Latent Variable Analysis of Antipsychotic Adherence Among South Carolina Medicaid Beneficiaries With Schizophrenia

Charmi Patel,[1] Carmela Benson,[1] Pujing Zhao,[2] Ismaeel Yunusa,[2] Chris Kozma,[2] Gene Reeder,[2] Chao Cai[2]

[1]Janssen Scientific Affairs, LLC, Titusville, NJ; [2]University of South Carolina, College of Pharmacy, Columbia, SC

Background

- Schizophrenia is a chronic mental disorder characterized by delusions, hallucinations, and disorganized thinking, leading to relapses that are often due to poor medication adherence.[1,2] About 56% of US patients do not consistently take their antipsychotics, increasing comorbidity and reducing life expectancy[3,4]
- WHO identifies 2 types of medication adherence measurements: subjective (self-reports and healthcare evaluations) and objective (pill counts, electronic monitoring, and administrative claims data analysis).[5,6] For claims data, the most common measures of medication adherence are the medication possession ratio (MPR) and the proportion of days covered (PDC).[7,8] However, using a straightforward cut-off for MPR or PDC has limitations because it fails to differentiate between various adherence patterns
- Latent profile analysis (LPA) has been proposed to overcome this limitation. LPA can identify distinct adherent subgroups or profiles within a population based on patterns of medication adherence[9]

Objectives

- To explore via a latent variable framework, an underlying structure of medication adherence, for patients with schizophrenia who are prescribed antipsychotics
- To identify demographic and clinical factors that predict the likelihood of patients belonging to different latent adherence classes using multinominal logistic regression
- To assess the effects of various index long acting injectable (LAI) dosing schedules (14 days, 30 days, and 90 days) on latent adherence class membership using multinomial logistic regression

Methods

Design

- A retrospective database cohort analysis using South Carolina Medicaid paid claims from January 1, 2012 through December 31, 2019
- The database is fully compliant with the HIPAA privacy and security rules and includes provider and recipient files, eligibility file, medical and prescription drug claims files, inpatient and outpatient hospital files, and nursing home files
- The project was approved by SC Medicaid, the SC RFA, and the University of South Carolina Institutional Review Board

Patient selection

- Inclusion criteria:
  - Patients with age ≥18 years at the potential index date and age <65 years at the end of the study
  - ≥2 diagnoses (≥30 days apart) for schizophrenia (ICD-9-CM 295.xx or ICD-10-CM F20.x) or schizoaffective disorder (ICD-10-CM F25.0, F25.1, F25.8, F25.9) 12 months before the potential index date
  - At least 1 pharmacy billed (NDC) or medically billed (HCPCS) claim for an LAI or oral antipsychotic (OAP) drug
  - 12 months of Medicaid eligibility before and after the potential index date
- Exclusion criteria:
  - A diagnosis of bipolar disorder or pregnancy during the 12 months before the potential index date
  - A claim for residential inpatient facilities 12 months before and after the potential index date
  - Dual eligibility in 12 months before and after the potential index date
- Among the potentially qualifying index dates, the date that occurred closest (most recently) to the end of the patient identification window was set as the analysis index date
- If patient's index medication was an LAI, the patient was assigned to the LAI cohort. The remainder of the patients were assigned to the OAP cohort

Latent variable and indicator variables

- To explore the underlying structure of medication adherence for patients with schizophrenia, medication adherence was considered a latent variable. A latent variable is one that cannot be directly observed but is inferred from the observed adherent measures, known as an "indicator variable" in the latent variable framework. In this project, the indicator variables were defined as PDC, MPR, persistence, and the largest gap in therapy with antipsychotics (**Figure 1**)
- The first step was to determine the optimal number of latent classes using fit statistics such as Akaike's Information Criterion (AIC), Bayesian Information Criterion (BIC) and entropy, along with the principle of parsimony, and the interpretability of latent classes
- For the BIC and AIC, smaller values indicate better fitting models. For entropy, ranging from 0 to 1, a value closer to 1 signifies higher accuracy. Entropy values exceeding 0.8 are considered acceptable
- After establishing the number of latent classes, we assigned the latent classes meaningful labels

Calculations of indicator variables

- Adherence was observed using 4 measures: (1) PDC with a fixed denominator, (2) MPR with variable denominator while patients were persistent on therapy, (3) persistence, and (4) maximum gap of therapy in observational period
- PDC assesses the total number of days covered by medication over the fixed 1-year observational period; MPR was calculated with a variable denominator (i.e., between the index and the last prescription) and measures how consistently patients intend to take their medication when they have medication available; persistence was calculated as the percentage of days within the 365-day period between the first and last dispensing dates in which patients showed evidence of 'intent to treat' irrespective of drug usage in between
  - PDC (fixed denominator)

$$\frac{\text{no. of days covered (i.e., sum of days' supply) during observation period}}{365}$$

  - MPR (variable denominator)

$$\frac{\text{no. of days covered (i.e., sum of days' supply) from index to the date of the last dispensing event in the observation period (i.e., not counting the last dispensing days-supply)}}{\text{no. of days between the last dispensing event in the observation period and index + 1}}$$

  - Persistence (i.e., discontinuation)

$$\frac{\text{no. of days between the last evidence of therapy available during the observation period and index + 1}}{365}$$

  - Maximum gap of therapy (GAP) was calculated as the longest number of consecutive days without medication (i.e., days with no coverage as indicated by the days supplies and the dispensing dates) during observational period (i.e., 365 days)

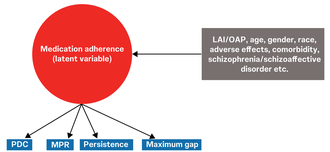
Potential predictors

- LAI/OAP, index year, sex, age group (18-34 years, ≥35 years), race (White/Caucasian, Black/African American, and Other/Unknown), Charlson-Elixhauser combined comorbidity score, user type (switcher, incident user, and ongoing user), specific comorbidity indicators (schizoaffective, depressive disorder, anxiety and fear-related disorder, substance-related disorder, suicidal ideation, chronic pulmonary disease, and diabetes), acute care visits, hospitalization, adverse effects, cognitive impairment (listed in the top right corner of **Figure 1**)

Statistical analysis

- Objective 1: use LPA to identify the underlying adherent classes
  - Observed adherent measures (PDC, MPR, persistence, maximum gap) were used to identify underlying a dherent classes in LPA
  - The key elements from LPA include identification of the conditional probability of being in each latent class given the observed indicator variables for each patient
  - Patients were placed into class membership based on the highest chance of membership to a class
  - A series of models were assessed assuming 2 through 6 latent classes and the BIC and AIC were compared to select the model with the best fit
  - Characteristics specific to each class were reported, including means and standard deviations for observed adherence measures (PDC, MPR, persistence, maximum gap)
- Objective 2: use multinomial logistic regression to evaluate the effects of demographic and clinical factors that predict the likelihood of patients belonging to different latent adherence classes
  - Multinomial logistic regression was conducted to assess the association between baseline characteristics and membership in latent classes
  - The best adherence class was treated as the reference group. Odds ratios were calculated by comparing the other classes with the reference group
  - The magnitude and significance of the effect for each predictor were estimated
- Objective 3: use multinomial logistic regression to evaluate the effects of different LAI dosing schedules
  - Multinomial logistic regression was conducted to assess the effect of different LAI dosing schedules on adherent class membership
  - LAIs were divided into three different dosing periods (14, 30, and 90 days)
- A *P*-value <0.05 was considered statistically significant
- All analyses were performed using SAS for Windows 9.4 (Cary, North Carolina) and R

FIGURE 1: Latent adherence variable diagram assuming 4 observed variables as indicators



LAI, long-acting injectable; OAP, oral antipsychotic; PDC, proportion of days covered; MPR, medication possession ratio.

Results

Sample characteristics

- A total number of 3,994 patients were included in our study. Among them, 1,421 were LAI users and 2,573 were OAP users (**Figure 2**)

FIGURE 2: Sample selection steps and attrition

Step 1: Identify potentially qualifying events	
≥1 LAI/OAP claim (1/1/2015 - 12/31/2018) with each claim being a potential index date n = 13,088 patients and 356,861 dates	
Step 2: Apply the remainder of the selection criteria to each of the potentially qualifying index dates	
≥12 months continuous Medicaid enrollment pre- and post-index date	n = 11,524 patients 328,029 dates
Age ≥18 years at index date and <65 years at the end of study date	n = 11,499 patients 302,074 dates
≥2 diagnoses (≥30 days apart) for schizophrenia or schizoaffective disorder 12 months pre-index	n = 7,344 patients 215,654 dates
No diagnoses for bipolar disorder or pregnancy 12 months pre-index	n = 6,513 patients 183,804 dates
No claims from residential inpatient facilities	n = 5,588 patients 137,824 dates
No dual eligibility	n = 3,994 patients 108,944 dates
Step 3: Select the closest qualifying date as the index date	
Step 4: If the index drug is LAI, then assign to LAI cohort n = 1,421	**Step 5: Assign remainder to OAP cohort n = 2,573**

Latent profile model selection

- The goodness of fit indices (**Table 1**) indicated that the best-fitting model was a 6-class solution; AIC and BIC decreased as the number of classes increased from 2 to 6. However, even though models with 5 and 6 classes show lower AIC and BIC values, an excessive number of classes could lead to overfitting, thereby reducing the accuracy in estimating the relationship between patient characteristics and membership in trajectory classes. We selected the models with 4 classes for the modeling of adherence

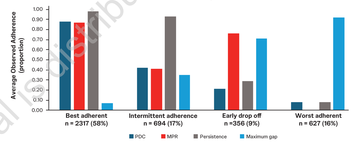
TABLE 1: Fit indices for a 2-class model through to a 4-class model

	Fit Statistics			
Number of Latent Classes	**AIC**	**BIC**	**Log Likelihood**	**Entropy**
2 Class	13,322	13,442	-6642.289	1.00
3 Class	10,843	10,994	-5397.734	0.96
4 Class	6,110	6,293	-3026.466	0.97
5 Class	5,150	5,364	-2802.786	0.95
6 Class	3,773	4,019	-986.317	0.96

Prevalence and profiles of latent adherence classes

- Our final model identified 4 latent classes: best adherent (n = 2317; 58%); intermittent adherent (n = 694; 17%); early drop-off (n = 356; 9%); worst adherent (n = 627; 16%) (**Figure 3**)

FIGURE 3: Prevalence and profile of 4 latent adherence classes



PDC, proportion of days covered; MPR, medication possession ratio.

Association between patient characteristics and adherence class membership

- **Table 2** shows the estimated coefficient for each predictor of belonging to a given latent class compared to best adherent class (reference group)
- Membership into latent classes was significantly associated with LAI/OAP use, age group, race group, index year, user type (switcher, incident user or on-going user), suicide attempt, tardive dyskinesia (TD, a proxy for adverse events), diabetes

TABLE 2: Association between patient characteristics and latent class membership with "best adherence" as reference using multinominal logistic regression model

	Latent Class					
	Intermittent Adherence		Early Drop-Off		Worst Adherence	
Predictor Variable	**OR**	***P***	**OR**	***P***	**OR**	***P***
LAI (OAP ref)	0.83	0.05	0.59	0.00	0.54	0.00
Male (Female ref)	0.90	0.24	0.99	0.92	0.80	0.04
18-34 (≥35 ref)	0.94	0.53	1.48	0.00	1.42	0.00
Black/African American (White/Caucasian ref)	1.54	0.00	1.17	0.65	1.27	0.09
Other/unknown (White/Caucasian ref)	1.70	0.00	0.90	0.50	1.38	0.03
Index year 2016 (2015 ref)	1.09	0.71	1.07	0.80	0.88	0.51
Index year 2017 (2015 ref)	1.11	0.64	0.86	0.57	0.96	0.84
Index year 2018 (2015 ref)	0.80	0.23	0.62	0.03	0.19	0.00
Incident user (Switcher ref)	7.17	0.00	10.59	0.00	32.79	0.00
On-going user (Switcher ref)	1.02	0.88	0.77	0.08	1.48	0.01
Schizoaffective (Absent ref)	1.06	0.49	1.00	0.97	1.19	0.11
Depressive disorder (Absent ref)	0.90	0.50	1.03	0.89	0.79	0.18
Anxiety and fear-related disorder (Absent ref)	1.20	0.20	1.22	0.25	1.34	0.05
Substance-related disorder (Absent ref)	1.31	0.08	1.39	0.09	1.13	0.46
Chronic pulmonary disease (Absent ref)	0.97	0.81	0.73	-0.15	0.73	0.07
Suicide (Absent ref)	1.70	0.03	1.57	0.13	1.77	0.03
Tardive dyskinesia (Absent ref)	0.60	0.01	0.49	0.00	0.36	0.00
Diabetes (Absent ref)	0.63	0.00	0.61	0.03	0.62	0.01
Cognitive impair (Absent ref)	0.66	0.40	0.81	0.73	1.07	0.89
Combined comorbidity score (1-unit change)	1.01	0.80	0.98	0.61	0.96	0.36
Acute visits (1-unit change)	1.00	0.43	1.01	0.45	1.01	0.17
Hospitalizations (1-unit change)	1.15	0.07	1.15	0.17	1.22	0.02

LAI, long-acting injectable; OAP, oral antipsychotic; OR, odds ratio

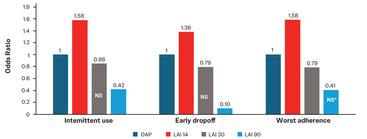
TABLE 3: Association between dosing schedules and latent class membership with "best adherence" as reference using a multinominal logistic regression model

	Latent Class					
	Intermittent Adherence		Early Drop-Off		Worst Adherence	
Predictor Variable	**OR**	***P***	**OR**	***P***	**OR**	***P***
LAI 14 days (OAP ref)	1.58	<0.01	1.36	0.04	1.58	<0.01
LAI 30 days (OAP ref)	0.86	0.19	0.79	0.11	0.79	0.05
LAI 90 days (OAP ref)	0.42	0.02	0.10	0.02	0.41	0.06

LAI, long-acting injectable; OAP, oral antipsychotic.
This model was also adjusted by other predictors (results were the same as shown in **Table 2**).

- Odds of being in the any labeled group versus "best adherence" for LAI subgroups versus OAP (reference) (**Table 3, Figure 4**)
  - 14-day LAIs had greater odds in all 3 non-adherence groups versus OAP for being in their group versus the best adherent group
    - The odds of being in the "intermittent adherent" group versus the "best adherence" group were 1.58 times greater for the shortest acting LAIs versus OAP (*P* < 0.01)
    - The odds for being in the "early drop-off" versus the "best adherence" group were 1.36 times greater for the shortest acting LAIs versus OAP (*P* = 0.04)
    - The odds of being in the "worst adherence" group versus the "best adherence" group were 1.58 times greater for the shortest acting LAIs versus OAP (*P* < 0.01)
  - 30-day LAIs only distinguished between the worst adherence and "best adherence" group
    - The odds for being in the "intermittent adherence" group versus the "best adherence" group were not significantly different for the 30-day LAIs versus OAP (*P* = 0.19)
    - The odds for being in the "early drop-off" versus the "best adherence" group were not significantly different for the 30-day LAIs versus OAP (*P* = 0.11)
    - The odds for being in the "worst adherence" group versus the "best adherence" group were 21% less for the 30-day LAIs versus OAP (*P* = 0.05)
  - 90-day LAIs had lower odds in all 3 adherence groups versus OAP for being in their group versus the best adherent group
    - The odds for being in the "intermittent adherence" group versus the "best adherence" group were 58% less for the 90-day LAIs versus OAP (OR = 0.42, *P* = 0.02)
    - The odds for being in the "early drop-off" versus the "best adherence" group were 90% lower for the 90-day LAIs versus OAP (OR = 0.10, *P* = 0.02)
    - The odds for being in the "worst adherence" group versus the "best adherence" group were not statistically significantly different for the 90-day LAIs versus OAP (*P* = 0.06, borderline significant)

FIGURE 4: Odds of being in any labeled group versus best adherence for different LAI versus OAP (reference)



NS= Non-significant (*P*>0.05); NS* = borderline significant (*P*=0.06); all others are significant (*P*<0.05)

LAI, long-acting Injectable; OAP, oral antipsychotics; LAI 14, LAI with a 14-day dosing schedule; LAI 30, LAI with a 30-day dosing schedule; LAI 90, LAI with a 90-day dosing schedule

Limitations

- Data in administrative database represent paid claims for medications that are dispensed; no information is available regarding if the medication was taken
- Although the group assignment is determined at the index date, it is possible that 1 patient could be in a different group (i.e., different index medication) because of varying identification and follow-up time windows
- LAIs may be prescribed to patients known to have poor adherence in the past
- Methods used to classify claims as outpatient physician visits may differ among administrative databases
- The prevalent user design may provide a conservative estimate of differences in adherence between the cohorts
- The latent adherent class was assumed static rather than dynamic in this project

Conclusion

- This study used latent variable framework to assess medication adherence among South Carolina Medicaid beneficiaries with schizophrenia and identified 4 latent adherence classes: "best adherence"(consistent use), "intermittent adherence"(sporadic use), "early drop-off"(brief engagement then discontinuation), and "worst adherence"(minimal/no use)
- Findings highlight that OAP users showed higher likelihood of nonadherence compared to LAI users, with notable disparities in gender, age, race, clinical characteristics, treatment history and dosing schedules
- The study uncovered the heterogeneity of adherence profiles using latent variable framework, underscoring the need for personalized interventions to improve patient outcomes

Acknowledgements

We thank the South Carolina Revenue and Fiscal Affairs (SC RFA) office for providing the data on Medicaid beneficiaries with schizophrenia in South Carolina.

Neuropsychiatry

Scan the QR code

The QR code is intended to provide scientific information for individual reference, and the information should not be altered or reproduced in any way.

Supported by Janssen Scientific Affairs, LLC, a Johnson & Johnson company

Presented at Psych Congress Elevate; May 30-June 2, 2024; Las Vegas, Nevada

References

1. Patel KR, Cherian J, Gohil K, Atkinson D. Schizophrenia: overview and treatment options. P T. 2014;39(9):638-645 **2.** Emsley R, Chiliza B, Asmal L, Harvey BH. The nature of relapse in schizophrenia. *BMC Psychiatry*. 2013;13:50. Published 2013 Feb 8. doi:10.1186/1471-244X-13-50 **3.** Charlson FJ, Ferrari AJ, Santomauro DF, et al. Global Epidemiology and Burden of Schizophrenia: Findings From the Global Burden of Disease Study 2016. *Schizophr Bull*. 2018;44(6):1195-1203. doi:10.1093/schbul/sby058 **4.** Perkins AJ, Khandker R, Overley A, et al. The impact of antipsychotic adherence on acute care utilization. *BMC Psychiatry*. 2023;23(1):64. Published 2023 Jan 24. doi:10.1186/s12888-023-04558-6 **5.** Lam WY, Fresco P. Medication Adherence Measures: An Overview. *Biomed Res Int*. 2015;2015:217047. doi:10.1155/2015/217047 **6.** Anghel LA, Farcas AM, Oprean RN. An overview of the common methods used to measure treatment adherence. *Med Pharm Rep*. 2019;92(2):117-122. doi:10.15386/mpr-1201 **7.** Raau RS, Hunt SL, Dai J, Cui H, Phadnis MA, Jain N. Accurate Medication Adherence Measurement Using Administrative Data for Frequently Hospitalized Patients. *Hosp Pharm*. 2021;56(5):453-461. doi:10.1177/0018578720985508 **8.** Ihle P, Krueger K, Schubert I, et al. Comparison of Different Strategies to Measure Medication Adherence via Claims Data in Patients With Chronic Heart Failure. *Clin Pharmacol Ther*. 2019;106(1):211-218. doi:10.1002/cpt.1378 **9.** Ahn J, McCombs JS, Jung C, et al. Classifying patients by antipsychotic adherence patterns using latent class analysis: characteristics of nonadherent groups in the California Medicaid (Medi-Cal) program. *Value Health*. 2008;11(1):48-56. doi:10.1111/j.1524-4733.2007.00214.x