Primary Nonadherence to Medications in an Integrated Healthcare Setting

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Objectives: To measure primary nonadherence (PNA) rates for 10 therapeutic drug groups and identify factors associated with PNA to chronic and acute medications.

Study Design: Retrospective cohort study.

Methods: New prescriptions written in an integrated healthcare system for study drugs were identified between December 1, 2009, and February 28, 2010. PNA was defined as the failure to fill a prescription within 14 days of when it was written. PNA rates were calculated by drug group and descriptive statistics were performed. Multivariable logistic regression was used to identify significant patient, provider, and prescription characteristics associated with PNA. Results were stratified by acute versus chronic treatment.

Results: A total of 569,095 new prescriptions were written during the 3-month period. Across all drug groups, the PNA rate was 9.8%. PNA rates for individual drug groups varied and were highest for osteoporosis medications (22.4%) and antihyperlipidemics (22.3%). Patients who filled at least 1 prescription in the prior year (odds ratio [OR], 95% confidence interval [CI] for acute = 0.06 [0.06-0.07], for chronic = 0.11 [0.10-0.12]) or had a prescription for a symptomatic disease (OR = 0.51 [0.48-0.53]) were more likely to fill their prescription. Patients were more likely to be primary nonadherent if they were black (OR acute = 1.30 [1.25-1.36], chronic = 1.26 [1.18-1.33]) or treatment-naïve to therapy (OR acute = 2.52 [2.36-2.7], chronic=1.07 [1.03-1.12]).

Conclusions: Overall PNA was 9.8% but individual PNA rates varied by therapeutic drug group. Factors of PNA were mostly consistent across drug groups, but some depended on whether the treatment was acute or chronic.

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For author information and disclosures, see end of text.

Healthcare professionals and payers are constantly looking for ways to improve patient health outcomes while decreasing costs. One possible approach to this challenge is to improve medication adherence, which refers to the extent to which patients take their medications as prescribed by their provider.[1] Prior research has suggested that improved adherence is associated with better health outcomes and lower overall health costs for certain chronic diseases such as diabetes, hypertension, hypercholesterolemia, and congestive heart failure.[2-4]

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Most adherence research has focused on "secondary nonadherence," which occurs when patients do not refill their prescriptions on time or they discontinue their medications altogether. A less-studied form of medication nonadherence is called "primary nonadherence" (PNA), which occurs when patients fail to pick up a newly prescribed prescription from the pharmacy.[5] Incidence, causes, and outcomes of PNA are relatively unknown compared with those of secondary nonadherence. Since most chronic and acute diseases in the United States are often managed by prescription medications, PNA could potentially be a significant factor in determining healthcare outcomes and costs, especially if the rate of PNA is high.

PNA rates vary widely in the literature, ranging from 0.5% to 57.1% depending on the study setting, therapeutic drug group, and methodological factors such as the way PNA is defined.[6] PNA studies in integrated healthcare delivery systems have usually been limited to medications used to treat chronic diseases such as diabetes, hyperlipidemia, and hypertension, with PNA rates ranging from 3.2% to 13% depending on the drug therapeutic group.[7,8] Examining PNA to both chronic and acute medications provides a more comprehensive understanding. Identifying risk factors associated with PNA may help clinicians target patients who are at risk.

In this study, we examined the rates and risk factors of PNA in an integrated healthcare setting across 10 drug groups which included both chronic and acute medications. Study objectives were 1) to measure PNA rates for 10 therapeutic drug groups, and 2) to identify patient, prescriber, and prescription risk factors for PNA to chronic and acute medications.

METHODS

Setting

This retrospective cohort study was conducted at Kaiser

In this article
Take-Away Points / p427
www.ajmc.com
Full text and PDF
Web exclusive
eAppendices A-D

Permanente Southern California (KPSC) in Downey, California, and was approved by the KPSC Institutional Review Board. KPSC is a large managed care organization providing comprehensive healthcare to an estimated 3.3 million members at 14 medical centers. Patient information on demographics and healthcare encounters (diagnoses, procedures, laboratory results, and prescriptions) are captured in the Kaiser electronic medical record (eMR) system. KPSC members receive the majority of their healthcare and prescriptions at Kaiser Permanente facilities. Medical centers vary in population size from Kern County—serving only 92,745 patients, to San Diego—serving 490,154 members. All prescribers enter all prescriptions in the eMR system and the information is electronically sent to the Kaiser pharmacy of the patient's choice. Copay information is only available for sold prescriptions.

Take-Away Points

This retrospective cohort study of 569,095 new prescriptions in an integrated healthcare setting measures primary nonadherence (PNA) rates for 10 drug groups and examines patient, prescriber, and prescription factors associated with primary adherence to chronic and acute medications.

- PNA rates vary by drug group and are highest for antiosteoporosis medications and antihyperlipidemics.
- Patients who filled at least 1 prescription in the prior year or had a prescription for symptomatic disease were more likely to fill their prescription.
- Patients who were treatment-naïve to disease therapy, black or Hispanic, or had certain baseline comorbidities were less likely to fill their prescription.

Inclusion and Exclusion Criteria

A total of 10 therapeutic drug groups were selected based on disease prevalence, clinical interest, or the potential impact of PNA on healthcare outcomes: anti-infectives, analgesics, migraine medications, antidiabetics, osteoporosis medications, cardiovascular agents, antihyperlipidemics, antiasthmatics, antidepressants, and anticoagulants. The first 3 drug groups were categorized as acute therapy and the remaining were categorized as chronic therapy. Each therapeutic drug group consists of several drug classes (**eAppendix A**, available at **www.ajmc.com**). For example, the antidiabetics therapeutic drug group includes drug classes such as insulin and sulfonylureas. A total of 874 individual drug products were included in the study.

New prescriptions for a study drug prescribed between December 1, 2009, and February 28, 2010, were included. A new prescription was defined as a drug with no prior dispensing in the same drug class during the 12 months before the date the prescription was ordered (index date). For example, a sulfonylurea prescription would not be considered new if a prescription for a drug in the sulfonylurea class was dispensed during the 12 months prior to the index date. This minimized the effect of preexisting drug supplies on current filling and also excluded prescriptions used as augmentation therapy or those episodes where drugs were switched within a drug class.

Patients were required to have continuous membership and drug benefits for 12 months before and after the index date. The post-index drug benefit criterion was designed to maximize the likelihood that patients filled their medications at Kaiser rather than at outside pharmacies. The 12-month pre-index period was used to identify baseline patient characteristics.

Prescriptions that were renewed, transferred from an outside pharmacy, verbally ordered by the prescriber, printed out in the doctor's office, or were hard copy prescriptions from outside providers were excluded from the study. Prescriptions that were switched to a different drug or later cancelled by the prescriber before being picked up by the patient were also excluded. In addition, prescriptions that had missing patient demographic information or that were filled at a Kaiser pharmacy located outside of Southern California were excluded. Lastly, since pregnancy complicates medication therapy and may result in drug discontinuation, prescriptions written for female patients who had become pregnant (based on gestation date) during the study period were excluded.

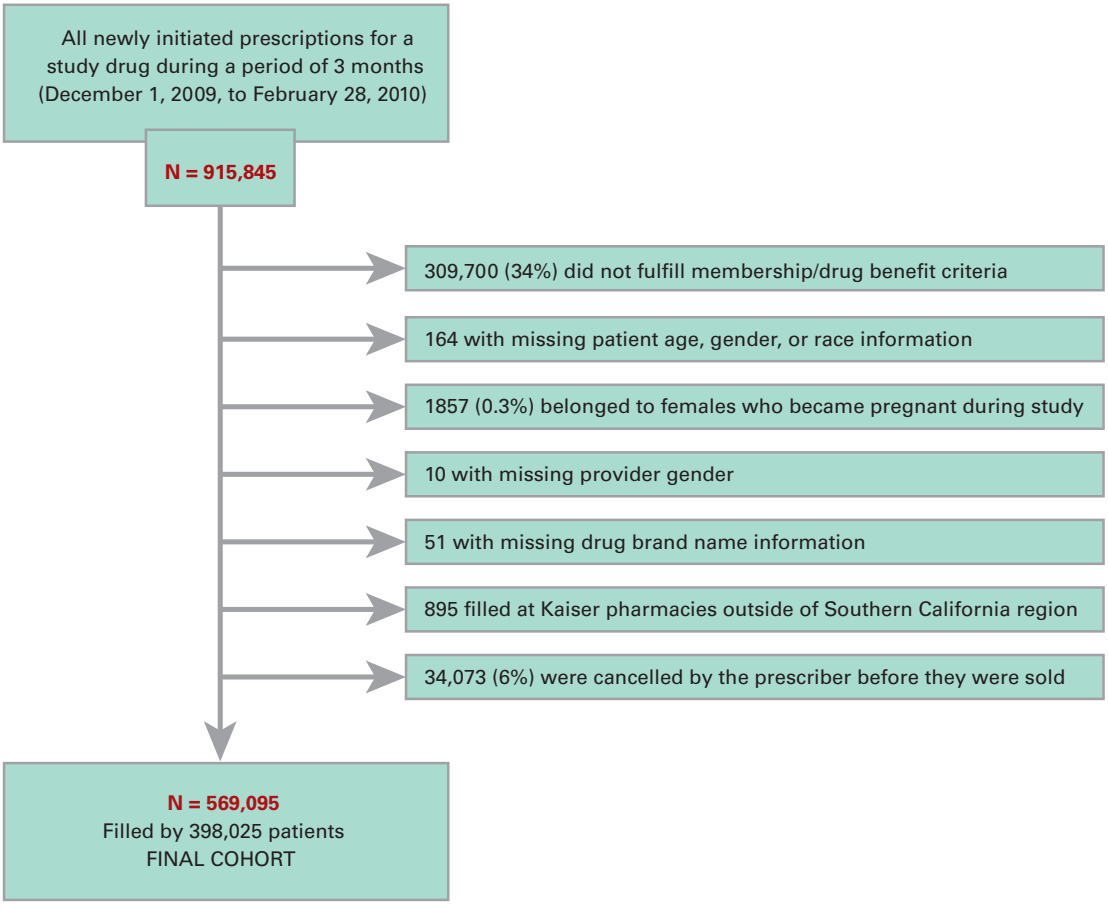
Study Outcome

The primary study outcome was PNA, which was defined as the failure to fill a prescription within 14 days of the index date. Previous studies have demonstrated that most patients fill their medications within the first 2 weeks of the index date.[7,9] Sensitivity analysis was performed to examine changes in PNA rates when the definition of PNA varied from 14 to 30 and 90 days.

Patient, Prescriber, and Prescription Characteristics

Patient characteristics included patient age at index date and gender as recorded in the eMR. Patient race was geocoded based on 2010 census tract data. The patient's zip code was linked to US Census 2000 data to assign median household income. The 12-month pre-index period was used to identify baseline comorbidities based on occurrence of at least 1 *International Classification of Diseases, Ninth Revision, Clinical Modification* code. Selected disease comorbidites included the 17 standard diseases used to calculate the Charlson Comorbidity Index[10] and 5 additional disease states (Alzheimer's disease, hyperlipidemia, migraine, depression, and osteoporosis) corresponding to the therapeutic drug groups examined in the study.

Figure 1. Identification of Study Cohort



The pre-index period was also used to calculate baseline healthcare utilization, which included the number of prior clinic visits, emergency department (ED) visits, or hospitalizations. Patients who did not have any prior use of prescriptions in the same therapeutic drug group were flagged as treatment-naïve to disease therapy. For example, diabetic patients who were treatment-naïve did not use sulfonylureas or any other classes of antidiabetic medications, such as insulin or biguanides, during the pre-index period. A flag was created to indicate if the patient had filled at least 1 prescription in the pre-index period as a measure of the patient's compliant medication behavior. Pharmacy benefits (dual insurance, primary/dependent, and plan type: Medicare, Medicaid, commercial) were also captured.

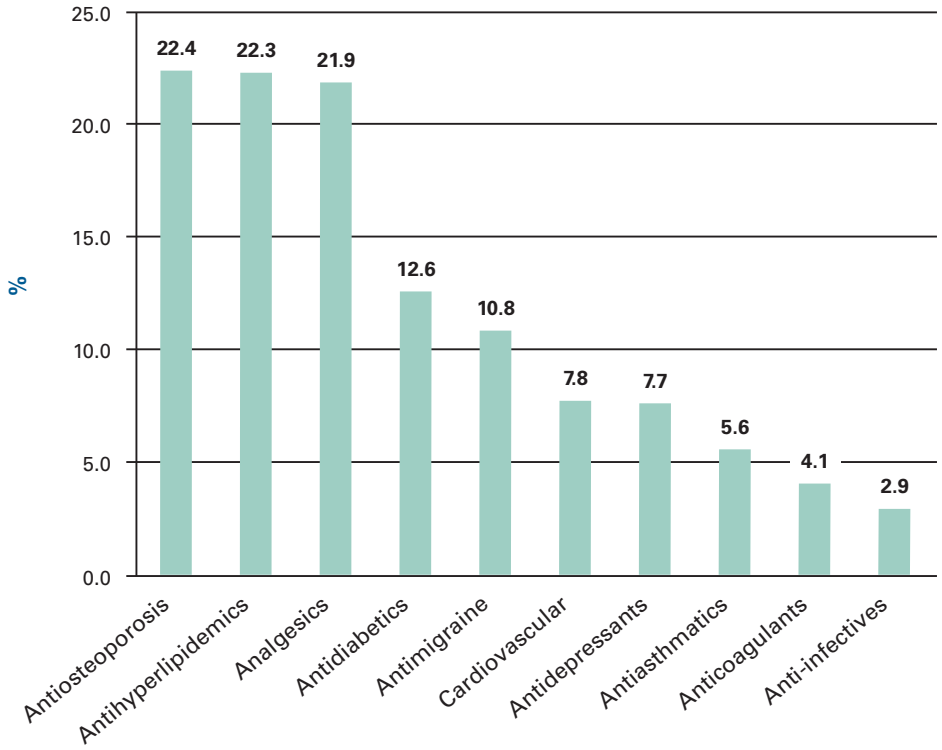
Prescriber characteristics included prescriber age and gender, as well as prescriber race/ethnicity, years of experience practicing at KPSC, and specialty. Dummy variables were used to indicate if the patient and physician were of the same gender or race/ethnicity in order to assess whether having a prescriber of the same gender or race/ethnicity would influence the patient-prescriber relationship and result in improved primary adherence.

Characteristics of the index prescription were identified from pharmacy records and included acute versus chronic therapy, generic versus brand, pharmacy regional location, month prescribed, and weekday versus weekend prescribing. Since copay information was unavailable for prescriptions that were not filled, it was not included in the analysis. The total number of prescriptions written for study drugs on the index date was examined to investigate if patients given multiple medications and likely facing an increased pill and copay burden are more likely to be primary nonadherent. Lastly, dummy variables were used to indicate if the prescription was used to treat symptomatic disease, and included any medication in the following drug groups: antimigraine, analgesics, anti-infectives, antiasthmatics, and antidepressants.

Statistical Analyses

This analysis was performed at the prescription level, so any patient may have had more than 1 observation in the data set. PNA rates were calculated overall and by drug group. The frequency distribution when new prescriptions were filled relative to the index date was examined. Descriptive statistics

Figure 2. Primary Nonadherence Rates by Therapeutic Drug Group



using *t* tests and χ^2 tests were used to compare unadjusted differences in characteristics of filled prescriptions with those of unfilled prescriptions.

Multivariable logistic regression was used to calculate odds ratios (ORs) and identify significant factors associated with PNA to study drugs when adjusting for other study variables. All patient, prescriber, and prescription characteristics were considered for inclusion in the model. Interaction terms with the acute versus chronic variable and patient characteristics were tested. The final inclusion of variables into the model was based on statistical significance or theoretical plausibility. A significance level of less than 0.05 was considered statistically significant. All statistical analyses were performed using the SAS statistical package version 9.1 (SAS Institute, Cary, North Carolina).

RESULTS

A total of 569,095 new prescriptions were written for 398,025 patients during the 3-month period that satisfied study inclusion and exclusion criteria (**Figure 1**). Most prescriptions were written for anti-infectives (43.5%) or analgesics (24.6%), followed by antiasthmatics (9.7%), cardiovascular (8.6%), antidepressants (4.8%), antihyperlipidemics (3.9%), antidiabetics (2.5%), antimigraine (1.0%), antiosteoporosis (0.9%), and anticoagulants (0.3%). The average (standard deviation [SD]) patient copay for sold prescriptions was $9.89 (14.06).

The overall PNA rate across all 10 drug groups was 9.8%. PNA varied by therapeutic drug group, ranging from 2.9% for anti-infectives to 22.4% for antiosteoporosis medications (**Figure 2**). Varying the definition of PNA from 14 days to 90 days only decreased the overall PNA rate to 8.0%. PNA rates were highest for antiosteoporosis medications, antihyperlipidemics, and analgesics. The predicted probability of a primary nonadherent patient for the baseline case (ie, reference group for each variable) was 34% for chronic and 17% for acute therapy. Of the 569,095 prescriptions included in the study, 437,940 (77%) prescriptions were filled on the same day as they were written and 525,449 (92%) prescriptions were eventually filled within 6 months of the index date.

An unadjusted comparison between primary adherent and nonadherent prescriptions revealed several small but significant differences in patient, prescriber, and prescription characteristics (**eAppendices B-D**). PNA was more common for minority race/ethnicities, lower household incomes, and patients prescribed a greater number of prescriptions on the index date. A significantly greater proportion of primary nonadherent prescriptions were written by younger prescribers with less than 10 years of Kaiser experience. Prescrip-

Table 1. Results for Patient Characteristics From Multivariable Logistic Regression Predicting Primary Nonadherence[a]

	Acute Treatments OR (95% CI)	Chronic Treatments OR (95% CI)
Female patient (vs male)	**0.87 (0.85-0.89)**	**1.04 (1.01-1.08)**
Patient age group (y)		
≤10	**1.35 (1.24-1.47)**	1.16 (0.98-1.37)
11 to 20	0.92 (0.85-1.00)	**1.55 (1.35-1.79)**
21 to 30	**0.75 (0.69-0.80)**	**1.66 (1.47-1.86)**
31 to 50	**0.76 (0.71-0.81)**	**1.44 (1.32-1.57)**
51 to 64	**0.9 (0.85-0.96)**	**1.27 (1.17-1.38)**
≥65 (reference group)	1.00	1.00
Patient race/ethnicity		
American Indian/Alaskan Native	0.87 (0.63-1.19)	1.24 (0.84-1.84)
Asian/Pacific Islander	**1.24 (1.18-1.29)**	0.99 (0.93-1.05)
Black	**1.3 (1.25-1.36)**	**1.26 (1.18-1.33)**
Hispanic	**1.19 (1.16-1.23)**	**1.06 (1.01-1.11)**
Multiracial	**1.37 (1.18-1.60)**	1.24 (0.97-1.58)
White (reference group)	1.00	1.00
Patient household income		
≤$30,000	1.03 (0.97-1.09)	1.07 (0.98-1.16)
>$30,000 to ≤$50,000	1.02 (0.98-1.07)	1.06 (0.99-1.13)
>$50,000 to ≤$70,000	1.00 (0.95-1.04)	1.05 (0.98-1.12)
Unknown	1.00 (0.93-1.07)	**1.20 (1.08-1.33)**
>$70,000 (reference group)	1.00	1.00
Baseline patient comorbidities		
Alzheimer's disease	1.07 (0.90-1.27)	**1.53 (1.24-1.89)**
Hyperlipidemia	**1.13 (1.09-1.16)**	**1.19 (1.15-1.24)**
Migraine	1.05 (0.99-1.11)	1.01 (0.92-1.10)
Cancer	**0.80 (0.75-0.86)**	**0.88 (0.80-0.97)**
Cerebrovascular disease	**1.28 (1.20-1.36)**	1.07 (0.98-1.16)
CHF	1.01 (0.94-1.08)	0.98 (0.90-1.06)
Dementia	1.19 (0.98-1.44)	1.44 (1.12-1.85)
Depression	0.98 (0.94-1.01)	1.08 (1.03-1.13)
Diabetes with complications	**0.78 (0.73-0.82)**	0.97 (0.90-1.03)
Diabetes without complications	**1.43 (1.37-1.49)**	**1.26 (1.20-1.32)**
HIV	0.82 (0.65-1.03)	1.07 (0.76-1.53)
Metastatic cancer	1.00 (0.87-1.16)	0.97 (0.79-1.19)
Mild liver disease	**0.91 (0.86-0.98)**	0.99 (0.90-1.07)
Myocardial infarction	**1.56 (1.48-1.66)**	**0.89 (0.82-0.97)**
Moderate-to-severe liver disease	**0.74 (0.57-0.96)**	0.78 (0.56-1.10)
Osteoporosis	1.03 (0.98-1.08)	**1.09 (1.02-1.16)**
Paraplegia	**1.21 (1.05-1.40)**	**1.39 (1.14-1.70)**
Peptic ulcer disease	1.00 (0.89-1.14)	**1.21 (1.02-1.44)**
Pulmonary disease	**0.84 (0.81-0.86)**	**1.18 (1.13-1.24)**
Peripheral vascular disease	**1.22 (1.15-1.29)**	**1.10 (1.02-1.19)**
Renal disease	**0.90 (0.86-0.95)**	**0.90 (0.85-0.96)**
Rheumatic disease	0.96 (0.88-1.05)	1.00 (0.89-1.13)
Commercial insurance	0.93 (0.86-1.02)	1.11 (0.95-1.31)
Medicaid insurance	0.92 (0.83-1.03)	**0.61 (0.49-0.78)**
Medicare insurance	1.04 (0.98-1.11)	1.02 (0.94-1.11)
Dual coverage from spouse	**0.78 (0.72-0.83)**	**0.73 (0.65-0.82)**
Primary subscriber	**1.04 (1.01-1.07)**	**1.08 (1.03-1.12)**
Filled prescription in prior year	**0.06 (0.06-0.07)**	**0.11 (0.10-0.12)**
Treatment-naïve patient	**2.52 (2.36-2.7)**	**1.07 (1.03-1.12)**
ED visit in prior year	**1.19 (1.16-1.22)**	**0.88 (0.85-0.92)**
Hospitalization in prior year	**0.96 (0.93-0.99)**	0.96 (0.91-1.01)

CHF indicates congestive heart failure; CI, confidence interval; ED, emergency department; HIV, human immunodeficiency virus; OR, odds ratio.
[a]Results from Tables 1 to 3 are all from the same multivariate logistic model, which controlled for all covariates listed in Tables 1 to 3. Results are reported separately for patient, prescriber, and prescription characteristics.

Table 2. Results for Prescriber Characteristics From Multivariable Logistic Regression Predicting Primary Nonadherence[a]

	Acute Treatments OR (95% CI)	Chronic Treatments OR (95% CI)
Prescriber female gender (vs male)	0.98 (0.96-1.00)	**1.11 (1.07-1.15)**
Prescriber age group (y)		
≤35	**1.18 (1.14-1.22)**	**0.87 (0.83-0.92)**
36 to 45	**1.18 (1.14-1.22)**	0.97 (0.92-1.01)
46 to 55	**1.07 (1.04-1.11)**	**1.07 (1.01-1.12)**
Unknown	0.89 (0.68-1.17)	**1.91 (1.24-2.96)**
>55 (reference group)	1.00	1.00
Prescriber race/ethnicity		
American Indian/Alaskan Native	0.95 (0.81-1.11)	0.87 (0.69-1.11)
Asian/Pacific Islander	**1.06 (1.03-1.09)**	0.97 (0.93-1.02)
Black	**1.18 (1.13-1.24)**	**1.10 (1.03-1.19)**
Hispanic	**1.08 (1.04-1.12)**	**0.91 (0.86-0.97)**
Multiracial	1.13 (0.82-1.56)	1.53 (0.90-2.60)
Unknown	**0.85 (0.75-0.96)**	0.95 (0.76-1.18)
White (reference group)	1.00	1.00
Prescriber Specialty		
Emergency medicine	0.97 (0.92-1.02)	**0.54 (0.45-0.64)**
Internal medicine	**1.18 (1.14-1.21)**	1.01 (0.97-1.05)
OBGYN	**0.67 (0.62-0.72)**	**0.69 (0.54-0.88)**
Other	1.03 (1.00-1.07)	**1.13 (1.08-1.18)**
Pediatrics	**0.39 (0.37-0.42)**	**0.86 (0.75-0.98)**
Urgent care	**0.63 (0.59-0.68)**	**0.47 (0.39-0.56)**
Family practice (reference group)	1.00	1.00
Patient/prescriber gender match	1.03 (1.00-1.05)	1.03 (1.00-1.07)
Patient/prescriber race/ethnicity match	**1.05 (1.02-1.08)**	1.04 (0.99-1.08)

CI indicates confidence interval; OBGYN, obstetrics and gynecology; OR, odds ratio.
[a]Results from Tables 1 to 3 are all from the same multivariate logistic model, which controlled for all covariates listed in Tables 1 to 3. Results are reported separately for patient, prescriber, and prescription characteristics.

tions written for brand name medications and treatments for asymptomatic diseases were more likely to be primary nonadherent.

Results from the preliminary multivariable logistic regressions revealed significant interaction effects between the acute versus chronic therapy variable and other important variables in the model. Thus, the multivariable logistic regression results were stratified by chronic or acute therapy. The adjusted OR and 95% confidence intervals (CIs) resulting from the logistic regression are presented separately in Tables 1 to 3 for patient, prescriber, and prescription characteristics, respectively.

Patient Characteristics (Table 1)

The effects of patient gender and age differed depending on whether the treatment was acute or chronic. However, when analgesics were excluded as part of a sensitivity analysis, the trend in effect of patient age was similar between acute and chronic treatments. Patient race had a consistent effect across medications where blacks (acute: OR = 1.30 [1.25-1.36], chronic: OR = 1.26 [1.18-1.33]) and Hispanics (acute: OR = 1.19 [1.16-1.23], chronic: OR = 1.06 [1.01-1.11]) were more likely to be primary nonadherent compared with whites. Baseline patient comorbidities such as hyperlipidemia, diabetes without complications, paraplegia, and peripheral vascular disease increased the risk of PNA. However, cancer and renal disease lowered the risk.

Patients with dual insurance or Medicaid coverage (for chronic drugs only) were less likely to be primary nonadherent. Patients who filled at least 1 prescription in the pre-index period were also less likely to be primary nonadherent (acute: OR = 0.06 [0.06-0.07], chronic: OR = 0.11 [0.10-0.12]).

Table 3. Results for Prescription Characteristics From Multivariable Logistic Regression Predicting Primary Nonadherence[a]

	Acute Treatments OR (95% CI)	Chronic Treatments OR (95% CI)
Brand name	**1.49 (1.42-1.56)**	0.99 (0.94-1.03)
Number of drugs prescribed on index date	**1.26 (1.25-1.28)**	**0.83 (0.81-0.85)**
Symptomatic disease[b]	—	**0.51 (0.48-0.53)**
Prescribed on weekend	**0.70 (0.68-0.73)**	**1.16 (1.09-1.24)**
Pharmacy area		
Antelope Valley	**1.77 (1.65-1.90)**	1.05 (0.94-1.16)
Baldwin Park	1.02 (0.97-1.08)	0.98 (0.91-1.06)
Coachella Valley	**1.38 (1.20-1.60)**	1.21 (1.00-1.46)
Downey	**1.20 (1.15-1.27)**	**0.86 (0.80-0.93)**
Fontana	1.02 (0.97-1.07)	0.94 (0.88-1.00)
Kern County	**1.16 (1.07-1.26)**	**1.19 (1.07-1.32)**
Los Angeles	**1.39 (1.32-1.46)**	0.99 (0.92-1.07)
Orange County	**1.15 (1.10-1.21)**	**0.87 (0.82-0.94)**
Panorama City	1.02 (0.96-1.08)	**0.80 (0.74-0.87)**
Riverside	**1.39 (1.32-1.46)**	1.02 (0.95-1.10)
South Bay	**1.25 (1.18-1.32)**	1.00 (0.93-1.08)
Ventura	**1.50 (1.33-1.68)**	1.04 (0.89-1.23)
West Los Angeles	**1.26 (1.19-1.34)**	0.98 (0.90-1.07)
Woodland Hills	**1.11 (1.05-1.18)**	0.99 (0.91-1.08)
Unknown	**9.46 (8.31-10.77)**	**2.56 (2.30-2.85)**
San Diego (reference group)	1.00	1.00

CI indicates confidence interval; OR, odds ratio.
[a]Results from Tables 1 to 3 are all from the same multivariate logistic model, which controlled for all covariates listed in Tables 1 to 3. Results are reported separately for patient, prescriber, and prescription characteristics.
[b]Since all acute medications were also symptomatic, this effect could not be estimated for acute medications.

Treatment-naïve patients were more likely to be primary nonadherent, especially to acute medications (acute: OR = 2.52 [2.36-2.70], chronic: 1.07 [1.03-1.12]). However, the effect of treatment-naïve patients for acute therapy becomes statistically insignificant when analgesics are excluded from the analysis. Lastly, patients with prior ED visits had mixed effects (acute: OR = 1.19 [1.16-1.22], chronic: 0.88 [0.85-0.92]), while prior hospitalization lowered the risk of PNA to acute medications (OR = 0.96 [0.93-0.99]).

Prescriber Characteristics (Table 2)

Patients given acute medications were more likely to be primary nonadherent if the prescriptions were written by younger providers or by providers of minority race/ethnicity. Patients given chronic medications were more likely to be primary nonadherent if they were prescribed by females (OR = 1.11 [1.07-1.15]) or blacks (OR=1.10 [1.03-1.19]). Patients who received prescriptions written by emergency medicine, obstetrics and gynecology, pediatrics, or urgent care prescribers were less likely to be primary nonadherent. Patient–provider concordance in terms of gender was not significant, but patients who were of the same race/ethnicity as the prescriber were more likely to be primary nonadherent to acute medications (OR = 1.05 [1.02-1.08]).

Prescription Characteristics (Table 3)

Patients given acute medications with brand names (OR = 1.49 [1.42-1.56]) or a higher number of other medications prescribed on the index date (OR = 1.26 [1.25-1.28]) were more likely to be primary nonadherent. For patients given chronic medications, having a higher number of medications prescribed on the index date (OR = 0.83 [0.81-0.85]) or symptomatic disease (OR = 0.51 [0.48-0.53]) decreased the risk of PNA. Prescriptions written on the weekend were more likely to be primary nonadherent for chronic medications (OR = 1.16 [1.09-1.24]) but less likely for acute medications (OR = 0.70 [0.68-0.73]).

DISCUSSION

Although the overall PNA rate across all 10 drug groups was only 9.8%, rates for certain therapeutic drug groups such as antiosteoporosis medications, antihyperlipidemics, and anal-

gesics were higher. For these drug groups, approximately 1 in 5 patients did not pick up their medications after 14 days. This causes concern, especially since medications for osteoporosis and hyperlipidemia have been shown to decrease morbidity and mortality.[11,12] In particular, statin and bisphosphonate therapy have also been demonstrated as cost-effective.[13,14] The availability of over-the-counter (OTC) analgesics may contribute to the relatively higher PNA rate associated with analgesics.

The PNA rates found in this study are somewhat higher than those reported in recent studies set in integrated healthcare settings.[7,8] These differences could be attributed to the criteria used to define PNA. Some studies defined PNA as the failure to fill prescriptions within 30 or 60 days. This study used 14 days to define PNA since most prescriptions were filled within 2 weeks and it would be unreasonable from a policy perspective for clinicians to wait 30 days or more to contact patients for intervention. Changing our definition from 14 to 30 days produced PNA rates closer to those of previous studies.

The analysis revealed that some factors consistently increased or decreased the likelihood of PNA across all drug groups. Black patients were more likely to be nonadherent, which is consistent with prior research.[15] However, the effect of race (and income) should be cautiously interpreted since these socioeconomic variables were geocoded. Patients with baseline comorbidities (except for cancer and renal disease) were less likely to fill their prescription, which is also consistent with findings from prior studies.[8,16-18] Patients with multiple comorbidities are likely taking several medications, and adding another medication to their current regimen is likely to increase pill burden, the complexity of the medication therapy, and the risk of drug interactions. However, if the prescription was used to treat symptomatic disease, the patient was more likely to fill the prescription.

Similar to a recent study by Liberman and colleagues (2010), we found that patients with prior fills were more likely to fill their current prescription.[9] Our study suggests that prior prescription fill history is a strong indicator of the patient's compliant behavior and willingness to take medications in the future. Treatment-naïve patients were more likely to be primary nonadherent to medications for chronic conditions. These patients may be at the early stage of their disease and elect to postpone filling their prescriptions in order to try alternative methods like diet and exercise or OTC products. Alternatively, prescriptions written by emergency medicine and urgent care prescribers may indicate increased severity and acuteness of the patient's illness, and thus were associated with a decreased likelihood of PNA.

The effects of some covariates differed based on whether the treatment was acute or chronic. Younger patients were more likely to fill their acute medications and less likely to fill their chronic medications relative to older patients. The effects of brand name medications and a greater prescription and copay burden on the index date only affected acute medications, suggesting that patients may be more sensitive to the cost of the drug when the disease is acute. Patients were less likely to pick up prescriptions prescribed on a weekend for chronic medications and more likely for acute medications, suggesting that patients may feel less urgency in treating chronic diseases compared with acute diseases.

Similar to Raebel and colleagues (2012),[8] only a few variables were strongly associated with PNA, such as prior prescription fill and being treatment-naïve. Such results highlight the difficulty of quantifying complex human medication-taking behavior using administrative data. Patient surveys have identified that the most common reasons for PNA are those related to patient concerns regarding the medication, such as potential side effects and the perceived need for the medication.[6] Capturing these effects can be difficult when using quantitative administrative data.

This is one of the first studies to examine PNA in both chronic and acute medications in an integrated healthcare setting. Strengths of study design include requiring membership and prescription benefits and the use of e-prescribing and eMR data, which allowed direct linkage of prescription orders to dispensing information and minimized the risk of outcome misclassification. Use of uniquely rich eMR data also allowed the inclusion of many more patient, prescriber, and prescription characteristics in the logistic regression model than in most other studies. In addition, the sample size for this study is very large (n = 398,025), which improves the robustness of our results. In comparison, Karter and colleagues (2009)[7] examined 27,329 patients and Raebel and colleagues (2012)[8] included 16,173 patients. A limitation of this study is the limited generalizability of our results to patient populations in nonintegrated healthcare systems, as well as Medicaid or uninsured patients, who were not well represented in this study.

The results of this study help clinicians and healthcare decision makers to understand the rate of PNA and how it varies by therapeutic drug group in an integrated healthcare setting. In addition, these results may assist clinicians and payers in making informed decisions when designing and implementing cost-effective patient interventions to improve adherence to chronic and acute medications, which may be one way to improve patient health outcomes while decreasing healthcare costs. Future research should focus on measuring the effect of PNA on patient health outcomes and cost.

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eAppendix A. Therapeutic Drug Groups and Drug Classes

Therapeutic Drug Group	Drug Class
Antimigraine	Ergotamine derivative
	Serotonin agonists
	Migraine combinations
Analgesics	Salicylates
	Analgesics other
	Analgesic combinations
	Narcotic agonists
	Narcotic partial agonists
	Narcotic combinations
	Nonsteroidal anti-inflammatory
	Pyrimidine synthesis inhibitors
	Soluble tumor necrosis factor receptor agents
Anti-infectives	Penicillins
	Cephalosporins
	Macrolide antibiotics
	Tetracyclines
	Fluoroquinolones
	Aminoglycosides
	Sulfonamides
	Antimycobacterial agents
	Antifungals
	Antivirals
	Antimalarial
	Amebicides
	Anthelmintic
	Miscellaneous anti-infectives
Anticoagulants	Coumarin anticoagulants
Antiosteoporosis	Calcium regulators
	Hormone receptor modulators
Antidiabetics	Insulin
	Amylin hormone analogue
	GLP-1 receptor agonist
	Sulfonylureas
	Biguanides
	Meglitinide analogues
	Diabetic other
	Alpha-glucosidase inhibitors
	Dipeptidyl peptidase-4 (DPP-4) enzyme inhibitor
	Thiazolidinediones
	Antidiabetic combinations
Antihyperlipidemics	Bile sequestrants
	Fibric acid derivatives
	HMG CoA reductase inhibitors
	Nicotinic acid derivatives
	Miscellaneous antihyperlipidemics
	Cholesterol absorption inhibitor
	Antihyperlipidemic combinations

(Continued)

eAppendix A. Therapeutic Drug Groups and Drug Classes *(Continued)*

Therapeutic Drug Group	Drug Class
Cardiovascular	Beta-blockers nonselective
	Beta-blockers cardio-selective
	Alpha-beta blockers
	Calcium blockers
	ACE inhibitors
	Angiotensin II receptor antagonist
	Adrenolytic antihypertensives
	Alpha blockers
	Vasodilators
	Antihypertensive MAOIs
	Miscellaneous antihypertensives
	Antihypertensive combinations
	Carbonic anhydrase inhibitors
	Loop diuretics
	Mercurial diuretics
	Osmotic diuretics
	Potassium-sparing diuretics
	Thiazides and thiazide-like diuretics
	Miscellaneous diuretics
	Combination diuretics
Antiasthmatics	Anticholinergics
	Anti-inflammatory agents
	Sympathomimetics
	Xanthines
	Steroid inhalants
	Leukotriene modulators
Antidepressants	Alpha-2 receptor antagonists (tetracyclics)
	MAOI inhibitors
	Modified cyclics
	Selective serotonin reuptake inhibitors
	Selective serotonin and norepinephrine reuptake inhibitors
	Tricyclic agents
	Miscellaneous antidepressants

ACE indicates angiotensin converting enzyme; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HMG CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; MAOI, monoamine oxidase inhibitor.

■ **eAppendix B.** Unadjusted Comparisons of Patient Characteristics for Primary Adherent Versus Nonadherent Prescriptions

	Primary Adherent Prescriptions	Primary Nonadherent Prescriptions	Total
Female patient[a]	302,613 (58.9%)	30,430 (54.8%)	333,043 (58.5%)
Mean age on first index date (SD), in years[a]	46.2 (22.2)	49.3 (21.6)	46.5 (22.1)
Patient age group[a]			
≤10	45,548 (8.9%)	3611 (6.5%)	49,159 (8.6%)
10 to 20	39,567 (7.7%)	3610 (6.5%)	43,177 (7.6%)
21 to 30	40,553 (7.9%)	3929 (7.1%)	44,482 (7.8%)
31 to 40	62,274 (12.1%)	5985 (10.8%)	68,259 (12%)
41 to 50	83,091 (16.2%)	8966 (16.1%)	92,057 (16.2%)
51 to 64	130,752 (25.5%)	15,296 (27.5%)	146,048 (25.7%)
≥65	111,761 (21.8%)	14,152 (25.5%)	125,913 (22.1%)
Patient race/ethnicity[a]			
White	236,882 (46.1%)	23,499 (42.3%)	260,381 (45.8%)
Hispanic	178,589 (34.8%)	19,679 (35.4%)	198,268 (34.8%)
Black	53,031 (10.3%)	7054 (12.7%)	60,085 (10.6%)
Asian/Pacific Islander	41,935 (8.2%)	4963 (8.9%)	46,898 (8.2%)
Multiracial	2318 (0.5%)	282 (0.5%)	2600 (0.5%)
American Indian/Alaskan Native	791 (0.2%)	72 (0.1%)	863 (0.2%)
Patient household income[a]			
≤$30,000	40,609 (7.9%)	5060 (9.1%)	45,669 (8%)
>$30,000 to ≤$50,000	256,798 (50%)	28,275 (50.9%)	285,073 (50.1%)
>$50,000 to ≤$70,000	149,673 (29.1%)	15,567 (28%)	165,240 (29%)
>$70,000	50,171 (9.8%)	4909 (8.8%)	55,080 (9.7%)
Unknown	16,295 (3.2%)	1738 (3.1%)	18,033 (3.2%)
Average (SD) Charlson Comorbidity Index[a]	0.97 (1.80)	1.13 (1.93)	0.98 (1.82)
Filled prescription in prior year[a]	508,291 (99.0%)	49,544 (89.2%)	557,835 (98.0%)
Average (SD) prescription count in prior year[a]	8.3 (6.5)	6.7 (6.2)	8.1 (6.5)
Average (SD) clinic visit count in prior year[a]	10.2 (10.9)	9.5 (10.4)	10.1 (10.8)
ED visit in prior year[a]	155,309 (30.2%)	18,332 (33%)	173,641 (30.5%)
Hospitalization in prior year[b]	79,130 (15.4%)	8887 (16%)	88,017 (15.5%)
Use of same drug class as index drug in prior year[a]	61,334 (11.9%)	4960 (8.9%)	66,294 (11.6%)
Medicare insurance[a]	108,313 (21.1%)	13,790 (24.8%)	122,103 (21.5%)
Medicaid insurance[a]	10,567 (2.1%)	887 (1.6%)	11,454 (2%)
Commercial insurance[a]	492,253 (95.9%)	53,689 (96.7%)	545,942 (95.9%)
Primary subscriber[a]	333,435 (64.9%)	37,953 (68.3%)	371,388 (65.3%)
Dual coverage (from spouse)[a]	16,623 (3.2%)	1292 (2.3%)	17,915 (3.1%)

ED indicates emergency department; SD, standard deviation.
[a] $P < .0001$.
[b] $P < .0.01$.

eAppendix C. Unadjusted Comparisons of Prescriber Characteristics for Primary Adherent Versus Nonadherent Prescriptions

	Primary Adherent Prescriptions	Primary Nonadherent Prescriptions	Total
Prescriber female gender[a]	209,782 (40.8%)	22,186 (39.9%)	231,968 (40.8%)
Prescriber age group[a]			
≤35	97,433 (19%)	10,845 (19.5%)	108,278 (19%)
36 to 45	182,666 (35.6%)	20,720 (37.3%)	203,386 (35.7%)
46 to 55	123,909 (24.1%)	13,232 (23.8%)	137,141 (24.1%)
>55	108,286 (21.1%)	10,633 (19.1%)	118,919 (20.9%)
Unknown	1252 (0.2%)	119 (0.2%)	1371 (0.2%)
Prescriber race/ethnicity[a]			
White	220,799 (43%)	22,766 (41%)	243,565 (42.8%)
Asian/Pacific Islander	195,514 (38.1%)	21,795 (39.2%)	217,309 (38.2%)
Hispanic	58,344 (11.4%)	6471 (11.6%)	64,815 (11.4%)
Black	29,544 (5.8%)	3652 (6.6%)	33,196 (5.8%)
American Indian/Alaskan Native	2976 (0.6%)	270 (0.5%)	3246 (0.6%)
Multiracial	481 (0.1%)	63 (0.1%)	544 (0.1%)
Unknown	5888 (1.1%)	532 (1%)	6420 (1.1%)
Prescriber experience (years)[a]			
≥10	255,373 (49.7%)	26,553 (47.8%)	281,926 (49.5%)
<10	257,273 (50.1%)	28,922 (52.1%)	286,195 (50.3%)
Unknown	900 (0.2%)	74 (0.1%)	974 (0.2%)
Prescriber specialty[a]			
Family practice	216,910 (42.2%)	23,337 (42%)	240,247 (42.2%)
Internal medicine	93,239 (18.2%)	12,319 (22.2%)	105,558 (18.5%)
Urgent care	18,748 (3.7%)	1344 (2.4%)	20,092 (3.5%)
Emergency medicine	26,842 (5.2%)	3469 (6.2%)	30,311 (5.3%)
OBGYN	13,343 (2.6%)	974 (1.8%)	14,317 (2.5%)
Pediatrics	53,675 (10.5%)	3113 (5.6%)	56,788 (10%)
Other	90,789 (17.7%)	10,993 (19.8%)	101,782 (17.9%)
Patient/prescriber match			
On gender[a]	283,875 (55.3%)	31,867 (57.4%)	315,742 (55.5%)
On race/ethnicity[b]	170,439 (33.2%)	18,194 (32.8%)	188,633 (33.1%)

OBGYN indicates obstetrics and gynecology.
[a] $P < .0001$.
[b] $P < .05$.

■ **eAppendix D.** Unadjusted Comparisons of Prescription Characteristics for Primary Adherent Versus Nonadherent Prescriptions

	Primary Adherent Prescriptions	Primary Nonadherent Prescriptions	Total
Therapeutic Drug Group[a]			
Anti-infectives	240,207 (46.8%)	7220 (13%)	247,427 (43.5%)
Analgesics	109,484 (21.3%)	30,641 (55.2%)	140,125 (24.6%)
Antiasthmatics	52,330 (10.2%)	3091 (5.6%)	55,421 (9.7%)
Cardiovascular	45,178 (8.8%)	3804 (6.8%)	48,982 (8.6%)
Antidepressants	25,275 (4.9%)	2108 (3.8%)	27,383 (4.8%)
Antihyperlipidemics	17,280 (3.4%)	4969 (8.9%)	22,249 (3.9%)
Antidiabetics	12,605 (2.5%)	1812 (3.3%)	14,417 (2.5%)
Antimigraine	5306 (1%)	645 (1.2%)	5951 (1%)
Antiosteoporosis	4100 (0.8%)	1183 (2.1%)	5283 (0.9%)
Anticoagulants	1781 (0.3%)	76 (0.1%)	1857 (0.3%)
Average (SD) drugs prescribed on index date[a]	1.47 (0.78)	1.54 (1.02)	1.48 (0.81)
Chronic treatment	158,549 (30.9%)	17,043 (30.7%)	175,592 (30.9%)
Acute treatment	354,997 (69.1%)	38,506 (69.3%)	393,503 (69.1%)
Symptomatic treatment[a]	432,602 (84.2%)	43,705 (78.7%)	476,307 (83.7%)
Asymptomatic treatment[a]	80,944 (15.8%)	11,844 (21.3%)	92,788 (16.3%)
Brand name[a]	74,009 (14.4%)	6901 (12.4%)	80,910 (14.2%)
Weekend fill[a]	58,180 (11.3%)	4906 (8.8%)	63,086 (11.1%)
Month filled[a]			
December	163,229 (31.8%)	18,436 (33.2%)	181,665 (31.9%)
January	170,562 (33.2%)	18,291 (32.9%)	188,853 (33.2%)
February	179,755 (35.0%)	18,822 (33.9%)	198,577 (34.9%)
Pharmacy area[a]			
Antelope Valley	13,134 (2.6%)	1736 (3.1%)	14,870 (2.6%)
Baldwin Park	35,293 (6.9%)	3491 (6.3%)	38,784 (6.8%)
Coachella Valley	2790 (0.5%)	373 (0.7%)	3163 (0.6%)
Downey	41,871 (8.2%)	4752 (8.6%)	46,623 (8.2%)
Fontana	65,222 (12.7%)	6248 (11.2%)	71,470 (12.6%)
Kern County	14,439 (2.8%)	1448 (2.6%)	15,887 (2.8%)
Los Angeles	34,398 (6.7%)	4728 (8.5%)	39,126 (6.9%)
Orange County	61,306 (11.9%)	5938 (10.7%)	67,244 (11.8%)
Panorama City	28,947 (5.6%)	2694 (4.8%)	31,641 (5.6%)
Riverside	44,965 (8.8%)	5016 (9%)	49,981 (8.8%)
San Diego	80,457 (15.7%)	7674 (13.8%)	88,131 (15.5%)
South Bay	32,287 (6.3%)	3733 (6.7%)	36,020 (6.3%)
Ventura	4248 (0.8%)	586 (1.1%)	4834 (0.8%)
West Los Angeles	25,285 (4.9%)	3212 (5.8%)	28,497 (5%)
Woodland Hills	26,637 (5.2%)	2823 (5.1%)	29,460 (5.2%)
Unknown	2267 (0.4%)	1097 (2%)	3364 (0.6%)

SD indicates standard deviation.
[a] $P < .0001$.