Volume 11 • Number 1 • 2008
VALUE IN HEALTH

Classifying Patients by Antipsychotic Adherence Patterns Using Latent Class Analysis: Characteristics of Nonadherent Groups in the California Medicaid (Medi-Cal) Program

Jeonghoon Ahn, PhD,[1] Jeffrey S. McCombs, PhD,[1] Changun Jung, MA,[1] Tim J. Croudace, PhD,[2] David McDonnell, MD,[3] Haya Ascher-Svanum, PhD,[3] Eric T. Edgell, PharmD, MS,[3] Lizheng Shi, PhD[4]

[1]University of Southern California, Los Angeles, CA, USA; [2]University of Cambridge, Cambridge, U.K.; [3]Lilly Research Laboratories, Eli Lilly and Company, Greenwood, IN, USA; [4]Tulane University, New Orleans, LA, USA

ABSTRACT

Objectives: This study identifies latent classes defined by varying degrees of adherence to antipsychotic drug therapy and examines the sociodemographic, clinical, and resource utilization correlates associated with membership in each adherence class.

Data and methods: Patient-level data were drawn from the 1994 to 2003, 100%-sample California Medicaid fee-for-service paid claims data for patients with schizophrenia (N = 36,195). The date of the first antipsychotic medication filled after January 1, 1999 was then used to divide each patient's data into a 6-month preindex (baseline) and a 12-month postindex (follow-up) period. Three categorical adherence indicators—a dichotomous variable of medication possession ratio greater than 0.80, the number of antipsychotic treatment attempts, and time to a change in antipsychotic medications—and two covariates—a categorical variable of duration of therapy and a dichotomous variable of polypharmacy—were used in the latent class model.

Results: A three-class model returned the lowest values for all the information criteria and was therefore interpreted as follows: The prevalence rates of the latent classes were 1) 14.8% for the adherent; 2) 20.7% for the partially adherent; and 3) 64.5% for the nonadherent. Membership in the nonadherent class was associated with minority ethnicity, being female, eligibility due to welfare status, prior hospitalizations, and a higher number of prior treatment episodes. Membership in the partially adherent class was associated with higher use of outpatient care, higher rates of depot antipsychotic drug use, and polypharmacy.

Conclusion: Multiple indicators of adherence to antipsychotic medication can be used to define classes of adherence that are associated with patient characteristics and distinct patterns of prior health-care use.

Keywords: adherence, latent class analysis, Medicaid, schizophrenia.

Introduction

Antipsychotic medication treatment can improve outcomes in schizophrenia, but poor outcomes have been associated with nonadherence to antipsychotic drug therapy. Nonadherence can precipitate clinical (symptomatic) relapse and trigger intensive resource utilization that significantly increases the total costs of care. Several studies using the California Medicaid (Medi-Cal) database have shown negative effects of antipsychotic nonadherence. For example, Gilmer et al. reported that only 41% of Medi-Cal patients take their antipsychotic medication on a regular basis and significantly higher outpatient and hospital medical costs are incurred to the patients who are not regularly adherent to their prescribed drug regimen [1]. Weiden et al. found an association between partial adherence and hospitalization risk among Medi-Cal patients with schizophrenia across a continuum of adherence behaviors [2]. McCombs et al. reported that delays in starting antipsychotic therapy and changes in therapy were associated with a significantly higher total cost of health care over 1 year using a sample of Medi-Cal patients with schizophrenia [3]. Patients who received some form of therapy, with no delay, exhibited lower costs than untreated patients, especially for psychiatric hospital treatment costs.

Adherence to medication has been measured in numerous ways [4], with the most prevalent measures being patient self-report, pill count, use of electronic monitoring devices, and review of prescription records and claims. Taken individually, none of these methods is error-proof (totally reliable), even direct patient observation. Therefore, clinicians and researchers must consider a range of adherence indicators when making determinations of whether or not the patient is adherent to the prescribed drug therapy.

Address correspondence to: Jeonghoon Ahn, Department of Pharmaceutical Economics and Policy, University of Southern California, 1540 East Alcazar Street CHP-140, Los Angeles, CA 90089-9004, USA. E-mail: jeonghoo@usc.edu

10.1111/j.1524-4733.2007.00214.x

1098-3015/08/48 48–56

Many studies in the published literature define nonadherence as either deliberate or unintended patient behavior that is not consistent with medical advice. For example, Marland defined nonadherence as occurring when patients passively failed to keep to their prescribed medication regime [5], while Blackwell states that nonadherence is the failure to comply with the prescribed medication regime [6]. In a large observational study, failure to refill was considered the most reliable objective measure of adherence to drug therapy [7]. McCombs et al. used medication persistence—measured as the time from the initiation of drug therapy to discontinuation of therapy—as their measure of medication adherence [8].

This study uses a statistical model employing multiple observable indicators of adherence to identify groups of patient adherence. Specifically, latent class analysis (LCA) is used to define otherwise unobserved groups of patients with different adherence behaviors that may be complex and nontrivial in their structure. The resulting adherence typology system is then used to examine the sociodemographic, clinical, and resource utilization/economic correlates of adherence classes and to document the relationship between adherence and the patient's health service utilization during the 1-year follow-up period across the adherence/nonadherence latent classes.

The conventional way of studying adherence is classifying patients into trivial groups of adherence, typically using arbitrary cutoff values of single indicators of adherence, and later examining the sensitivity of imposed adherence group assignments by applying other arbitrary adherence assignments. On the other hand, the introduction of LCA in adherence research has two main advantages: (i) it can answer the aforementioned significant measurement issues in determining the rates of nonadherence; and (ii) it will yield more precise estimation of adherence patterns because an appropriate LCA can classify patients based on multiple profiles of adherence. Specifically, identification of adherence groups is enhanced by multiple adherence indicators and their correlation/association structure. As more adherence indicators are available and the correlation/association of those indicators are stronger (unlike the conventional way of adherence assignment based on multiple adherence indicators implicitly assumes independence among the indicators), the advantages of LCA will be bigger.

Methods

Data

Data for this study were derived from a 100%-sample of the paid claims data files for the fee-for-service portion of the California Medicaid (Medi-Cal) program from 1994 to mid-2003 (available through the State of California Department of Health Services Medical Care Statistics Section with legal and human subject protection review approvals). The original data set included all patient episodes of antipsychotic treatment over this 10-year period. For this study, a patient-level data set was created by taking the first antipsychotic treatment episode of each patient initiated after January 1, 1999 to avoid some systematic changes possibly caused by a Medi-Cal event in October 1997 of removing prior authorization restriction on atypical antipsychotic agents [9]. All patients in the study sample had at least one claim with a recorded diagnosis of schizophrenia (International Classification of Diseases, Ninth Revision [ICD-9] = 295.0–295.9 or the word "schiz") during the study period (1999–2003).

These patient-level data included information on previous treatment attempts during the 6-month period before the index date (the start day of the first antipsychotic treatment episode initiated after January 1, 1999) with an exception of annualized number of episodes (1994–index date), demographic characteristics, medical and mental-health diagnostic profiles, and prior use of health services. Patients were excluded in the analysis if any of the following diagnoses was found: nonschizophrenic psychosis (ICD-9 = 291.xx–294.xx), bipolar disorder (ICD-9 = 296.00–296.19, 296.40–296.89), depression (ICD-9 = 296.20–296.39, 300.4x), other affective disorders (ICD-9 = 296.9x), anxiety (ICD-9 = 297.xx, 300.xx), substance abuse (ICD-9 = 303.xx–305.xx), personality disorder (ICD-9 = 301.xx), dementia (ICD-9 = 290.xx), and other mental-health diagnoses (ICD-9 = 299.xx, 302.xx, 306.xx–314.xx, 3216.xx). In addition, patients younger than 18 years of age at the index date and patients who used nursing home care before the index date were excluded from the analysis. In total, 36,195 patients were selected for the LCA.

Statistical Methods

Latent class analysis was developed in the 1960s to model attitudinal variables captured by social survey items with categorical responses [10]. LCA is now widely used and has become a standard tool for analysis in social, psychological, and biomedical research (see McCutcheon [11] for an elementary introduction, and Hagenaars and McCutcheon [12] for a summary of contemporary developments). Application of the LCA model has been facilitated by developments in statistical software. We used LatentGold 3.0 (Statistical Innovations, Inc., Belmont, MA, 2003) for LCA estimation [13] and STATA 8.2 SE (STATA Corporation, College Station, TX, 2005) for the additional statistical analyses.

For this study, an LCA cluster model was set up by using only adherence proxy variables (see variables subsection for more details) to interpret the identified

clusters as adherence groups. Specifically, an LCA cluster model with K-number of clusters can be expressed as follows [13]:

$$f(y_i|z_i) = \sum_{x=1}^{K} P(x|z_i) f(y_i|x, z_i)$$
$$= \sum_{x=1}^{K} P(x|z_i) \prod_{h=1}^{H} f(y_{ih}|x, z_i) \quad (1)$$

where y_i and z_i are a vector of the indicator variable and a vector of covariates included in estimation (active covariates) and x represents a latent class index unobservable from the data (no distributional assumption is needed). $f(\cdot|\cdot)$ and $p(\cdot|\cdot)$ denote conditional probability density function and conditional probability, i.e., $P(x \mid)$ is the mixing weight for conditional density $f(\cdot|x)$. H is the number of subsets where local independence (independent in this subset) among the indicator variables holds. Once the parameters of the latent class model had been estimated and class memberships established (LatentGold 3.0 uses posterior mode allocation to assign individuals to their most likely latent class membership [14]), inactive covariates of nonadherence were examined by profiling each latent class in terms of demographic, clinical, and utilization outcomes.

A difficulty in LCA cluster modeling is determining the number of clusters, K. Because there is no dominant criterion to choose the best model in terms of the number of classes, it was determined by comparing several criteria, including the likelihood ratio chi-square statistic (L^2) and information criteria such as the Akaike's information criterion (AIC), Bayesian information criterion (BIC), Consistent Akaike's information criterion (CAIC), and sample size adjusted Bayesian information criterion (ssaBIC). Information criteria penalize more complex models for the number of parameters, using different constants for model penalty. The classification error, which is measured by the difference between the calculated class sizes by assigning each individual proportionally to the estimated probability of class membership and the modal probability-assigned class sizes, was also reported.

Variables

Two types of variables were used in the LCA: 1) latent class indicators of drug therapy adherence, and 2) covariates (listed in Table 1).

Latent Class Indicators

The variables directly used in nonadherence latent class estimation are listed in Table 2. These variables are used to define or measure a latent index of adherence. Three observable categorical adherence indicators and two covariates were used in this study (see Eq. 1):

Table 1 Patient characteristics (N = 36,195)

Patient demographics	Number of patients	Percentage
Age		
18–25	1,917	5.3
25–35	6,154	17.0
35–45	11,386	31.5
45–55	9,634	26.6
55–65	4,598	12.7
65+	2,506	6.9
Race		
White	17,546	48.5
Black	6,785	18.8
Hispanic	1,590	4.4
Asian	1,351	3.7
Other/unknown	8,923	24.7
Male	19,505	53.9
Urban residence	28,309	78.2
Medi-Cal eligibility category		
Disabled	30,630	84.6
Aid for dependent children	3,584	9.9
Old age assistance	479	1.3
Blind	122	0.3
Other aid categories	1,380	3.8
Prior use of health care (baseline)		
Acute hospitalization	1,006	2.8
Psychiatric hospitalization	1,478	4.1
Ambulatory care services	23,546	65.1
Rehabilitation services	77	0.2
Community health center services	23,520	65.0
Suicide attempts	200	0.6
Annualized number of annual treatment episodes		
Number ≤ 1	5,822	16.1
1 < Number ≤ 2	12,018	33.2
2 < Number ≤ 3	8,115	22.4
3 < Number ≤ 4	4,444	12.3
Number > 4	5,796	16.0
Depot antipsychotic use	2,017	5.6
Annual health-care costs (follow-up)	Average	S.D.
Ambulatory outpatient care	$1,117	$4,263
Prescription drugs	$4,175	$4,666
Long-term care	$584	$5,489
Acute hospitalization	$317	$2,457
Psychiatric hospitalization	$938	$8,085
Community mental health centers	$2,524	$5,866
Total	$9,888	$14,658
Use of institutional service in follow-up period		**Percentage**
Long-term care		2.0
Acute hospital admission		5.1
Psychiatric hospital admission		7.2

1. a dichotomous adherence variable derived from the medication possession ratio (MPR; cutoff value of 0.8 used; Gilmer et al. [1]) for all antipsychotics;
2. a variable of the number of prior treatment attempts (five levels: 1, 2, 3, 4, ≥5); and
3. a variable documenting time to first change in antipsychotic medications during the first post-treatment year (five levels: no switch, time < 30, 30 ≤ time < 90, 90 ≤ time < 180, 180 ≤ time < 365 days).

Covariates in the LCA

Two types of covariates are used in LCA: active covariates and inactive covariates [15]. The former is used

Table 2 Distribution of adherence indicator variables and active covariates

	Number of patients	Percentage
Indicator variables		
Time to switch of antipsychotic		
No switch in 1 year	29,775	82.3
Switched in <30 days	1,629	4.5
Switched in 30–<90 days	1,983	5.5
Switched in 90–<180 days	1,408	3.9
Switched in 180–<365 days	1,400	3.9
Medication possession ratio		
<0.8	20,744	57.3
0.8	15,451	42.7
Number of treatment attempts		
1	9,036	25.0
2	9,019	24.9
3	7,329	20.3
4	4,972	14.7
>4	5,839	16.1
Active covariates		
Days of uninterrupted therapy		
<30	2,549	7.0
30–60	12,029	33.2
60–120	7,028	19.4
120–365	8,409	23.6
≥365	6,080	16.8
Polypharmacy		
Yes	2,941	8.1
No	33,254	91.9

in defining the latent index, i.e., actively involved in the estimation process, and the latter is used to profile the class but is not involved in the estimation process. Active covariates can be also considered predictors to determine whether they are associated with adherence class memberships, whereas inactive covariates are typically cross-tabulated with class memberships to describe each class.

Active covariates

1. a variable relating to the duration of uninterrupted therapy (less than 15-day gap) for all antipsychotics (five levels: duration < 30, 30 ≤ duration < 60, 60 ≤ duration < 120, 120 ≤ duration < 365, duration > 365 days); and
2. a dichotomous variable of polypharmacy defined as the concomitant use of two or more antipsychotic prescriptions for more than 60 days.

In this study, those variables involved in the LCA cluster estimation (indicators and active covariates) were limited to adherence proxy variables to reflect multiple profiles of adherence while minimizing the influences from other covariates not directly related to adherence, i.e., our focus is on adherence grouping not a mixed grouping of adherence and other covariates such as age or cost. Thus, our model-building process can be summarized as using adherence proxy variables to find a parsimonious LCA cluster model.

The inactive covariates used in this study include demographic variables at treatment initiation (age, sex, ethnicity, urban residence, and aid category), clinical and resource use variables during 6 months before the treatment initiation (e.g., dummy variables of various health-care services), the annualized number of prior episodes, and utilization outcome variables (cost variable for each health-care service) during the 12 months after the treatment initiation. The 6 months period before the treatment initiation and the 12 months period after the treatment initiation will be referred to as the baseline period and the follow-up period, respectively, for the remainder of this article.

Results

Characteristics of Study Population

The descriptive statistics of patient characteristics are shown in Table 1. The majority of patients in this study were 35 to 55 years of age (58.1%). Whites were the largest ethnic group (48.5%) and the difference between sexes was approximately 8% (female 46.1% vs. male 53.9%). Most patients lived in urban areas (78.2%) and had a disability (84.6%). During the 6 months before treatment initiation (baseline period), few patients had acute hospitalization (2.8%) or psychiatric hospitalization (4.1%). Most patients used outpatient care (65.1%) and community mental-health centers (65.0%). Patients had low rates of suicide attempts (0.6%) and depot formulation use (5.6%). Half of the patients (55.6%) had an annualized number of treatment episodes greater than 1 but less than or equal to 3.

During the 1-year follow-up period, the single most costly health-care cost category was prescription drugs ($4175), followed by ambulatory care provided by community mental-health centers ($2524), or physicians and other community-based providers ($1117). Use of institutional services was limited as only 2% of patients used nursing home care ($584); 5.1% used acute hospital services ($317) and 7.2% were admitted to a psychiatric hospital or psychiatric service in a community hospital ($938). The total average cost for all services over the 1-year follow-up period was $9888 (SD = $14,658).

The distributions of indicators and active covariates used in the adherence estimation are shown in Table 2.

During the year after treatment initiation, approximately 43% of patients had an MPR equal to or greater than 0.8, which implies that patients used at least 288 days of therapy during the first treatment year (not necessarily consecutive). Only 26% of patients, however, had a minimum of 240 days of uninterrupted drug therapy (not reported in Table 2). Additionally, approximately 18% of the patients were switched to a different antipsychotic agent. Taken together, these results indicate that a significant proportion of patients experienced a period of nonadherence in excess of 15

Table 3 Comparison of cluster analysis (active covariates: duration of therapy, polypharmacy)

No. of classes	L^{2*}	BIC	AIC	ssaBIC	CAIC	Degree of freedom	Proportion of classification errors
1	57,395	215,592	215,515	215,563	215,601	579	0.000
2	31,347	189,606	189,479	189,558	189,621	573	0.033
3	17,721	176,043	175,864	175,976	176,064	567	0.053
4	12,542	179,390	179,160	179,304	179,417	561	0.104

*All the *P*-values of likelihood ratio statistic L^2 are <0.01.
BIC, Bayesian information criterion; AIC, Akaike's information criterion; ssaBIC, sample size adjusted Bayesian information criterion; CAIC, consistent Akaike's information criterion.

consecutive days during the treatment episodes, but restarted their therapies relatively quickly.

Model Selection

Results for the one- to four-class LCA models using the three indicators mentioned earlier and two active covariates are presented in Table 3. All information criteria (AIC, BIC, ssaBIC, and CAIC) indicated that the three-class model had the lowest (best) values compared with the other LCA models. This model was considered the best model and is therefore further demonstrated in this section. One criterion that did not support the three-class model was the likelihood ratio chi-square statistic, which is conventionally used to find a model satisfying observed versus expected frequencies $P > 0.05$, but the bootstrapped *P*-value of this model was less than 0.01. This may have been caused by the large sample size in this study, which favors a higher number of clusters.

Adherence Classes

The model estimation results based on three latent classes are presented in Table 4.

The nonadherent group (class 1, 64.5% of the sample) had the lowest MPR values (86% had an MPR less than 0.8). Class 2 was the partially adherent group (20.7%) in which more than 91% of patients had an MPR equal to or greater than 0.8, but 58% of patients switched antipsychotic drug therapy. Class 3 was the "adherent" group (14.8%) with more than 99% of its patients having an MPR equal to or greater than 0.8. The adherent group was unlikely to switch therapy as more than 99% of patients in this group had only one treatment attempt, i.e., all three indicators were almost perfect markers of latent adherence. These results suggest that patients who need to change medication or augment their therapy are at much higher risk of discontinuation.

Table 5 shows the profile of each covariate for each of the three latent class groups. There were some noticeable characteristics in each group. Patients classified into the nonadherent group were more likely to be nonwhite female, and recipients of Aid for Family with Dependent Children, i.e., a representative patient in this group is a minority single mother with dependent children. Nonadherent patients were also more likely to use acute hospitalization and psychiatric hospitalization in both baseline and follow-up periods.

The partially adherent group had the highest rate of polypharmacy (34% vs. 2% in the nonadherent group

Table 4 Distribution of clusters: indicators

	Cluster 1 (Nonadherent)	Cluster 2 (Partially adherent)	Cluster 3 (Adherent)
Cluster size	0.6452	0.2068	0.1479
Standard error (SE)	(0.0029)	(0.0032)	(0.0012)
Indicators			
Time to switch to another antipsychotics			
0 Time to switch = 0	91%	42%	100%
1 Time to switch < 30	5%	7%	0%
2 30 ≤ Time to switch < 90	3%	17%	0%
3 90 ≤ Time to switch < 180	1%	16%	0%
4 180 ≤ Time to switch < 365	<1%	18%	0%
SE	0.0043	0.025	<0.0001
Medication possession ratio (MPR)			
0 MPR < 0.8	86%	9%	<1%
1 MPR ≥ 0.8	14%	91%	>99%
SE	0.0035	0.0052	0.0015
Number of antipsychotic treatment attempts			
1 Treatment attempts = 1	12%	12%	98%
2 Treatment attempts = 2	29%	29%	2%
3 Treatment attempts = 3	24%	24%	<1%
4 Treatment attempts = 4	16%	16%	0%
5 Treatment attempts > 4	19%	19%	0%
SE	0.0089	0.0179	0.0039

Table 5 Distribution of clusters: covariates

	Nonadherent (N)	Partially adherent (P)	Adherent (A)	*P*-value* (3-way comparison)	*P*-value† (N vs. P)	*P*-value† (N vs. A)	*P*-value† (P vs. A)
Active covariates							
Duration of therapy				<0.001	<0.001	<0.001	<0.001
<30	11%	1%	0%				
30–60	49%	6%	0%				
60–120	25%	15%	0%				
120–365	15%	58%	14%				
>365	<1%	19%	86%				
Polypharmacy				<0.001	<0.001	NA	NA
No	98%	66%	100%				
Yes	2%	34%	0%				
Inactive covariates							
Age				<0.001	<0.001	<0.001	<0.001
18–25	6%	5%	3%				
25–35	18%	16%	14%				
35–45	32%	31%	31%				
45–55	26%	28%	28%				
55–65	12%	13%	14%				
>65	7%	6%	9%				
Race				<0.001	<0.001	<0.001	<0.001
Asian	4%	3%	4%				
African American	22%	15%	12%				
Hispanic	5%	4%	3%				
Other	24%	25%	25%				
White	45%	53%	55%				
Male	53%	55%	57%	<0.001	<0.001	<0.001	0.041
Urban residence	79%	78%	78%	0.067	0.029	0.143	0.815
Medi-Cal aid category				<0.001	<0.001	<0.001	0.024
AFDC	12%	7%	6%				
Blind	<1%	<1%	<1%				
Disabled	83%	88%	89%				
Old age assistance	1%	1%	2%				
Other aid	4%	4%	4%				
Use of health-care services							
Long-term care (follow-up)	2%	3%	1%	<0.001	0.122	<0.001	<0.001
Acute hospitalization (baseline)	3%	2%	2%	<0.001	<0.001	<0.001	0.027
Acute hospitalization (follow-up)	6%	5%	3%	<0.001	<0.001	<0.001	<0.001
Psychiatric hospitalization (baseline)	4%	4%	3%	<0.001	0.236	<0.001	<0.001
Psychiatric hospitalization (follow-up)	8%	7%	3%	<0.001	<0.001	<0.001	<0.001
Ambulatory outpatient care (baseline)	65%	66%	65%	0.026	<0.001	0.234	0.06
Ambulatory outpatient care (follow-up)	75%	80%	76%	<0.001	<0.001	0.025	<0.001
Community mental-health center use (baseline)	64%	68%	66%	<0.001	<0.001	<0.001	0.003
Community mental-health center use (follow-up)	71%	76%	71%	<0.001	<0.001	0.635	<0.001
Annualized number of episodes (1 year)				<0.003	<0.001	<0.001	<0.001
≤1	18%	20%	28%				
≤2	18%	21%	26%				
≤3	19%	21%	21%				
≤4	21%	21%	15%				
>4	23%	18%	10%				
Suicide attempts	1%	1%	0%	0.013	0.154	0.004	0.06
Prior suicide attempts	4%	4%	1%	<0.001	0.04	<0.001	<0.001
Follow-up depot formulation use	5%	10%	1%	<0.001	<0.001	<0.001	<0.001
Follow-up health-care costs (SD‡)							
Ambulatory outpatient care	$1,170 ($4,390)	$1,121 ($3,846)	$877 ($4,253)	<0.001	0.123	<0.001	0.001
Prescription drugs	$3,355 ($4,427)	$6,119 ($5,040)	$5,033 ($4,094)	<0.001	<0.001	<0.001	<0.001
Long-term care	$579 ($5,489)	$827 ($6,356)	$268 ($3,981)	<0.001	<0.001	<0.001	<0.001
Acute hospitalization	$371 ($2,767)	$265 ($1,961)	$158 ($1,446)	<0.001	<0.001	<0.001	0.002
Psychiatric hospitalization	$992 ($7,212)	$1,134 ($10,793)	$433 ($7,194)	<0.001	0.241	<0.001	<0.001
Community mental-health centers	$2,301 ($5,515)	$3,350 ($7,001)	$2,338 ($5,504)	<0.001	<0.001	0.63	<0.001
Total	$8,988 ($14,280)	$13,050 ($16,774)	$9,396 ($12,374)	<0.001	<0.001	<0.001	<0.001

*Three-way comparison *P*-values were calculated by estimated class membership by the modal conditional probability for each patient. Chi-square test (r × c extended Fisher's exact test) was used for categorical variables (if any cell with <5% frequency) and ANOVA *F*-test was used for continuous variables.
†Pairwise comparison *P*-values were calculated by chi-square test (Fisher's exact test) for the categorical variables (if any cell with <5% frequency) and *t*-test for the continuous variables.
‡Standard deviations were calculated by modal probability assignment of each patient into an adherence group.
AFDC, Aid for Family with Dependent Children.

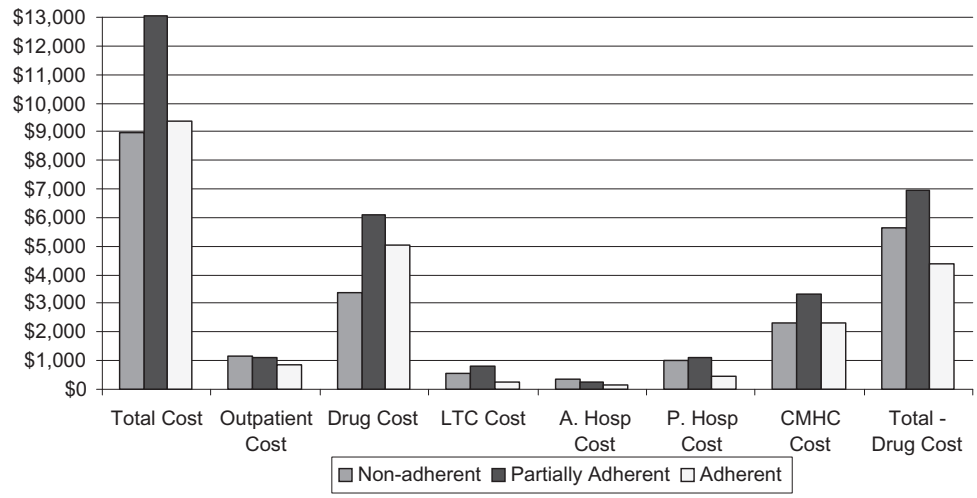

Figure 1 Comparison of cost outcomes.

and 0% in the adherent group), of depot formulation use (10% vs. 5% in the nonadherent group and 1% in the adherent group), of long-term care in the follow-up period, and the highest outpatient care use and community mental-health center use in both the baseline and the follow-up periods.

The adherent group was more likely to be white, male, and included a slightly higher number of seniors. Adherent patients also had the lowest rates of acute and psychiatric hospitalizations, suicide attempts, number of treatment episodes, depot drug use, and polypharmacy. All the covariates show significant difference at the 5% level in three-way comparison among the adherence classes except for urban residence.

Figure 1 shows a comparison of cost outcomes among the three latent classes. The total cost for the 12-month period after the index prescription was calculated for each patient and then averaged by each latent class. Interestingly, the nonadherent group showed the lowest average total cost ($8988) and the partially adherent group showed the highest average total cost ($13,050). The low average total cost for the nonadherent group was achieved despite the high rate of acute and psychiatric hospitalizations in the follow-up period. The adherent group has a lower average cost than the nonadherent group in all the cost categories except drug cost ($1678 higher) and community mental-health care center cost ($37 higher). The partially adherent group dominated the adherent group in all the cost categories and had the highest average costs in drugs, long-term care, psychiatric hospitalization, and community mental-health centers.

Discussion

Although conventional adherence research would have categorized patients as adherent or nonadherent using MPR in an arbitrary manner, the use of LCA in this study has helped identify three unique empirically derived adherence groups. If one were to group the patients by MPR equal to or greater than 0.8, as is typically done in adherence research, 42.7% of patients would have been defined as adherent whereas LCA identified only 14.8% as adherent. This difference could mean that LCA helped identify a subgroup of high-cost patients (labeled as partially adherent group), who could not be distinguished from the adherent group when using the conventional definition of adherence by MPR. Note that approximately 91% of the partially adherent group had an MPR equal to or greater than 0.8.

This study found that approximately two-thirds of the schizophrenia patients (64.5%) enrolled in the Medi-Cal program was nonadherent with their antipsychotic regimens. This rate is consistent with previous nonadherence rates reported in the literature, which ranged from 40% to 70% [16]. Nevertheless, the LCA estimated rate of full adherence found here based on MPR and four other proxies of adherence (14.8%) was much lower than that of a recent study among Medi-Cal beneficiaries with schizophrenia in San Diego County, California, which was based only on MPR (41%, Gilmer et al. [1]). While 91% of partially adherent patients in this study and almost 100% of adherent patients had an MPR equal to or greater than 0.8, the identification of three adherence groups by the LCA techniques has taken into account other profiles of adherence, such as the number of treatment attempts, switching drug therapy, polypharmacy, and duration of drug therapy. Hence, this study demonstrated that LCA is a useful methodology for estimating a typology of medication adherence, thus expanding its already wide applicability in medical research [17,18] and demonstrating its utility

in the study of adherence to antipsychotic medications in the treatment of patients with schizophrenia.

Current findings suggest that interruptions or changes in therapy before 90 days is a key indicator of nonadherence. Partially adherent patients frequently stay on their initial medication beyond 90 days, after which they discontinue therapy for a short time (>15 days), resulting in 44% of these patients switching to a different medication. Although the MPR for these partially adherent patients are typically greater than 80%, this group of patients may require greater attention from clinicians to help minimize gaps in therapy and facilitate a seamless transition to alternative drugs.

Nonadherent and partially adherent patients exhibited higher rates of utilization for all categories of health-care utilization other than medication utilization compared with adherent patients. Similar to results in Gilmer et al. [1], however, the total treatment cost over the 1-year follow-up period was higher for adherent patients because substantial drug costs. Nevertheless, any increase in costs associated with medication adherence must be balanced by the well-documented adverse consequences associated with nonadherence in other important areas, namely the reductions in patient well-being, disruptions of the therapeutic alliance between the patient and the physician, increased substance abuse [19], and increased hospitalization [1], all of which have long-term economic consequences.

The number of antipsychotic treatment attempts and time to change in antipsychotic medications reported here may be biased because of the exclusion of patients with gaps in their Medi-Cal paid claims history of more than 90 days. Specifically, well-functioning, continuously eligible Medi-Cal patients with schizophrenia may have been excluded. These patients would have been identified as having low cost and classified as nonadherent had they remained in the analysis. These patients would have increased the estimated difference in cost between adherent and nonadherent patients in favor of the nonadherent group. For example, a study on the health-care utilization of Michigan Medicaid enrollees with schizophrenia [20] reported an average total treatment cost of $14,512 in the follow-up period. If nursing home residents at treatment initiation are not excluded, the corresponding cost increases from $9888 to $13,786. Because nursing home patients tend to be adherent as a result of medication oversight provided in such environments, it may be more appropriate to exclude them in studies investigating the role of adherence. Another issue related to sample size is that a large sample size can affect the statistical significance. Some of significant differences reported in Table 5 may have been driven by the large sample size.

The prior use of depot formulations was found to be associated with nonadherence and partial adherence to oral antipsychotic medication. This is not surprising because these depot formulations are often used to treat patients with recurring adherence problems. Moreover, prior depot use can be used as a risk factor to identify patients who may benefit from closer adherence monitoring. Unfortunately, our study analysis was not able to track the depot-use patterns over time, because of anomalies in paid claims database for these medications [21], as data for days supply recorded on prescription claims for depot formulations are typically unreliable. This is a common problem with prescriptions for injectable medications. Second, multiple-dose depot prescriptions are commonly stored at the physician's office or other outpatient facilities and are frequently used to treat other patients once the vial has been opened. This practice makes it impossible to document medication adherence based on pharmacy purchase of refills. There is a clear need either to better identify the pattern of depot drug use in the Medi-Cal database or to find a new database suitable for analyzing such types of drugs.

Despite inherent limitations associated with paid claims data, LCA analysis was able to combine multiple widely used indicators of adherence based on medication refill record into a single model, and these adherence indicator-classified individuals to groups differing in adherence behaviors, with high accuracy (low classification error). Our typology of three patient adherence groups is supported by findings of outcomes in health-care utilization in a similar environment [1]. When data of patient-reported and clinician-reported adherence were available for the LCA analysis, a physician rating along with other three factors (e.g., substance abuse, recent hospitalization) defines adherence groups that may be targeted for intervention [22]. Further exploration of the utility of LCA in a clinically based, prospective study is warranted because it would enable the inclusion of additional adherence measures, such as self-report (patient or clinician), electronic devices, and review of prescription records or claims, to more accurately describe patients' adherence to medication regimens than LCA based on paid claims data.

Conclusions

This study identified latent classes related to adherence, partial adherence, and nonadherence using LCA. Three observable indicators of medication adherence (time to switch antipsychotic therapy, MPR, and number of treatment attempts) along with two active covariates (duration of antipsychotic therapy and polypharmacy) were used to construct a latent class index for adherence. Despite the need for continuous treatment with antipsychotic medications in the care of schizophrenia patients, there were high rates of nonadherence and partial adherence among patients with

schizophrenia covered by Medicaid. The adverse consequences associated with nonadherence and partial adherence call for closer patient monitoring to tailored interventions to improve patients' adherence to antipsychotic treatment regimens.

This study was funded by an unrestricted research grant from Eli Lilly and Company (Lilly) to the University of Southern California (principal investigator, Dr. Ahn). Lilly markets an antipsychotic agent olanzapine worldwide. Dr. Lizheng Shi coordinated this project and conceptualized the data analysis during his employment with Lilly. The article was completed during his employment with Tulane University. The authors are also grateful to the California Department of Health Services for providing access to the Medicaid 100% claims data. Dr. Croudace is an advisory board member of the Eli Lilly Schizophrenia Outpatient Health Outcomes study. University of Cambridge Department of Psychiatry has received research and infrastructure support from Eli Lilly and Company. In addition, Dr. Croudace has received remuneration to develop latent variable typologies for the Eli Lilly SOHO datasets. Drs Haya Ascher-Svanum and Eric T. Edgell are employees of Eli Lilly and Company.

Source of financial support: This study was funded by an unrestricted research grant from Eli Lilly and Company (Lilly) to the University of Southern California and the authors have no conflicts of interest that are relevant to the contents of this article.

References

1 Gilmer TP, Dolder CR, Lacro JP, et al. Adherence to treatment with antipsychotic medication and health care costs among Medicaid beneficiaries with schizophrenia. Am J Psychiatry 2004;161:692–9.
2 Weiden PJ, Kozma C, Grogg A, Locklear J. Partial compliance and risk of rehospitalization among California Medicaid patients with schizophrenia. Psychiatr Serv 2004;55:886–91.
3 McCombs JS, Nichol MB, Johnstone BM, et al. Antipsychotic drug use patterns and the cost of treating schizophrenia. Psychiatr Serv 2000;51:525–7.
4 Cleemput I, Kesteloot K, DeGeest S. A review of the literature on the economics of noncompliance. Room for methodological improvement. Health Policy 2002;59:65–94.
5 Marland GR. Atypical neuroleptics: autonomy and compliance? J Adv Nurs 1999;29:615–22.
6 Blackwell B. Treatment adherence. Br J Psychiatry 1976;129:513–31.
7 Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. J Clin Epidemiol 1997;50:105–16.
8 McCombs JS, Luo M, Johnstone BM, Shi L. The use of conventional antipsychotic medications for patients with schizophrenia in a medicaid population: therapeutic and cost outcomes over two years. Value Health 2000;3:222–31.
9 McCombs JS, Mulani P, Gibson PJ. Open access to innovative drugs: treatment substitutions or treatment expansion? Health Care Financ Rev 2004;25:35–53.
10 Lazarsfeld PF, Henry NW. Latent Structure Analysis. Boston, MA: Houghton Mill, 1968.
11 McCutcheon AL. Latent Class Analysis, Sage University Paper. Newbury Park: Sage Publications, 1987.
12 Hagenaars JA, McCutcheon AL, eds. Applied Latent Class Analysis. Cambridge: Cambridge University Press, 2002.
13 Vermunt JK, Magidson J. Latent GOLD User's Guide. Belmont, MA: Statistical Innovations Inc., 2000.
14 Gelman A, Carlin JB, Stern HS, Robin DB. Bayesian Data Analysis. London, UK: Chapman & Hall, 1995.
15 Magdison J, Vermunt JK. Latent class factor and cluster models, bi-plots, and related graphical displays. Sociol Methodol 2001;31:223–64.
16 Gray R, Wykes T, Gournay K. From compliance to concordance: a review of the literature on interventions to enhance compliance with antipsychotic medication. J Psychiatr Mental Health Nurs 2002;9:277–84.
17 Formann AK, Kohlmann T. Latent class analysis in medical research. Stat Methods Med Res 1996;5:179–211.
18 Croudace TJ, Jarvelin MR, Wadsworth ME, Jones PB. Developmental typology of trajectories to nighttime bladder control: epidemiologic application of longitudinal latent class analysis. Am J Epidemiol 2003;157:834–42.
19 Weiss KA, Smith TE, Hull JW, et al. Predictors of risk of nonadherence in outpatients with schizophrenia and other psychotic disorders. Schizophr Bull 2002;28:341–9.
20 Gibson PJ, Damler R, Jackson EA, et al. The impact of olanzapine, risperidone, or haloperidol on the cost of schizophrenia care in a Medicaid population. Value Health 2004;7:22–35.
21 Shireman TI, Svarstad BL, Sweeney JK. Validity of claims data for long-acting injectable medications. J Pharmacoepidemiol 1999;7:41–55.
22 Croudace TJ, Jones PB, Hammond GC, et al. Classifying and predicting antipsychotic adherence among schizophrenia outpatients in Europe: a latent class analysis. Value Health 2005;8:A8.