequent 360 days.

These models were analyzed for the All, New, and Existing patient subsets.

TABLE 1 Patient Characteristics

Variable	Existing Patients (n = 2,268)		New Patients (n = 2,338)		*P* Value[a]	All Patients (n = 4,606)	
Age, years, mean (SD)	47.8	(8.7)	44.3	(9.7)	<0.0001	46	(9.4)
Sex, female, n (%)	1,799	(79.3)	1,827	(78.1)	0.3291	3,626	(78.7)
PDC, mean % (SD)	84.2	(21.9)	76.0	(29.1)	<0.0001	80.1	(26.1)
Non-MS hospitalization, n (%)	147	(6.5)	258	(11.0)	<0.0001	405	(8.8)
Physical difficulty, n (%)	577	(25.4)	854	(36.5)	<0.0001	1,431	(31.1)
Forgetfulness, n (%)	55	(2.4)	41	(1.8)	0.1108	96	(2.1)
Depression/anxiety, n (%)	538	(23.7)	512	(21.9)	0.1405	1,050	(22.8)

[a]*Tested with independent 2-sample t-tests for continuous measures and chi square tests for categorical variables.*
PDC = proportion of days covered; SD = standard deviation.

TABLE 2 Regression Parameters Predicting 360-Day Post-Index Adherence, All Patients, Base Model[a]

Parameter	Estimate	Standard Error	*t* Value[b]	Probability of > *t* Value[c]
Age (in years)	0.00259	0.00043	6.02	<0.0001
Gender (male = 1)	0.00551	0.00935	0.59	0.5558
Sum number of days supply from all prescriptions in the 180 days pre-index	0.00003	0.000009	3.19	0.0014
Presence of a non-MS hospitalization in the 360 days pre-index	-0.07305	0.01361	-5.37	<0.0001
Physical difficulty diagnosis	0.0161	0.00833	1.93	0.0534
Forgetfulness diagnosis	0.0028	0.02697	0.1	0.9174
Depression/stress diagnosis	-0.03975	0.0095	-4.19	<0.0001

[a]*Base model: Covariates only without early adherence; 360-day post-index = first DMD in period.*
[b]*t value is the value for the statistical test that is calculated in the multiple regression model.*
[c]*The probability of a > t value is the probability of obtaining a t value that was at least as great as what was observed. This value reflects the significance of the test for the parameter as a predictor of adherence.*
DMD = disease-modifying drug; MS = multiple sclerosis.

A secondary analysis of sensitivity and specificity of the predicted values was conducted. The dichotomized adherence measures were used for this analysis, since this is reflective of how many payers evaluate adherence. The cut points of ≥80% or <80% were used to assign patients to adherent or nonadherent groups, respectively. The percentage of patients that were predicted by the model as adherent or nonadherent was compared with the actual values. Sensitivity measured the percentage of patients that were predicted to be adherent and who were actually adherent. Specificity measured the percentage of patients that were predicted to be nonadherent and who were actually nonadherent. A simple descriptive model examining the hypothetical cost of an intervention was evaluated for the 60- and 150-day models that included the early adherence measure and covariates.

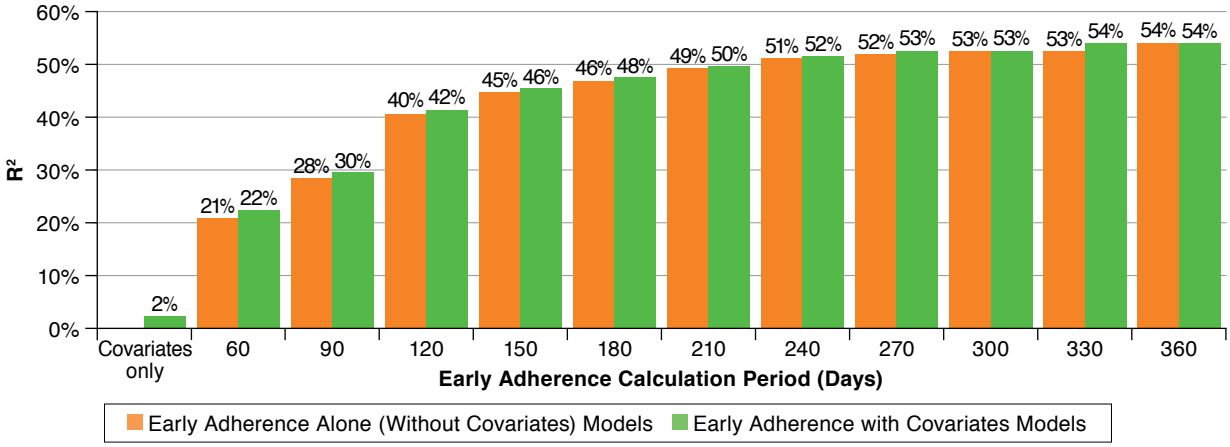
Results

After application of the inclusion and exclusion criteria as shown in Appendix B (available in online article), there were 4,606 adult patients with 12 months of continuous insurance eligibility before and 24 months after their first DMD claims in the database between January 1, 2006, and May 31, 2010 (Table 1). The cohort was 78.7% female and had an average age of 46 (standard deviation [SD] 9.4) years. There was little variation in the New and Existing patient cohorts in terms of age (P = <0.0001) and gender (P = 0.3291). Mean PDC was greater among the Existing patient cohort (84.2% [SD 21.9]) compared with the New patient cohort (76.0% [SD 29.1], P < 0.0001). A greater percentage of the New patient cohort had a non-MS hospitalization (11.0% vs. 6.5% for the Existing patient cohort, P < 0.0001). A higher percentage of the New patient cohort had a physical difficulty diagnosis (36.5% vs. 25.4% of the Existing patient cohort, P < 0.0001). A diagnosis of "forgetfulness" was not very common (2.1% of the sample overall, P = 0.1108). Diagnoses of depression and/or anxiety were similar between the cohorts and occurred in 22.8% of the sample overall (P = 0.1405).

Covariates-Only Model Without Early Adherence Measure

The base model (Model 1: Covariates only without a measure of early adherence) was used to predict adherence in the 360 days post-index. The base model results are shown in Table 2. Age, the sum number of days' supply from all prescriptions in the 180 days pre-index (proxy for diseases burden), having a

FIGURE 2 R^2 Values for Models with Early Adherence Measure with and Without Covariates Included in Model, All Patients



non-MS hospitalization, and having a depression/stress diagnosis were all significant predictors. While 4 of the predictive variables were statistically significant, the percentage of explained variance (R^2) was 2.26%; thus, the percentage of variance explained by these variables is relatively low. Models for New and Existing patient cohorts have similar levels of explained variance, so these subgroups are not shown separately, but the R^2 values illustrating the predictive value of the 2 models are shown in Appendix C (available in online article).

Early Adherence Measure Models with and Without Covariates

Using the early adherence measure as a lone predictor (Model 2) or adding an early adherence measure as a predictor of 360-day adherence to the base model (Model 3) results in substantially greater proportions of explained variance than the base model (Model 1: Covariates only without a measure of early adherence; Figure 2). Using just 60 days of early adherence alone resulted in R^2 values of approximately 20%. Ninety days of early adherence data added another 8% for a total of 28% of variance explained. As the time period increased monthly up to 360 days in the early adherence calculation period, the percentage of explained variance rose steadily to over 50%. Addition of the base model covariates added only 1% to 2% to the R^2 values of each early adherence model. In Appendix B (available in online article), model results are also shown for the New and Existing patient cohorts, with the models' predictive abilities being similar in both cohorts.

Sensitivity and Specificity

To illustrate the change in sensitivity and specificity of the different models, the base model (Model 1), 60-day early adherence with covariates (Model 2), and 150-day early adherence with covariates models (Model 3) were compared. Each of the early adherence models represented approximately a 20-percentage point incremental difference in R^2. The sensitivity of the model in accurately identifying the patients who will be adherent and the specificity of the model in accurately predicting the patients who will be nonadherent are shown in Table 3. Sensitivity (i.e., predicting adherent when they are actually adherent) of these 3 models ranged from 58% to 91%, and specificity (predicting nonadherent when they are actually nonadherent) ranged from 50% to 74%.

The sensitivity and specificity information can be used to help make adherence intervention allocation decisions as shown in Table 4. In this calculation, an intervention is delivered to all patients predicted by the model to be nonadherent, but not all patients predicted to be nonadherent actually will be nonadherent. So, the cost of reaching each actual nonadherent patient is calculated. For example, if the same $30 adherence intervention is given to each of the 4,606 MS patients in an effort to reach the 32.7%, or 1,506, who are actually nonadherent, $138,180 would be spent. In this case, $91.75 would be spent per successfully delivered intervention in an effort to deliver a $30 intervention to the nonadherent patient. By employing the covariate model, the efficiency is increased because $77.90 is needed to reach each nonadherent patient with a $30 intervention. Employing the 60- and 150-day models increases the efficiency of intervention delivery to $50.30 and $37.82, respectively, per $30 intervention delivered to a nonadherent patient. The increase in efficiency is indicated by the reduction in cost per intervention delivery.

Discussion

Most administrative databases are limited in the types of variables that are available for predicting adherence. The types of

TABLE 3 Number and Percentage of Patients by Model and Categorical Adherence Status[a] with Sensitivity and Specificity of the Prediction

Model	Adherent (≥80%)		Nonadherent (<80%)		Sensitivity[b]	Specificity[c]
	n	%	n	%	%	%
Actual adherence	3,100	67.3	1,506	32.7	NA	NA
Predicted adherence						
Covariate only (Model 1)	2,505	54.4	2,101	45.6	58.3	53.7
Covariate plus 60-day early adherence measure (Model 2)	3,351	72.8	1,255	27.2	83.7	49.7
Covariate plus 150-day early adherence measure (Model 3)	3,205	69.6	1,401	30.4	90.7	73.8

[a]*Patients were categorized as adherent based on an actual or predicted adherence of 0.80 or greater.*
[b]*Sensitivity is defined as the percentage of patients who were predicted to be adherent when they were actually adherent.*
[c]*Specificity is defined as the percentage of patients who were predicted to be nonadherent when they were actually nonadherent.*
NA = not applicable.

TABLE 4 Application of the Sensitivity and Specificity Results to Assess the Efficiency of Intervention Expenditures in Successfully Reaching Nonadherent Patients

Case	% Assumed or Predicted to be Nonadherent[a]	Number of Patients for Intervention	Total Cost Assuming $30 Cost for Each Intervention	Number Actually Nonadherent[b]	Cost Per Successful Targeted Intervention
All patients get the same intervention	100% assumed to be nonadherent	4,606	$138,180	1,506	$91.75
Covariate only (58% sensitivity, 54% specificity)	45.6%	2,101	$63,030	809	$77.90
Covariate plus 60-day early adherence measure (84% sensitivity, 50% specificity)	27.2%	1,255	$37,650	748	$50.30
Covariate plus 150-day early adherence measure (91% sensitivity, 74% specificity)	30.4%	1,401	$42,030	1,111	$37.82

Note: Sensitivity was defined as the percentage of patients who were predicted to be adherent when they were actually adherent. Specificity was defined as the percentage of patients who were predicted to be nonadherent when they were actually nonadherent.
[a]*Patients were categorized as adherent based on an actual or predicted adherence of ≥80%.*
[b]*There were 1,506 patients who were nonadherent (PDC < 80%) out of the 4,606 in the sample (32.7%). The remainder of the column is the number out of the 1,506 who were predicted nonadherent (i.e., specificity).*
PDC = proportion of days covered.

variables that are typically available may be significant predictors of adherence; however, they still may only explain a relatively small percentage of the variance in patients' future adherence. Addition of even short periods of early adherence in the time window under investigation improves the ability to predict future adherence, with diminishing returns as a longer time window of adherence data is added. The model works similarly for both New and Existing patient cohorts. Adding covariates to the early adherence models had a minimal effect on the proportion of explained variance.

While this analysis only evaluated an early adherence measure as a predictor of future adherence in MS patients, we expect that it would also apply to other disease states, but the strength of the relationships may differ. Predictive models for other diseases will have different needs, depending on the time course of the sequelae of the disease. While the simplicity of the linear models employed in this analysis has its advantages, because of the skewed nature of adherence data, models that assume different distribution properties may produce incremental improvements in this model, if additional accuracy is required. However, it is noteworthy that these simple models provide adequate predictive ability and are relatively easy to implement. As with any analysis of administrative claims data, coding may not always be accurate, and there may be missing information that limits the inferences that can be made from the data.

Early adherence did not specifically address reasons for discontinuation. Patients may have discontinued early because of lack of efficacy or tolerability issues. These patients would have a high likelihood of future nonadherence. Additional research distinguishing among different types of nonadherence is warranted, especially in chronic conditions where discontinuation of therapy is an issue.

A limited set of variables was used in this analysis of a nonexperimental observational design. Use of a broader range of variables, such as the more sophisticated 400-variable model that was previously mentioned,[7] would produce different

results than the abbreviated covariate-only model used in this analysis. MS is not a curable disease, and despite effective treatments, even with 100% adherence patients are not expected to be free of relapses. It is noted that adherence is only 1 predictor of relapse; other clinical variables that were not available in an administrative database would be expected to provide additional explanatory ability. Addition of clinical data available in electronic medical records could add additional predictive ability to the covariate portion of the models. This analysis is not an attempt to be critical of sophisticated multivariate models if no early adherence data are available; however, it is an effort to describe what additional predictive capability can be obtained when early adherence data are available for a particular patient. Our goal was to describe simple patient-specific models with small numbers of variables that could be implemented by health care organizations with minimal effort.

Models such as these could be used in decision algorithms to help target or focus the efforts of clinicians as they strive to increase adherence in an effort to improve patient outcomes and/or reduce cost of care. Such models can be added to the patient counseling/modeling software to help target efforts. The choice of which model to use (60-day, 90-day, 120-day, etc.) will be a function of the treatment goal, the interventions, and the amount of data available for the patient population of interest. For example, the less data available for prediction, the lower the sensitivity and specificity of the model. Use of a lower cost intervention may be justified with models that have lower predictive ability. As the cost and effectiveness of the intervention increases, the sensitivity and specificity of the model may need to be higher to justify the higher cost of the adherence intervention.

An advantage of using a patient's early adherence data to target adherence effort is the increased efficiency. As the duration of adherence data is increased, the efficiency is increased. But this advantage needs to be counterbalanced with the rate at which adverse consequences occur before an adherence intervention is administered. In some actual practice situations, an adherence intervention may need to be implemented before the early adherence data are available. There also may be an advantage to modifying the adherence behavior before it becomes a habit and is more difficult to change. These factors, along with the efficacy and cost of the adherence intervention, can be considered in a model that can predict the optimal timing of interventions.

Limitations

Administrative databases have limited availability of clinical variables, and this analysis predicted adherence using a relatively restrictive subset of the administrative data. Use of clinical data or additional combinations of claims data could result in improved predictive ability. However, the goal of this analysis was to use a simple approach relying on readily available data. The balance between model complexity and predictability warrants further exploration. Given the lack of clinical details in claims data, it is not possible to identify or differentiate the models on the basis of reason for nonadherence. Clarity about the reasons for nonadherence might influence the cohort for which modeling would be conducted and the types of interventions that might be delivered.

Conclusions

Predictive models that include a measure of early adherence with DMDs were able to describe the variance in future adherence outcomes to a greater extent than models based solely on baseline characteristics. The optimal amount of early adherence data needed to improve outcomes will vary based on the characteristics of the disease consequences and the adherence interventions. Statistical predictive models should be considered along with clinical relevance when making intervention decisions.

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DISCLOSURES

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Study concept and design was contributed by Kozma and Phillips, with assistance from Meletiche. Data were collected primarily by Kozma, with help from Phillips and Meletiche, and interpreted by Kozma, Phillips, and Meletiche, with assistance from Mackowiak. The manuscript was written by Kozma, Phillips, and Mackowiak, with assistance from Meletiche, and revised by Kozma and Mackowiak, with assistance from Phillips and Meletiche.

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APPENDIX A ICD-9-CM Codes Used for Symptom Indicators Potentially Related to MS

Symptom Category	Code Category	Codes
Physical difficulty	Rheumatoid arthritis	714.XX
	Hand osteoarthritis	715.04, 715.14, 715.24, 715.34, 715.94
	Ataxia	781.2X, 781.3X, 334.0X, 334.4X, 438.84
	Optic neuritis	377.3X
	Macular degeneration	362.5X
	Blindness	369.XX
	Tremor	781.0X, 331.1X
	Balance disorders	780.4X
Forgetfulness	Alzheimer's disease	331.0X
	Dementias	290.XX
	Alcohol dementia	291.2X
	Unspecified brain damage	310.9X
	Persistent unclassified mental disorders	294.XX
	Mild cognitive impairment	331.83
	Altered mental state	780.97
Depression/stress	Depression	296.2, 296.3, 296.9, 300.4, 311.XX, 309.0, 309.1X
	Anxiety	300.0X, 300.2X, 300.3X, 306.9X, 308.XX, 309.2X, 309.4X, 309.9X
	Bipolar disorder	296.0X, 296.1X, 296.4X, 296.5X, 296.6X, 296.7X, 296.8X

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; MS = multiple sclerosis.

APPENDIX B Application of Exclusion Criteria for Final Study Sample

Exclusion Criterion	Number of Patients Excluded	Number of Patients Remaining
Number of patients with a DMD claim based on NDC numbers between January 1, 2006, and May 31, 2010	NA	32,041
Exclude patients with more than 1 DMD at index (i.e., date of first DMD in time period)	13	32,028
Exclude patients with any natalizumab claims within 360 days before or 720 days after the index date	321	31,707
Retain patients with 12 months of pre-index eligibility and 24 months of post-index eligibility	23,813	7,894
Retain patients that are aged ≥18 years and aged ≤ 63 years	442	7,452
Exclude patients with unknown gender	1	7,451
Retain patients that are marked with a continuous Rx benefit for 12 months pre-index date and 24 months post-index date	2,373	5,078
Exclude fingolimod patients	3	5,075
Exclude patients that have missing, zero, or negative values for the days supply variable	469	4,606

DMD = disease-modifying drug; NA = not applicable; NDC = National Drug Code; Rx=prescription.

APPENDIX C Adjusted R^2 from the Continuous Regression Models

Predictor	Predicting	All Patients		New Patients		Existing Patients	
		No Covariate Model (%)	Covariate Model (%)	No Covariate Model (%)	Covariate Model (%)	No Covariate Model (%)	Covariate Model (%)
Pre-covariates only	360 post-index	NA	2.3	NA	2.1	NA	2.9
60 days	Next 360	20.6	22.4	19.4	21.1	22.0	24.1
90 days	Next 360	28.1	29.7	26.5	28.0	30.0	31.7
120 days	Next 360	40.2	41.5	39.5	40.5	40.4	41.8
150 days	Next 360	44.5	45.6	43.9	44.8	43.9	45.2
180 days	Next 360	46.4	47.5	45.9	46.7	45.5	46.9
210 days	Next 360	49.1	50.1	48.6	49.4	47.9	49.0
240 days	Next 360	50.9	51.8	51.1	51.8	48.3	49.3
270 days	Next 360	51.7	52.5	52.6	53.3	47.7	48.6
300 days	Next 360	52.5	53.2	53.1	53.8	49.0	49.9
330 days	Next 360	53.3	54.0	53.7	54.2	50.3	51.0
360 days	Next 360	53.5	54.0	53.8	54.2	50.4	51.0

NA = not applicable.