The Effect of Opioid Use and Mental Illness on Chronic Disease Medication Adherence in Superutilizers

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ABSTRACT

BACKGROUND: Nonadherence to essential chronic medications has been identified as a potential driver of high health care costs in superutilizers of inpatient services. Few studies, however, have documented the levels of nonadherence and factors associated with nonadherence in this high-cost, vulnerable population.

OBJECTIVE: To examine the factors associated with nonadherence to essential chronic medications, with special emphasis on mental illness and use of opioid medications.

METHODS: This study was a retrospective panel analysis of 2-year baseline data for Medicare Part D beneficiaries eligible for the SafeMed care transitions program in Memphis, Tennessee, from February 2013 to December 2014. The 2-year baseline data for each patient were divided into four, 6-month patient periods. The study included Medicare superutilizers (defined as patients with ≥ 3 hospitalizations or ≥ 2 hospitalizations with ≥ 2 emergency visits in 6 months) with continuous Part D coverage who had filled at least 1 drug class used to treat hypertension, diabetes mellitus, congestive heart failure, coronary artery disease, or chronic lung disease. The outcome included medication nonadherence assessed using proportion of days covered (PDC), with PDC $< 80\%$ defined as nonadherent, and the main exposure variables included mental illness (defined as a diagnosis of depression or anxiety or ≥ 1 anxiolytic or antidepressant fill) and opioid medication fills assessed in each 6-month period. Pooled observations from the four 6-month periods were used for multivariable analyses using the patient periods as the unit of analysis. A random effects model with robust standard errors and a binary distribution were used to examine associations between independent variables (time invariant and time variant factors) and medication nonadherence. The model included lagged effects of time variant factors measured in each period.

RESULTS: Overall nonadherence to essential chronic medications ranged from 39.3% to 58.4%, with the highest for chronic lung disease medications (49.1%-64.4%). Factors associated with nonadherence included ≥ 4 opioid medication fills in the previous 6-month period (adjusted odds ratio [OR] = 1.90, 95% CI = 1.32-2.73); age 22-44 and 45-64 years vs. ≥ 65 years (OR = 3.57, 95% CI = 2.07-6.16, and OR = 2.07, 95% CI = 1.49-2.88); and a higher number of unique prescribers (OR = 1.10, 95% CI = 1.04-1.17). Factors protecting against nonadherence included higher number of unique medications filled (OR = 0.95, 95% CI = 0.92-0.98) and ≥ 1 physician office visit in the previous 6-month period (OR = 0.66, 95% CI = 0.46-0.94).

CONCLUSIONS: This study demonstrated that high levels of opioid medication use are significantly associated with essential chronic disease medication nonadherence among superutilizers. Other risk factors for nonadherence were aged < 65 years, low-income status, and a higher number of unique prescribers. Factors protecting against nonadherence were physician office visits and filling higher number of medications. Medication management interventions targeting superutilizers should focus on supporting chronic disease medication adherence.

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What is already known about this subject

- Medication nonadherence is a major health care concern, with studies showing that it is associated with poor health outcomes and higher health care use and costs.
- According to existing research, the most important factors associated with medication nonadherence include age < 65 years, black race, medication copay, anxiety/depression, multiple comorbidities, and therapy complexity.
- Superutilizers have high rates of multimorbidity and are at particularly high risk for drug therapy problems, which may contribute to suboptimal medication adherence

What this study adds

- Superutilizers who filled high levels of opioid medications in a 6-month period were at higher risk for nonadherence and may merit targeted medication management interventions.
- Other risk factors for medication nonadherence among superutilizers were aged < 65 years, low-income status, and higher number of unique prescribers.

Nearly 50% of Medicare health care spending is incurred by 5% of its population.^{1,2} These high-cost health care users are commonly referred to as “superutilizers.”³ They have complex health issues and high rates of multimorbidity that include mental health disorders.^{1,4} Therapeutic regimens for patients with multimorbidity are complex, often involving multiple concurrent medications, which put these patients at greater risk of nonadherence.⁵⁻⁷ In addition, patients who experience frequent transitions of care are at particularly high risk for drug therapy problems, which may also contribute to low medication adherence.⁸⁻¹² Medication management is critical for superutilizers, since nonadherence to medications is associated with poor health outcomes and higher hospital admissions and costs.^{13,14} Previous studies have demonstrated short-term and long-term benefits of improving medication adherence among high-risk patients.¹⁵⁻¹⁷ For instance, the study by Rosen et al. (2017) found that among high-risk patients, low and intermediate adherence were associated with a higher 30-day readmission,¹⁵ whereas Zhang et al. (2014) found that, among patients with myocardial infarction, 6-month medication adherence was associated with lower heart disease-related readmissions within a year after a myocardial infarction event.¹⁶

The World Health Organization has reported that nearly 50% of patients do not take their medications as directed by physicians.¹⁸ According to existing research, the most important factors associated with medication nonadherence include young age, black race, medication copay, anxiety/depression, multiple comorbidities, and therapy complexity.^{19,20-27} However, to our knowledge, no research has examined the factors associated with medication nonadherence among superutilizers.

Emerging evidence indicates that superutilizers have a high prevalence of chronic pain and mental illness.^{4,28,29} Recent studies have demonstrated that mental illness is associated with worse clinical outcomes and higher costs for patients with multimorbidity.^{30,31} Early evidence suggests that chronic pain and high rates of opioid use are common among those with multiple chronic conditions.^{28,32} However, the effect of opioid use and mental illness on essential chronic disease medication adherence remains unclear in this vulnerable population.

This study sought to determine potential factors associated with nonadherence to essential chronic medications in Medicare superutilizers, with special emphasis on anxiety/depression and opioid medication use. We also assessed prevalence and patterns of essential chronic disease medication nonadherence in this vulnerable population. The study findings have important implications for improving medication management among Medicare superutilizers.

Methods

Design and Setting

This study was a retrospective panel analysis of the 2-year baseline data for Medicare Part D beneficiaries meeting the SafeMed Program eligibility criteria during the enrollment period from February 2013 to December 2014. SafeMed, a Centers for Medicare & Medicaid Services Health Care Innovations Award-funded care transitions program with a focus on medication management, targeted superutilizers in Memphis, Tennessee.³³ The 2-year baseline data for each patient were divided into four, 6-month patient periods, with the qualifying period for SafeMed serving as the last patient period for the study. This study included patients eligible for SafeMed, who had been diagnosed with chronic conditions (hypertension, diabetes mellitus, congestive heart failure [CHF], coronary artery disease [CAD], chronic obstructive pulmonary disease [COPD], and asthma) that were identified as ambulatory care-sensitive conditions for which outpatient care improvement (e.g., medication adherence) can reduce inpatient utilization.³⁴⁻³⁶ The panel design helped to examine patterns of medication nonadherence in the baseline period before the intervention and the association of time-varying and time-invariant factors with medication nonadherence. Appendix A displays the overall study design (available in online article).

Study Population

SafeMed Program eligibility was determined during an inpatient admission or an observation stay (index admission) and was based on the following inclusion criteria: (a) adults aged 18+ years with Medicare enrollment; (b) ≥ 3 hospital admissions in the past 6 months or 2 inpatient admissions and ≥ 2 emergency department (ED) visits in the 6 months before SafeMed enrollment; and (c) diagnosis of ≥ 1 of the following chronic conditions: hypertension, CHF, CAD, diabetes mellitus, asthma, or COPD.

Patients were excluded from the SafeMed Program and this study if the primary reason for the index admission was related to conditions less likely to be affected by outpatient chronic disease care or medication management. Exclusions included cancer, pregnancy, or surgical procedures for acute problems, following the approach of Jencks et al. (2009).³⁷ Patients were also excluded if they had diagnoses of active psychosis, drug abuse, substance abuse, or suicidal ideation during the index admission or if they were discharged to a skilled nursing facility or hospice. We employed *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes and diagnosis-related group (DRG) codes used by Harris et al. (2016) for inclusion and exclusion criteria.²⁸

Of the 1,714 Medicare patients meeting SafeMed criteria, the final sample included the 1,092 (63.7%) patients who were continuously eligible for Medicare Part D and had filled at least 1 medication within 17 drug classes during the 2-year baseline period. These drug classes included angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), statins, antiplatelet agents, beta blockers, calcium channel blockers, diuretics, alpha-1 blockers, central alpha-2 agonists, direct vasodilators, sulfonyleureas, biguanides, thiazolidinediones, meglitinides, dipeptidyl peptidase-4 inhibitors, anticholinergic inhalers, inhaled corticosteroids alone or in combination with long-acting beta-agonists, and other COPD/asthma medications (theophylline and leukotriene modifiers).

Outcomes

The study outcome was medication nonadherence measured as an interval-based proportion of days covered (PDC).³⁸ PDC was measured if patients had ≥ 2 medication fills within a class for any of the 17 drug classes during a 6-month period. The numerator was defined as the number of days of medication supplied from the first through the last prescription in a period. The denominator was defined as the number of days during the interval from the index date, which was the first day of the medication fill in a 6-month period, to the last day of that period. In order to adjust for hospitalizations, we subtracted the inpatient days from the denominator. The average PDC measure was calculated at the patient level by adding the PDC for each drug class and then dividing by the number of drug classes used by the patient. Patients were then classified as nonadherent if they

had an overall PDC < 80% over the 6-month period. In addition, adherence was also measured based on therapy-specific medication adherence classifications, which included diabetes, cardiovascular, and COPD/asthma medications.

Drugs that belonged to the same therapeutic class were considered interchangeable. Also, ACE inhibitors and ARBs were considered a single class for this study.³⁹ Antiplatelet agents did not include aspirin because aspirin is usually purchased without a prescription and is not included in Part D claims data. Moreover, patients using insulin were not included, since days supply information on this drug is not operationally reliable.⁴⁰

Independent Variables

Primary independent variables assessed included mental illness and opioid medication use for each 6-month period. We identified patients with mental illness if they had ≥ 1 anxiolytic or antidepressant fill in the 6-month period or a diagnosis of depression or anxiety (at least 1 diagnosis claim present in Medicare inpatient, outpatient, or Part B claims in that period or any previous 6-month period; ICD-9-CM codes 296, 298.0, 300, 309.1, and 311). Opioid medication use was based on number of opioid medication fills in each 6-month period (0 fills, 1 fill, 2-3 fills, and ≥ 4 fills).

Sociodemographic variables included age, gender, and race/ethnicity measured at baseline. Other sociodemographic factors measured for each 6-month period included whether patients were fully or partially eligible as dual beneficiaries in ≥ 1 month, and income was assessed according to patient receipt of the low-income cost-sharing subsidy (LICS) for index drug classes. The income threshold to be eligible for Tennessee Medicaid is 105% of the federal poverty level (FPL), while the income threshold for receiving LICS is higher—150% of the FPL. We combined these factors to create an income variable with 3 groups (nondual non-LICS, nondual LICS, and dual LICS), with nondual LICS and dual LICS serving as low-income nonduals and low-income dual eligibles, respectively.

Clinical factors that were assessed at baseline included whether beneficiaries qualified for Medicare because of end-stage renal disease and/or disability. Disability was not included in the models, since patients aged < 65 years were also disabled. The ICD-9-CM diagnosis codes present on at least 1 Medicare inpatient, outpatient, or Part B claim were used to identify patients in each 6-month period who had qualifying chronic conditions and comorbidities in that period or any previous period. Overall comorbidity was measured using the Charlson Comorbidity Index.⁴¹ In addition, the SafeMed Program's qualifying chronic conditions included diabetes, hypertension, CHF, CAD, COPD, and asthma. We only included the Charlson Comorbidity Index in the multivariable models as a comorbidity measure, since it includes the qualifying conditions and end-stage renal disease. We also assessed tobacco use disorder (ICD-9-CM code 305.1).

Therapeutic complexity was assessed for each 6-month period, using prescription drug event files. Factors related to therapeutic complexity included number of unique medications filled, number of unique prescribers, and number of unique pharmacies. The presence of ≥ 1 physician office visit, number of inpatient admissions (inpatient and observation stays), and number of ED visits were also assessed in each period.

Statistical Analysis

Descriptive analyses were conducted to show the characteristics of superutilizers and medication nonadherence rates in each 6-month period. Pooled observations from the four 6-month periods were used for bivariate and multivariable analyses using the patient period as the unit of analysis. Pearson chi-square tests and 2-sample t-tests were conducted as part of the bivariate statistics. A random effects model with robust standard errors and a binary distribution was used to examine associations between independent variables (time invariant and time variant factors) and medication nonadherence. The model included lagged effects of factors measured for each 6-month period. We used SAS 9.4 (SAS Institute, Cary, NC) and STATA 13 (StataCorp, College Station, TX) for data analysis. A significance level of $P < 0.05$ and 2-sided tests were used for all analyses.

Sensitivity Analysis

Recognizing that the previously mentioned definition for measuring PDC might overestimate adherence, a sensitivity analysis was conducted using an alternative PDC definition. Patients were followed continuously from the time they had ≥ 2 fills during a 6-month period for a drug class to the last 6-month period. We modified the denominator by using the first day of medication fill as the index date only if patients had ≥ 2 fills for a drug class for the first time in a period. If patients filled ≥ 2 medications for a drug class in the previous period, we considered the denominator as 180 days. Also, we subtracted the inpatient days from the denominator. For the numerator, if the days supply extended into the next period, it contributed to both periods. Other sensitivity analyses conducted included a subgroup analysis, in which we estimated separate models for elderly beneficiaries (aged ≥ 65 years) and disability eligible nonelderly Medicare patients (aged < 65 years) to understand associations specific to these Medicare populations. In addition, we measured adherence by changing the fill criteria of ≥ 2 medication fills for a drug class to ≥ 1 medication fill using our main PDC definition.

Results

Characteristics of the study population ($N = 1,092$) in each 6-month evaluation period are shown in Table 1. The median age of the study population was 67.1 years, and 42.9% were aged < 65 years. The study population was predominantly

female (58.8%), non-Hispanic black (68.6), dual eligible (63.7%), and low income (68.7%). In the fourth period, when patients met the SafeMed superutilizer definition, they had a mean (SD) of 3.1 (0.9) inpatient stays and 1.7 (2.6) ED visits. In the same period, 97.2% of patients had ≥ 2 chronic conditions; 57.0% had anxiety/depression; and 69.0% had filled ≥ 1 opioid. These proportions were higher in the fourth period than in the previous periods.

Rates of nonadherence to essential chronic disease medications are shown in Table 2—36.2% of patients were nonadherent to their diabetes medications; 37.9% were nonadherent to their cardiovascular medications; and 49.1% were nonadherent to their COPD/asthma medications. When examining the overall nonadherence rate, 39.3% of patients were nonadherent to their essential chronic medications. The nonadherence rates for the drug classes were similar to the overall rates for disease categories (data not shown). When examining medication nonadherence among elderly and nonelderly Medicare beneficiaries, we found that Medicare beneficiaries aged < 65 years were more likely to be nonadherent to diabetes and cardiovascular medications compared with elderly Medicare beneficiaries.

In the multivariable analysis (Table 3), patients who filled ≥ 4 opioids in the previous 6-month period had higher odds of nonadherence compared with patients with no opioid fills (adjusted odds ratio [OR]=1.90, 95% confidence interval [CI]=1.32-2.73). Compared with patients with no anxiety/depression, those with anxiety/depression had lower odds of nonadherence; however, this association was not statistically significant (OR=0.76, 95% CI=0.56-1.03). Among sociodemographic factors, patients aged 22-44 years and 45-64 years were more likely to be nonadherent than patients aged ≥ 65 years (OR=3.57, 95% CI=2.07-6.16 and OR=2.07, 95% CI=1.49-2.88). Among factors related to therapy complexity, patients who visited a higher number of unique prescribers were more likely to be nonadherent (OR=1.10, 95% CI=1.04-1.17), whereas patients who filled a higher number of different medications were less likely to be nonadherent (OR=0.95, 95% CI=0.92-0.98). Furthermore, patients who made ≥ 1 physician office visit in the previous period were less likely to be nonadherent (OR=0.66, 95% CI=0.46-0.94).

Sensitivity Analysis

Our main adherence definition—based on patients who had at least 2 fills in a period—may underestimate nonadherence because it did not include patients who had only 1 fill or did not fill their medications in subsequent periods. Using the alternative PDC definition, which assumes continuous chronic disease drug class use once begun (≥ 2 fills for a drug class in a period), the proportion of patients who were nonadherent was about 19% higher (58.4%). Also, nonadherence rates were higher in the fourth period rather than previous periods across all therapy classes (Appendix B, available in online article). The

multivariable model using this alternate PDC calculation demonstrated similar findings in terms of direction and statistical significance to our main analysis regarding opioid medication use, age, the number of different medications filled, unique prescribers, and physician office visits. However, there were a few differences: low-income status and comorbidity index scores were found to be significantly associated with nonadherence (data not shown).

Table 4 shows the multivariable associations among Medicare beneficiaries aged ≥ 65 years. Risk factors for nonadherence in this age group included ≥ 4 opioid medications filled in the previous period and a higher number of unique prescribers. We also found that ≥ 1 physician office visit in the previous period was protective against nonadherence. Table 5 shows the multivariable associations among Medicare beneficiaries aged < 65 years. Similar to the model for elderly Medicare beneficiaries, opioid medication use was a significant risk factor for nonadherence in this age group. However, there were a few differences: low-income status was significantly associated with nonadherence, whereas filling higher number of unique medications was protective against nonadherence. In the sensitivity analysis using the criteria of ≥ 1 medication fill for our main PDC definition (data not shown), the study findings were similar in terms of significance and directionality to our main multivariable analysis.

Discussion

This study is the first to document the association between opioid medication use and medication nonadherence among superutilizers. Notably, it provides evidence of high opioid use as a risk factor for nonadherence in this high-risk population. We found evidence of a paradox in medication use. While superutilizing patients with multimorbidity had high rates of opioid use, their use of essential chronic disease medications with proven clinical benefits was poor.

Furthermore, use of essential chronic disease medications is inversely associated with opioid use, suggesting that opioid use could causally contribute to nonadherence of other critical medications. Several potential mechanisms could help explain this observed association. First, the immediate reward through relief from pain could encourage patients to preferentially choose to fill narcotic prescriptions. Chronic pain is common in patients with multimorbidity, and our group previously demonstrated very high prevalence of chronic pain in superutilizing SafeMed-eligible patients.²⁸ Second, since Medicare Part D copays are similar for narcotic and non-narcotic drugs, it is likely that lower-income patients using narcotics for chronic pain are particularly inclined to preferentially pay for medicines with immediate perceived benefit. Regardless, this study suggests that efforts to address nonadherence among opioid-consuming superutilizers may need to include specific strategies to help these vulnerable patients deal more effectively with chronic pain.

TABLE 1 Study Sample Characteristics in Each 6-Month Patient Period

Characteristics	Period 1 n (%)	Period 2 n (%)	Period 3 n (%)	Period 4 n (%)
Sociodemographic factors				
Age, years				
<65	468 (42.9)	—	—	—
≥65	624 (57.1)	—	—	—
Age, median (25th-75th percentiles)	67.1 (55.7-75.4)	—	—	—
Female	642 (58.8)	—	—	—
Race/ethnicity				
Non-Hispanic white	326 (29.9)	—	—	—
Non-Hispanic black	749 (68.6)	—	—	—
Other	17 (1.6)	—	—	—
Medicare eligibility status				
Disabled	407 (37.3)	—	—	—
End-stage renal disease	324 (29.7)	—	—	—
Dual eligible	696 (63.7)	694 (63.6)	697 (63.8)	692 (63.4)
Receiving low-income cost-sharing subsidy	750 (68.7)	790 (72.3)	791 (72.4)	803 (73.5)
Clinical characteristics				
Qualifying chronic conditions				
Diagnosis of hypertension	852 (78.0)	950 (87.0)	1,028 (94.1)	1,086 (99.5)
Diagnosis of diabetes	571 (52.3)	638 (58.4)	696 (63.7)	784 (71.8)
Diagnosis of congestive heart failure	338 (31.0)	467 (42.8)	603 (55.2)	799 (73.2)
Diagnosis of coronary artery disease	368 (33.7)	481 (44.1)	590 (54.0)	785 (71.9)
Diagnosis of asthma	134 (12.3)	199 (18.2)	262 (24.0)	377 (34.5)
Diagnosis of COPD	246 (22.7)	343 (31.4)	448 (41.0)	583 (53.4)
Number of qualifying chronic conditions				
1 chronic condition	335 (30.8)	226 (20.7)	131 (12.0)	31 (2.8)
2 chronic conditions	262 (24.0)	236 (21.6)	204 (18.7)	115 (10.5)
3 chronic conditions	247 (22.6)	244 (22.3)	250 (23.0)	211 (19.3)
≥4 chronic conditions	246 (22.5)	386 (35.3)	507 (46.4)	735 (67.2)
Comorbidity				
Charlson Comorbidity Index score, mean (SD)	3.2 (2.7)	4.2 (3.1)	5.2 (3.3)	6.9 (3.2)
Anxiety/depression ^a	389 (35.6)	460 (42.1)	533 (48.8)	622 (57.0)
Diagnosis of tobacco use disorder	106 (9.7)	163 (14.9)	266 (24.4)	351 (32.1)
Therapy complexity factors				
Number of unique medications filled, mean (SD)	11.9 (6.2)	12.3 (6.4)	12.5 (6.5)	14.9 (6.3)
Number of unique prescribers, mean (SD)	4.4 (2.9)	4.6 (3.0)	4.7 (3.0)	5.8 (3.1)
Number of unique pharmacies, mean (SD)	1.8 (1.3)	1.8 (1.3)	1.9 (1.3)	2.1 (1.4)
0 opioid filled	499 (45.7)	479 (43.9)	480 (44.0)	337 (31.0)
1 opioid filled	147 (13.5)	165 (15.1)	157 (14.4)	187 (17.1)
2-3 opioid filled	159 (14.6)	143 (13.1)	151 (13.8)	211 (19.3)
≥4 opioid filled	287 (26.3)	305 (27.9)	304 (27.8)	357 (32.7)
Health services utilization factors				
≥1 physician office visit ^b	900 (82.4)	903 (82.7)	909 (83.2)	915 (83.8)
Number of inpatient stays, mean (SD)	0.8 (1.4)	0.8 (1.4)	0.7 (1.4)	3.1 (0.9)
Number of ED visits, mean (SD)	0.8 (2.1)	0.8 (2.2)	0.9 (2.2)	1.7 (2.6)

Note: N=1,092. Factors including age, gender, race/ethnicity, and Medicare eligibility status (including disabled and end-stage renal disease) were measured only for period 1.

^aAnxiety/depression was defined as ≥1 antidepressant or anxiolytic fill or diagnosis of depression/anxiety.

^bPhysician office visits were identified using Part B claims and were defined as “location, other than a hospital, skilled nursing facility, military treatment facility, community health center, state or local public health clinic, or intermediate care facility (ICF), where the health professional routinely provides health examinations, diagnosis, and treatment of illness or injury on an ambulatory basis.” For qualifying chronic conditions, anxiety/depression, and tobacco use disorder, we considered cumulative diagnoses in periods 2, 3, and 4.

COPD=chronic obstructive pulmonary disease; ED=emergency department; SD=standard deviation.

TABLE 2 Medication Nonadherence to Essential Chronic Disease Medications by Therapy Class

Therapy Class	Percentage Nonadherent (PDC < 80%)		
	Overall Sample	Aged < 65 Years	Aged ≥ 65 Years
Diabetes medications			
Period 1 (n = 250)	38.8	50.5	31.9
Period 2 (n = 241)	39.0	48.8	33.6
Period 3 (n = 232)	37.1	40.9	34.7
Period 4 (n = 195)	29.7	39.1	24.6
Overall (n = 916 patient periods)	36.2	44.8	31.2
Cardiovascular medications			
Period 1 (n = 933)	36.6	44.5	31.2
Period 2 (n = 962)	40.8	49.9	33.3
Period 3 (n = 956)	37.0	46.0	31.1
Period 4 (n = 999)	37.1	44.9	29.3
Overall (n = 3,763 patient periods)	37.9	46.3	31.2
COPD/asthma medications			
Period 1 (n = 169)	52.7	53.1	52.4
Period 2 (n = 166)	50.0	50.8	49.5
Period 3 (n = 169)	45.0	43.1	46.2
Period 4 (n = 183)	48.6	51.5	47.0
Overall (n = 687 patient periods)	49.1	49.6	48.8
Diabetes, cardiovascular, and COPD/asthma medications combined			
Period 1 (n = 961)	39.1	46.2	34.2
Period 2 (n = 971)	41.4	51.6	34.2
Period 3 (n = 961)	38.8	46.6	33.5
Period 4 (n = 999)	37.9	47.3	31.3
Overall (n = 3,892 patient periods)	39.3	47.9	33.3

COPD = chronic obstructive pulmonary disease; PDC = proportion of days covered.

Unlike previous studies of Medicare beneficiaries and other vulnerable populations,^{26,42,43} we did not find a statistically significant independent association of anxiety/depression with nonadherence to essential chronic medications. The different patient populations may account for differences in results. However, similar to previous studies on superutilizers,^{1,4} we found high rates of anxiety/depression—57% of patients were found to have depression or anxiety either based on diagnosis or prescription drug use during the final 6-month evaluation period.

We found high rates of medication nonadherence among superutilizers. Specifically, we found that the overall nonadherence rate for essential chronic medications ranged from 39.3% to 58.4%, with the highest rate for COPD/asthma medications (49.1%-64.4%). The high rates of nonadherence found in this study are similar to those previously found in patients using diabetes, cardiovascular, and COPD/asthma medications.^{26,44-47} However, this study extends these findings to the superutilizing Medicare population, a population at particularly high risk for adverse events associated with nonadherence.

TABLE 3 Multivariate Association with Medication Nonadherence in Medicare Superutilizers^a

Characteristics	Nonadherence	
	Odds Ratio (95% CI)	P Value ^b
Anxiety/depression ^c	0.76 (0.56-1.03)	0.070
Opioid medication use		
0 opioid medication filled (reference)		
1 opioid medication filled	1.27 (0.91-1.77)	0.170
2-3 opioid medications filled	1.08 (0.76-1.53)	0.670
≥ 4 opioid medications filled	1.90 (1.32-2.73)	0.001
Sociodemographic factors		
Aged ≥ 65 years (reference)		
Aged 45-64 years	2.07 (1.49-2.88)	<0.001
Aged 22-44 years	3.57 (2.07-6.16)	<0.001
Female	0.98 (0.73-1.31)	0.900
Non-Hispanic black	1.29 (0.93-1.78)	0.120
Nondual, non-LICS (reference)		
Nondual LICS	1.12 (0.68-1.84)	0.660
Dual LICS	1.36 (0.94-1.96)	0.100
Comorbidity		
Charlson Comorbidity Index	0.98 (0.93-1.02)	0.290
Tobacco abuse disorder	0.81 (0.58-1.13)	0.210
Therapy complexity factors		
Number of unique medications filled	0.95 (0.92-0.98)	0.001
Number of unique prescribers	1.10 (1.04-1.17)	0.002
Number of unique pharmacies	0.98 (0.88-1.09)	0.710
Health care utilization factors		
≥ 1 physician office visit	0.66 (0.46-0.94)	0.020
Inpatient stays	1.08 (0.97-1.19)	0.150
ED visits	1.00 (0.91-1.08)	0.920

^aN = 2,828 patient periods.

^bSignificant at P < 0.05. The model included lagged effects of anxiety/depression, opioid medication use, comorbidity, therapy complexity, and health care utilization factors.

^cAnxiety/depression was defined as ≥ 1 antidepressant or anxiolytic fill or diagnosis of depression/anxiety.

CI = confidence interval; ED = emergency department; LICS = low-income cost-sharing subsidy.

Furthermore, when we measured nonadherence using an alternative PDC definition that followed the same patients across the entire study period, we saw an increase in the nonadherence rates in the final 6-month period when patients met the SafeMed superutilizer criteria. These findings suggest that nonadherence to essential chronic medications worsens over time, reaching highest levels in periods of superutilization. These findings further suggest that early intensive intervention may be needed to address nonadherence when high utilization rates are first identified.

This study also demonstrated that nonelderly Medicare superutilizers, who were eligible for disability, were at higher risk of medication nonadherence. Furthermore, unlike other studies

TABLE 4 Multivariate Association with Medication Nonadherence Among Medicare Superutilizers Aged ≥ 65 Years^a

Characteristics	Nonadherence Odds Ratio (95% CI)	P Value ^b
Anxiety/depression ^c	0.74 (0.49-1.13)	0.170
Opioid medication use		
0 opioid medication filled (reference)		
1 opioid medication filled	1.26 (0.81-1.97)	0.300
2-3 opioid medications filled	1.05 (0.65-1.68)	0.860
≥ 4 opioid medications filled	2.14 (1.27-3.60)	0.004
Sociodemographic factors		
Female	1.08 (0.72-1.61)	0.720
Non-Hispanic black	1.38 (0.89-2.14)	0.150
Nondual, non-LICS (reference)		
Nondual LICS	0.83 (0.43-1.61)	0.580
Dual LICS	1.22 (0.78-1.90)	0.380
Comorbidity		
Charlson Comorbidity Index	0.97 (0.90-1.04)	0.380
Tobacco abuse disorder	0.79 (0.46-1.36)	0.400
Therapy complexity factors		
Number of unique medications filled	0.95 (0.91-0.99)	0.030
Number of unique prescribers	1.14 (1.04-1.26)	0.007
Number of unique pharmacies	0.89 (0.73-1.08)	0.230
Health care utilization factors		
≥ 1 physician office visit	0.66 (0.40-1.10)	0.110
Inpatient stays	1.20 (1.03-1.39)	0.020
ED visits	1.01 (0.85-1.19)	0.920

^aN = 1,676 patient periods.

^bSignificant at $P < 0.05$. The model included lagged effects of anxiety/depression, opioid medication use, comorbidity, therapy complexity, and health care utilization factors.

^cAnxiety/depression was defined as ≥ 1 antidepressant or anxiolytic fill or diagnosis of depression/anxiety.

CI = confidence interval; ED = emergency department; LICS = low-income cost-sharing subsidy.

TABLE 5 Multivariate Association with Medication Nonadherence Among Medicare Superutilizers Aged < 65 Years^a

Characteristics	Nonadherence Odds Ratio (95% CI)	P Value ^b
Anxiety/depression ^c	0.77 (0.50-1.20)	0.250
Opioid medication use		
0 opioid medication filled (reference)		
1 opioid medication filled	1.26 (0.75-2.12)	0.380
2-3 opioid medications filled	1.06 (0.63-1.78)	0.840
≥ 4 opioid medications filled	1.84 (1.11-3.04)	0.020
Sociodemographic factors		
Female	0.92 (0.60-1.41)	0.700
Non-Hispanic black	1.38 (0.85-2.25)	0.200
Nondual, non-LICS (reference)		
Nondual LICS	1.97 (0.83-4.66)	0.130
Dual LICS	2.15 (1.02-4.52)	0.040
Comorbidity		
Charlson Comorbidity Index	0.97 (0.91-1.03)	0.290
Tobacco abuse disorder	0.82 (0.55-1.23)	0.340
Therapy complexity factors		
Number of unique medications filled	0.94 (0.91-0.98)	0.004
Number of unique prescribers	1.07 (0.99-1.15)	0.070
Number of unique pharmacies	1.07 (0.93-1.22)	0.340
Health care utilization factors		
≥ 1 physician office visit	0.66 (0.40-1.09)	0.110
Inpatient stays	1.03 (0.92-1.16)	0.620
ED visits	1.01 (0.92-1.11)	0.860

^aN = 1,152 patient periods.

^bSignificant at $P < 0.05$. The model included lagged effects of anxiety/depression, opioid medication use, comorbidity, therapy complexity, and health care utilization factors.

^cAnxiety/depression was defined as ≥ 1 antidepressant or anxiolytic fill or diagnosis of depression/anxiety.

CI = confidence interval; ED = emergency department; LICS = low-income cost-sharing subsidy.

conducted with Medicare patients,^{48,49} we found that among nonelderly superutilizers, low-income dual-eligible patients had lower adherence than others. Our study had high representation of nonelderly disabled dual-eligible beneficiaries, who had on average higher comorbidity index scores than patients aged ≥ 65 years. Our findings suggest that for nonelderly disabled low-income dual-eligible superutilizers, medication subsidies may not be sufficient to achieve optimal adherence. These nonelderly disabled low-income Medicare beneficiaries may need particularly intensive medication management interventions.

We also found that a higher number of unique prescribers placed superutilizers at higher risk of medication nonadherence, while physician office visits were protective. Moreover, for elderly Medicare beneficiaries, higher numbers of hospitalizations in the previous period were identified as a risk factor for nonadherence. These findings are consistent with previous

studies showing that coordination of care and receipt of recommended chronic disease care are poorer in areas where patients receive care from higher numbers of providers.^{50,51} Similarly, previous studies in other populations have demonstrated that outpatient physician office visits are protective for adherence, while emergency visits and higher number of prescribers place patients at increased risk.^{14,26,52} These findings suggest that aggressive efforts are needed to promote continuity of care with regular providers who can play an important role in helping patients adhere to their essential chronic medications and to limit the number of prescribers for superutilizing patients.

This study also showed that a higher number of different medications filled was associated with lower odds of nonadherence. Other studies evaluating this relationship have reported mixed results. Choudhry et al. (2011) found that, in patients who were prescribed a cardiovascular medication, those with

a large number of concurrent medications were more likely to be adherent.⁵² However, Chapman et al. (2005) found that patients consuming a higher number of other medications had lower adherence to lipid-lowering and antihypertensive medications.⁵³ Filling a higher number of concurrent medications may reflect behavioral characteristics of patients who are more likely to use a higher number of medications and also adhere to their therapies.

This study has important implications. The literature on superutilizers is sparse and mainly focuses on describing the population and hospitalization patterns.^{4,28} This study extends the literature on superutilizers by focusing on the issue of medication nonadherence. The risk factors identified in this study may enable accountable care organizations and managed care organizations to identify superutilizing populations in need of medication management interventions. Our findings suggest that superutilizers filling ≥ 4 opioid medications in a 6-month period are at higher risk for nonadherence and may merit targeted medication management interventions. Given the magnitude and clinical importance of medication nonadherence in this population, a more collaborative and holistic approach may be needed to improve adherence in this high-risk population, which experience frequent care transitions that exposes them to more drug therapy problems and medication discrepancies.

Limitations

Our study is subject to several limitations. First, the study used administrative data and relied on variables that were available in the database. Medicare claims data do not capture factors such as health literacy, social support, and other health care system factors that may affect medication adherence in superutilizers.

Second, the PDC measure for calculating adherence is an indirect method and may not accurately capture medication use. To address limitations of using claims-based PDC, we calculated PDC using 2 different definitions, which allowed us to check the reliability of our main findings. Using these approaches, the overall nonadherence rate ranged from 39.3% to 58.4%, and most of the findings of multivariable models remained similar. Given that the main approach could overestimate adherence and the alternative method could underestimate adherence, we suspect that the population estimates for nonadherence of these superutilizers could lie somewhere between the nonadherence ranges reported in this study.

Third, since this study is based on superutilizers living in Memphis, Tennessee, the study findings may only be generalizable to similar populations and similar settings across the country. Finally, because this is an observational study, we cannot establish any causal relationship.

Conclusions

The overall medication nonadherence rate for essential chronic disease medications was high among superutilizers, especially in patients using COPD/asthma medications. This study identified protective and risk factors associated with medication nonadherence. Previously identified factors—including physician office visits and higher number of medications—were found to protect against nonadherence, while age < 65 years, low-income status, and higher number of unique prescribers were risk factors for nonadherence. Of note, opioid medication use was identified as a novel and significant risk factor for essential medication nonadherence in superutilizers.

The findings of this study highlight the critical need for improving medication adherence in vulnerable Medicare superutilizers. However, targeting interventions to superutilizers with complex medical and social issues is challenging and would require a comprehensive multimodal approach that not only addresses the important barriers identified in this study but can also address other important system-level and socioeconomic barriers faced by these vulnerable patients in managing their chronic conditions.

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DISCLOSURES

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Study concept and design were contributed by Surbhi, Bailey, and Graetz. Surbhi and Wan collected the data, and data interpretation was performed primarily by Surbhi, along with Graetz, Bailey, and Gatwood. The manuscript was primarily written by Surbhi, with assistance from Bailey and Graetz, and revised by Bailey, Graetz, Gatwood, and Surbhi.

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APPENDIX A Study Design

APPENDIX B Medication Nonadherence to Essential Chronic Disease Medication by Therapy Class Using Alternative PDC Definition

Therapy Class	Percentage Nonadherent (PDC < 80%)
Diabetes medications	
Period 1 (n = 250)	41.2
Period 2 (n = 269)	48.7
Period 3 (n = 298)	58.4
Period 4 (n = 300)	67.3
Overall (n = 1,117 patient periods)	53.3
Cardiovascular medications	
Period 1 (n = 933)	40.2
Period 2 (n = 987)	53.1
Period 3 (n = 1,010)	60.8
Period 4 (n = 1,045)	66.0
Overall (n = 3,955 patient periods)	54.2
COPD/asthma medications	
Period 1 (n = 169)	54.4
Period 2 (n = 191)	63.4
Period 3 (n = 216)	66.7
Period 4 (n = 258)	74.8
Overall (n = 834 patient periods)	64.4
Diabetes, cardiovascular, and COPD/asthma medications combined	
Period 1 (n = 961)	43.2
Period 2 (n = 1,011)	56.1
Period 3 (n = 1,031)	65.5
Period 4 (n = 1,060)	72.8
Overall (n = 4,043 patient periods)	58.4

COPD = chronic obstructive pulmonary disease; PDC = proportion of days covered.