Healthcare Costs and Nonadherence Among Chronic Opioid Users

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Objectives: To assess the health economic burden of chronic opioid users and to determine whether opioid regimen nonadherence contributes to increased healthcare costs.

Study Design: Retrospective claims-based analysis of patients with long-term prescription opioid use (>120 days of supply over 6 months).

Methods: Twelve-month healthcare utilization and costs were compared for chronic opioid users (n = 49,425) and, among chronic opioid users with urine drug-monitoring results (n = 2100), between adherent patients versus patients with evidence of nonadherence to their opioid regimen. Likely nonadherence was based on urine test results indicating absence of the prescribed drug, higher or lower than expected drug levels based on a proprietary algorithm, or presence of unprescribed or illegal drugs. The influence of nonadherence on total healthcare costs was assessed using multivariate models.

Results: Prevalence of chronic opioid use was 1.3%. Chronic opioid users had significantly greater healthcare utilization and costs than matched nonusers ($23,049 vs $4975; P <.001). Adherent patients (n = 442) had lower total healthcare costs than likely nonadherent patients (n = 1658; $23,160 vs $26,433; P = .036). After adjustment for demographics, likely nonadherence was significantly associated with elevated total healthcare costs (cost ratio [CR] 1.136; 95% confidence interval [CI] 1.00, 1.29; P = .048). When adjusting for other types of nonadherence, the presence of higher than expected levels of the prescribed opioid was associated with significantly elevated costs (CR 1.121; 95% CI 1.01, 1.25; P = .039).

Conclusions: Chronic opioid users represent a substantial cost burden relative to similar patients without evidence of chronic pain. Among likely nonadherent chronic opioid users, those with evidence of opioid overuse had significantly elevated healthcare costs.

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For author information and disclosures, see end of text.

Pain is a common reason to seek medical care. In contrast to acute pain, chronic pain ceases to serve a protective purpose, is persistent, and disrupts normal living.[1] Chronic pain is highly prevalent by some estimates; in a US survey, 42% of participants aged ≥20 years and 57% of those aged ≥65 years reported pain lasting 1 year or more.[2] Patients experiencing chronic pain have been found to use healthcare services more frequently than those without pain.[3,4]

Opioid analgesics have a recognized role in pain management.[5-10] For chronic pain, opioids are often effective when prescribed and used appropriately as part of a structured pain management plan.[7,8,10] Current pain management recommendations include periodic monitoring of pain control and functional goal achievement, as well as monitoring medication use and aberrant behaviors.[7,10,11]

The need for oversight of prescription opioid use is supported by multiple recent studies. One 2010 report indicated that nearly 10% of patients admitted for substance abuse treatment in 2008 reported prescription pain reliever abuse—an increase from 2% among admissions in 1998.[12] The 2008 National Survey on Drug Use and Health reported that among Americans aged ≥12 years, the prevalence of nonmedical use of prescriptions (ie, pain relievers, tranquilizers, stimulants, sedatives) was second only to marijuana use among types of illicit drug use.[13] Changes in the prevalence of prescription pain reliever abuse paralleled an increase in hospitalizations for poisoning by prescription opioids, sedatives, and tranquilizers: from 1999 to 2006, US hospitalizations for these medications increased by 65%.[14]

Monitoring adherence, or the accuracy and consistency with which a patient follows the pharmacological regimen, is an important aspect of a chronic pain management plan. Nonadherence could include taking too much of the prescribed medication, diverting medication to other individuals, self-medicating with unprescribed or illegal drugs, or taking medication inconsistently.[15-17] Urine toxicology testing is one means of monitoring opioid adherence and assessing whether the prescribed regimen is being followed.[7,10,17-20]

In order to understand the health economic burden of patients with chronic opioid regimens, we assessed the costs and utilization of chronic opioid users (who are presumably being treated for chronic pain) rela-

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tive to similar patients without evidence of chronic pain. In a separate analysis of chronic opioid users with urine drug testing results, we explored whether opioid regimen nonadherence contributed to an increase in annual healthcare costs.

Take-Away Points

Healthcare utilization and costs were compared between patients on chronic opioid therapy and matched controls, and between chronic opioid users who were likely nonadherent based on urine drug monitoring results versus adherent users.

- Over 1 year of follow-up, chronic opioid users had more ambulatory, emergency, and hospital visits than controls, and higher annual healthcare costs.
- Likely nonadherent chronic opioid users were predicted to be 14% more expensive than adherent patients, and had significantly more hospital days.
- Nonadherence to the opioid regimen, likely overuse of the prescribed drug, appears to contribute to elevated costs.

METHODS

Data Sources

Data were obtained from a managed care claims database including geographically diverse commercial, Medicare Advantage, and Medicaid health plan members in the United States. Approximately 18 million people were enrolled in the health plans during the study period from July 1, 2005, through September 30, 2008. Data for adherence classification were obtained from an independent database of urine drug testing results.

Identification of Chronic Opioid Users and Matched Controls

Patients with evidence of long-term prescription opioid use during January 1, 2006, through September 30, 2007 (identification period) were selected for the study. Chronic opioid use was defined as at least 120 days of a qualifying opioid (**eAppendix A** available at **www.ajmc.com**) over any consecutive 6 months during the identification period. The date of the first qualifying opioid fill was the index date.

A control cohort of patients with no evidence of chronic pain or chronic opioid use was also identified (**eAppendix B** at **www.ajmc.com**). Patients in the control cohort could have no more than 1 claim for any opioid, no more than 2 claims for any other pain-related medications (nonsteroidal anti-inflammatory drugs including salicylates and COX-2 inhibitors, and migraine therapies), and no diagnosis for chronic pain (*International Classification of Diseases, Ninth Revision, Clinical Modification* codes 338.0, 338.2x-338.4, 780.96) during the study period. An index date was randomly assigned during the identification period. Both chronic opioid users and matched controls were required to have continuous medical and pharmacy benefits coverage for 6 months prior to (baseline period) through 1 year following (follow-up period) the index date (eAppendix B).

The chronic opioid and control cohorts were matched 1 to 1 based on age (±1 year), sex, geographic region, insurance type, mental health benefit, and preindex Charlson comorbidity score[21] (±2). Patients who could not be matched were excluded. All data were de-identified and accessed with protocols compliant with the Health Insurance Portability and Accountability Act.[22]

Identification of Chronic Opioid Users With Urine Drug Testing and Adherence Classification

A subset of chronic opioid users with 4 or more claims with codes indicating urine drug testing for opiates, benzodiazepines, barbiturates, and amphetamines on the same date of service was identified. These patients were matched with a database of urine drug test results based on patient date of birth, sex, 5-digit zip code, and testing date (±3 days). Privacy board approval was obtained for the use of protected health information for database matching purposes.

For patients with urine drug monitoring results, results from the first test following the index date were used to assign patients to adherent and likely nonadherent cohorts. Nonadherence was determined using urine testing data, which indicated whether individual assay results aligned with reported medication type (ie, presence of prescribed opioid, absence of unprescribed controlled or illegal drugs).[23] Patients were also classified as likely nonadherent if their urine drug levels were not within the concentration ranges expected for their prescribed regimen (eg, total daily dose) after adjustment for physiologic factors as determined by applying a proprietary algorithm (Rx Guardian, Ameritox, Ltd, Baltimore, MD) to the urine assay.[23-26] The likely nonadherent classification is not synonymous with substance abuse, although certain types of nonadherence could suggest abuse or misuse of controlled or illicit drugs.

For patients with urine drug monitoring results, the baseline period was the 6 months before the test, and the follow-up period was the year following the test.

Determination of Cohort Characteristics

Enrollment and claims information were used to determine baseline demographic information, comorbid conditions, and medication use for the cohorts of interest. The Charlson comorbidity score, an estimate of comorbidity burden, was calculated.[21,27,28] General comorbid conditions in the baseline period were identified from claims using Healthcare Cost & Utilization Project Comorbidity Software, version 3.2 (Agency for Healthcare Research and Quality, Rockville, MD). Opioid (including heroin) abuse/dependence, opioid

Table 1. Baseline Characteristics of Chronic Opioid Users Versus Matched Nonusers and Adherent Versus Likely Nonadherent Chronic Opioid Users

	Chronic Opioid Users (n = 49,425)		Nonusers (n = 49,425)			Adherent (n = 442)		Likely Nonadherent (n = 1658)		
Characteristic	**No.**	**%**	**No.**	**%**	***P*[a]**	**No.**	**%**	**No.**	**%**	***P*[a]**
Age group, y					>.99					.651
0-17	74	0.2	74	0.2		0	0.0	0	0.0	
18-44	14,856	30.1	14,852	30.1		174	39.4	685	41.3	
45-64	24,889	50.4	24,898	50.4		261	59.1	953	57.5	
≥65	9606	19.4	9601	19.4		7	1.6	20	1.2	
Female	27,835	56.3	27,835	56.3	1.000[b]	254	57.5	981	59.2	.518
Insurance type					1.000[b]					.044
Commercial	44,760	90.6	44,760	90.6		433	98.0	1581	95.4	
Medicare Advantage	3530	7.1	3530	7.1		5	1.1	51	3.1	
Medicaid	1135	2.3	1135	2.3		4	0.9	26	1.6	
Region					1.000[b]					.209
Northeast	4852	9.8	4852	9.8		16	3.6	74	4.5	
Midwest	14,074	28.5	14,074	28.5		75	17.0	235	14.2	
South	22,017	44.6	22,017	44.6		288	65.2	1148	69.2	
West	8482	17.2	8482	17.2		63	14.3	201	12.1	
Mental health benefit	43,826	88.7	43,826	88.7	1.000[b]	423	95.7	1602	96.6	.354
	Mean	**SD**	**Mean**	**SD**	***P*[c]**	**Mean**	**SD**	**Mean**	**SD**	***P*[c]**
Comorbidity score	0.81	1.29	0.76	1.23	<.001[d]	0.49	0.92	0.61	1.08	.016
Unique medications[e]	8.3	5.7	3.2	3.4	<.001	9.4	5.9	10.9	6.4	<.001
Total medication dispensings[e]	22.2	18.3	8.1	10.4	<.001	28.1	18.1	33.7	20.8	<.001
Unique opioids	—	—	—	—	—	1.85	0.97	2.08	1.06	<.001
Opioid dispensings	4.1	4.7	0.1	0.2	<.001	8.8	5.4	10.4	5.9	<.001
Days of supply of opioids	69.3	79.6	0.3	1.7	<.001	171.3	77.6	194.8	89.4	<.001

[a] χ^2 test.
[b] $P = 1.000$ resulted from exact-matching patients on these factors; the cohorts were not randomly selected.
[c] *t* test.
[d] $P < .05$ attributable to match process allowing scores ±2.
[e] Any medication, not exclusively opioids.

overdose/poisoning, alcoholism or drug abuse, depression, and anxiety during the baseline period were detected using the codes listed in eAppendix C at **www.ajmc.com**.

Determination of Healthcare Utilization and Costs

Healthcare resource utilization during the follow-up period was calculated for each patient as number of office visits, outpatient visits, emergency department visits, inpatient admissions, and hospital days.

Pharmacy costs and medical costs, including ambulatory, emergency service, inpatient, and other medical costs, were tabulated from claims in the follow-up period and adjusted to 2008 dollars.[29] Healthcare costs included both health plan and patient-paid amounts. "Other" medical costs include costs associated with durable medical equipment, home care, and services such as laboratory testing (including urine drug testing).

Claims with codes for pain-related services and procedures (eAppendix D at **www.ajmc.com**) were used to determine pain-related costs.

Analyses

Baseline characteristics, healthcare utilization, and costs were analyzed descriptively, comparing the chronic opioid cohort with the matched control cohort, and the cohorts of adherent and likely nonadherent chronic opioid users. Significance was determined as $P < .05$.

Table 2. One-Year Follow-up Healthcare Utilization (Visits per Patient)

Utilization Measure	Chronic Opioid Users, Mean (SD) (n = 49,425)	Nonusers, Mean (SD) (n = 49,425)	P[a]	Adherent, Mean (SD) (n = 442)	Likely Nonadherent, Mean (SD) (n = 1658)	P[a]
Ambulatory visits	28.5 (24.7)	10.2 (11.7)	<.001	32.3 (20.3)	33.3 (23.0)	.417
Emergency department visits	1.5 (4.1)	0.6 (2.6)	<.001	1.6 (6.2)	1.7 (4.0)	.805
Hospital admissions	0.4 (1.0)	0.1 (0.4)	<.001	0.3 (0.9)	0.4 (0.9)	.109

[a] *t* test.

The relationship between 12-month follow-up total healthcare costs and likely nonadherence to the prescribed opioid treatment regimen was modeled using a generalized linear model with gamma distribution and log link,[30] controlling for demographics, mental health benefit, insurance type, and index month. A similar model was developed to assess the relationship between individual categories of nonadherence and total healthcare costs while controlling for each type of nonadherence.

RESULTS

Chronic Opioid Users Versus Matched Controls

The prevalence of chronic opioid use was 1.3% among enrollees meeting the 18-month continuous enrollment requirement. Characteristics of chronic opioid and matched control cohorts are shown in Table 1. Most patients were commercially insured and, consistent with the health plan distribution, the South was the most heavily represented geographic region.

The number of unique medications and total medication dispensings in the baseline period was greater among chronic opioid users than matched control patients (Table 1). Eighteen of the 20 most common comorbidities identified in the cohorts occurred more frequently among chronic opioid users and are often associated with pain, including disorders such as spondylosis, intervertebral disc disorders, and other back problems; nontraumatic joint disorders; and mood disorders (**eAppendix E** at **www.ajmc.com**). Chronic opioid users had a greater frequency of alcoholism or other drug abuse than matched control patients, and although the proportion of patients with evidence of opioid abuse/dependence or overdose/poisoning was low overall, it was significantly greater for chronic opioid users compared with matched control patients (eAppendix E).

Chronic opioid users had more ambulatory and emergency visits, and more hospital admissions than nonusers (Table 2). Total healthcare costs were more than 4 times higher for the chronic opioid cohort compared with matched nonusers ($23,049 ± $42,798 vs $4975 ± $13,185; *P* <.001), with medical costs approximately 5 times greater and pharmacy costs 3.5 times greater for chronic opioid users (Table 3).

Adherent Versus Likely Nonadherent Chronic Opioid Users

Cohort Characteristics. The selection of the patient population with urine testing results is shown in eAppendix B. Baseline characteristics of this subsample (n = 2100) according to adherent/likely nonadherent classification are shown in Table 1. The adherent cohort comprised 21.1% of tested patients, but most patients were likely nonadherent (Figure). Nonadherence due to a higher than expected level of the prescribed opioid was the type observed most frequently (Figure).

During the baseline period, likely nonadherent patients filled a significantly higher number of unique prescriptions and had a greater total number of medication dispensings than adherent patients (Table 1). They also filled significantly more unique opioid types, had a greater number of opioid dispensings, and had more days of supply of opioids (Table 1). Hydrocodone and oxycodone were the most commonly filled opioids (**eAppendix F** at **www.ajmc.com**).

Comorbidity scores were higher for likely nonadherent patients (Table 1). These patients had a greater prevalence of mood-related disorders and alcoholism/other drug abuse, whereas prevalences of both opioid abuse/dependence and opioid overdose/poisoning were low and did not differ significantly between the cohorts (eAppendix E).

Healthcare Utilization in the Follow-up Period. The mean number of ambulatory and emergency department visits per patient did not differ significantly between adherent and likely nonadherent cohorts (Table 2); nor did the mean number of hospital admissions. However, the number of hospital days was significantly greater for likely nonadherent patients (2370 days per 1000 patients) compared with adherent patients (1753 days per 1000 patients; *P* <.001) because a greater percentage of patients in the likely nonadherent cohort had a hospital admission (24.3% vs. 19.5%; *P* = 0.032) with longer average length of stay per admission (6.2 ± 5.1 days vs. 5.7±

Table 3. Healthcare Costs (per Patient) in the 1-Year Follow-Up Period: Chronic Opioid Users Versus Matched Nonusers and Adherent Versus Likely Nonadherent Chronic Opioid Users[a]

Type of Cost	Chronic Opioid Users, Mean (SD), $ (n = 49,425)	Nonusers, Mean (SD), $ (n = 49,425)	P[a]	Adherent, Mean (SD), $ (n = 442)	Likely Nonadherent, Mean (SD), $ (n = 1658)	P[a]
Ambulatory	9358 (21,436)	2223 (6981)	<.001	9237 (12,473)	9734 (14,334)	.472
Emergency	339 (1185)	87 (409)	<.001	331 (976)	421 (1170)	.096
Inpatient	7231 (27,350)	980 (8776)	<.001	4855 (16,937)	6361 (20,831)	.115
Other medical	1165 (7777)	275 (1832)	<.001	1573 (2879)	1957 (4326)	.027
Total medical	18,092 (40,961)	3565 (12,406)	<.001	15,995 (25,680)	18,473 (29,226)	.081
Pharmacy	4956 (7175)	1410 (3145)	<.001	7165 (9673)	7960 (10,244)	.143
Total healthcare[b]	23,049 (42,798)	4975 (13,185)	<.001	23,160 (28,251)	26,433 (32,077)	.036

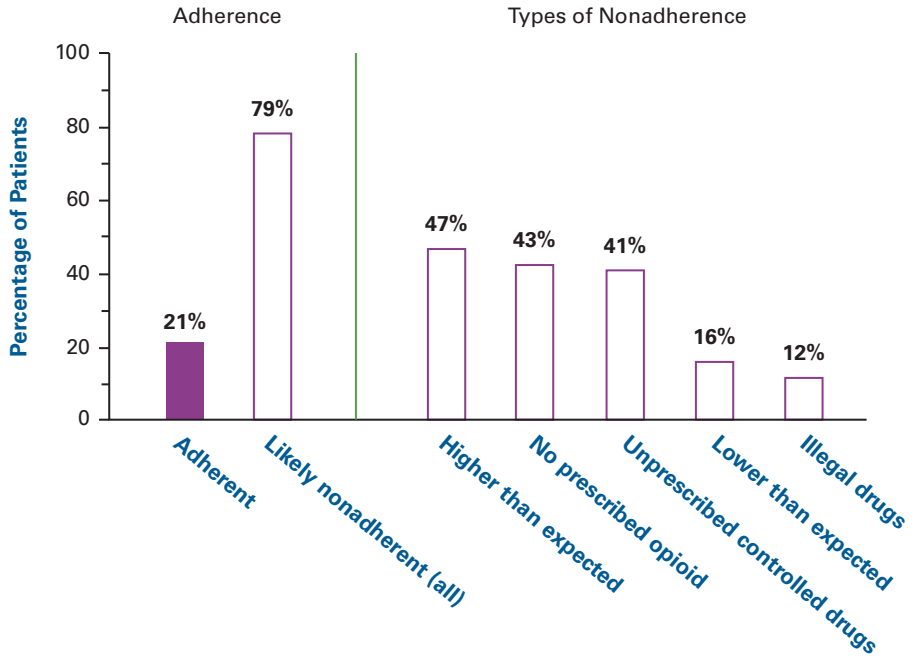
[a] *t* test.
[b] Total medical plus pharmacy costs.

6.1 days; $P = 0.049$). Likely nonadherent patients continued to have significantly more opioid dispensings (20.7 ± 11.1 vs 18.2 ± 8.6; $P < .001$) and more days of supply of opioids (414.9 ± 169.0 vs 391.8 ± 146.3; $P = .004$) than adherent patients in the follow-up period.

Healthcare Costs. Among chronic opioid users with urine testing results, total healthcare costs per patient during the follow-up period were approximately 14% higher for likely nonadherent patients, a statistically significant difference from the adherent cohort (Table 3).

No statistically significant cost differences were observed for pain-related services between the adherent and likely nonadherent cohorts, although the relative magnitude of spending was notable: costs for surgery of the spine among patients with at least 1 relevant service date were $33,290 for adherent patients (n = 28) and 23% higher for likely nonad-

Figure. Distribution of Urine Test Results[a]



[a] The percentages of patients who were adherent or had evidence of any type of nonadherence are shown on the left. The distribution of the different types of nonadherence within the likely nonadherent cohort is shown on the right. Patients could be nonadherent in multiple categories.

Table 4. Multivariate Analyses of Total Follow-up Cost Adjusted for Likely Nonadherence[a]

	Model 1			Model 2		
Variable	**Cost Ratio**	**95% CI**	***P***	**Cost Ratio**	**95% CI**	***P***
Likely nonadherent	1.136	1.00, 1.29	.048	—	—	—
Higher than expected	—	—	—	1.121	1.01, 1.25	.039
Lower than expected	—	—	—	1.090	0.93, 1.28	.283
No prescribed medication	—	—	—	0.992	0.89, 1.11	.888
Unprescribed medication present	—	—	—	1.063	0.95, 1.19	.276
Illegal drug present	—	—	—	0.704	0.59, 0.84	<.001
Age	1.004	1.00, 1.01	.155	1.003	1.00, 1.01	.335
Male	0.800	0.72, 0.89	<.001	0.815	0.73, 0.91	<.001
West region	1.155	0.87, 1.54	.328	1.100	0.83, 1.47	.515
Midwest region	0.807	0.61, 1.07	.141	0.793	0.60, 1.05	.107
South region	0.839	0.65, 1.08	.179	0.821	0.64, 1.06	.129
Mental health benefit	1.138	0.86, 1.50	.366	1.118	0.85, 1.48	.433
Medicare	0.691	0.50, 0.96	.025	0.718	0.52, 0.99	.044
Medicaid	0.797	0.51, 1.25	.320	0.807	0.52, 1.26	.344
Index month, by year	1.003	0.99, 1.01	.457	1.003	0.99, 1.01	.493

CI indicates confidence interval.
[a]There were 2100 observations in each model. Model 1 estimated total costs while adjusting for the composite definition of nonadherence and indicated covariates. Model 2 adjusted for each type of nonadherence and indicated covariates.

herent patients (n = 83) ($40,893; *P* = .468); mean cost for intrathecal or epidural drug infusion pump implantation and maintenance among patients with at least 1 relevant claim was $10,896 for adherent patients (n = 6) and 64% higher for likely nonadherent patients (n = 41) ($17,959; *P* = .370).

The relationship between adherence and total follow-up costs was further assessed using multivariate models (Table 4). Consistent with the unadjusted mean costs, costs predicted based on the adjusted model were also approximately 14% higher for the likely nonadherent cohort ($26,419) than for the adherent cohort ($23,263); this difference was significant (Table 4, Model 1).

Of the possible test results, patients with lower-than-expected urine drug levels and those with higher than expected levels had the highest predicted costs ($27,752 and $27,631, respectively), but only having higher than expected levels of the prescribed opioid was associated with statistically significantly greater predicted total healthcare expense in the adjusted model (Table 4, Model 2). Based on Model 2, patients with higher than expected opioid levels were predicted to have follow-up healthcare costs that were 12% higher than those of other patients. Predicted total healthcare costs for patients with evidence of an illegal drug ($18,606) were significantly lower than costs predicted for other patients.

DISCUSSION

Although the prevalence of chronic opioid therapy is not high, total medical spending on chronic opioid users is likely to be substantial in most managed care plans. Chronic opioid users had elevated healthcare resource use and incurred substantially greater healthcare costs than nonusers. Furthermore, some chronic opioid users generated higher costs than others and these excess costs were associated with indicators of nonadherence determined by urine drug monitoring. This was particularly evident in the cohort of patients with higher than expected drug levels.

Our results are consistent with previous studies suggesting that patients who use opioids for long-term pain incur greater healthcare costs than patients who are not on opioid therapy.[4,31] Higher costs in the chronic opioid population are likely related to moderate to severe chronic pain as well as pain-related comorbidities such as arthritis or diabetic neuropathy. Other possible explanations for the reported cost differences include disproportionate use of expensive services or increased risk of unintentional effects of opioid use, such as overdose.

The overall prevalence of nonadherence, while consistent with the finding of a previous study using the same urine drug testing database,[23] is higher than nonadherence rates typically

found in studies of drug treatment for other disease states. For example, nonadherence with treatment for chronic conditions such as diabetes, hypertension, and hyperlipidemia has been reported to range from approximately 22% to 50%.[32,33] Multiple reasons are likely to contribute to the higher proportion of likely nonadherent patients that we observed. First, nonadherence with therapy in most disease states refers exclusively to underuse or discontinuation of a drug. With respect to chronic opioid therapy, nonadherence includes underuse[34] as well as drug abuse, supplementation with additional opioids, potential diversion, illicit drug use, and the concomitant use of other controlled drugs unbeknownst to the provider ordering the opioid.[17,23] Criteria to detect abnormal results based on an expected range have not been applied in all studies of opioid nonadherence, and these additional criteria may also account for differences in the reported prevalence of nonadherence.[17]

Second, although opioid urine drug monitoring is an integral part of current pain management recommendations[7], patients with urine toxicology results in this study might have been selected for testing because they were perceived to be at high risk for misuse. The data in eAppendix E suggest that mood disorders and substance abuse were more prevalent among patients with urine testing than among the population of chronic opioid users as a whole. Since patients with these comorbidities are more likely to be nonadherent, testing bias could also contribute to the high overall rate of nonadherence among tested patients.

Finally, clinicians who ordered urine drug testing were asked to indicate on the lab requisition form whether patients were taking a controlled drug on an "as needed" basis. It is possible that this was not consistently documented, which could increase the rate of nonadherence in the categories of "no prescribed opioid" or "lower than expected" drug level.

Detection of higher than expected drug levels appears to be a useful addition to criteria for defining abnormal results, as likely overuse was found to be associated with increased costs. Higher than expected levels of the prescribed opioid could indicate inadequate pain control (requiring additional use of opioid medication) or potential abuse. This behavior could put patients at risk for side effects or overdose, further increasing their need for healthcare services and leading to higher costs. Overuse constituting abuse has been associated with increased costs,[35] but due to limitations of healthcare claims research, abuse was not specifically investigated here.

In contrast to the increased costs associated with overuse, use of illegal drugs was associated with lower healthcare costs. Possible explanations for this finding are that individuals who use illicit drugs might be less likely to seek healthcare,[36,37] they might be less likely to have commercial insurance (which could in turn affect costs associated with their care), or they might require fewer healthcare services because their pain is fictitious. It is also possible that clinician mistrust of patients with evidence of illicit drug use influences treatment plans. Further investigation is needed to confirm and explore reasons for this finding.

Our findings suggest that appropriate use of an opioid regimen moderates excess costs. Identifying nonadherent patients, particularly those with high urine drug levels, for treatment plan adjustments and care management interventions could help to improve pain control, reduce drug misuse, and reduce excess costs associated with nonadherence. Other strategies to monitor opioid use (eg, use of screening instruments to identify aberrant behaviors, other risk assessment tools, online prescription databases) complement urine testing, and determining concordance between these measures could be of value to physicians.[7,38,39] Additional research is needed to determine whether feedback to clinicians provided by drug monitoring directly reduces costs or guides care practices.

Limitations

All claims-based analyses are subject to certain limitations, such as possible coding errors, undercoding, and lack of generalizability. In this study, the classification of adherence was limited by possible misinformation provided to the testing facility regarding the prescribed opioid regimen. Determination of adherence based on expected urine drug levels was dependent on receipt of accurate information concerning the patient's opioid regimen prescriptions as well as clinical information such as sex, height, and weight. If incomplete or inaccurate information was provided, some patients identified as nonadherent could have in fact been following their prescribed regimen. In addition, although the study samples comprised all available patients who fulfilled the inclusion criteria, the comparisons may not have been powered to detect moderate differences.

CONCLUSIONS

A high level of healthcare resource use and costs was generated by patients on chronic opioid regimens in comparison with patients who did not use opioid medications or have evidence of chronic pain. Urine drug testing can identify patients who are likely to be nonadherent and have significantly higher healthcare costs. In particular, patients with urine drug levels that were higher than expected using a proprietary algorithm were predicted to have significantly

higher costs than patients whose test results were within an expected range. Improving adherence could reduce costs incurred by patients with chronic pain.

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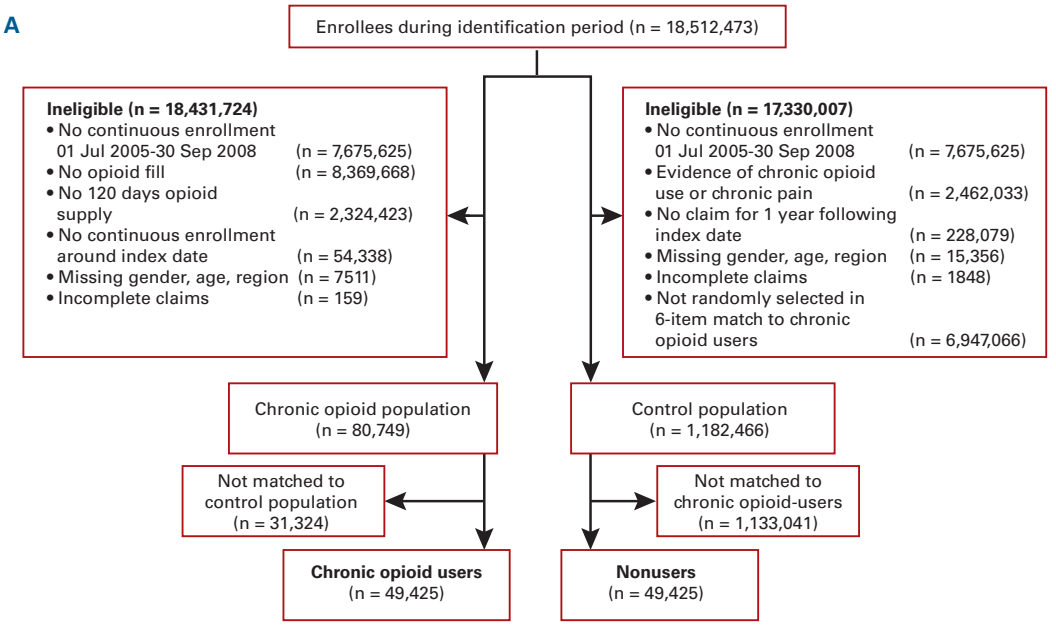
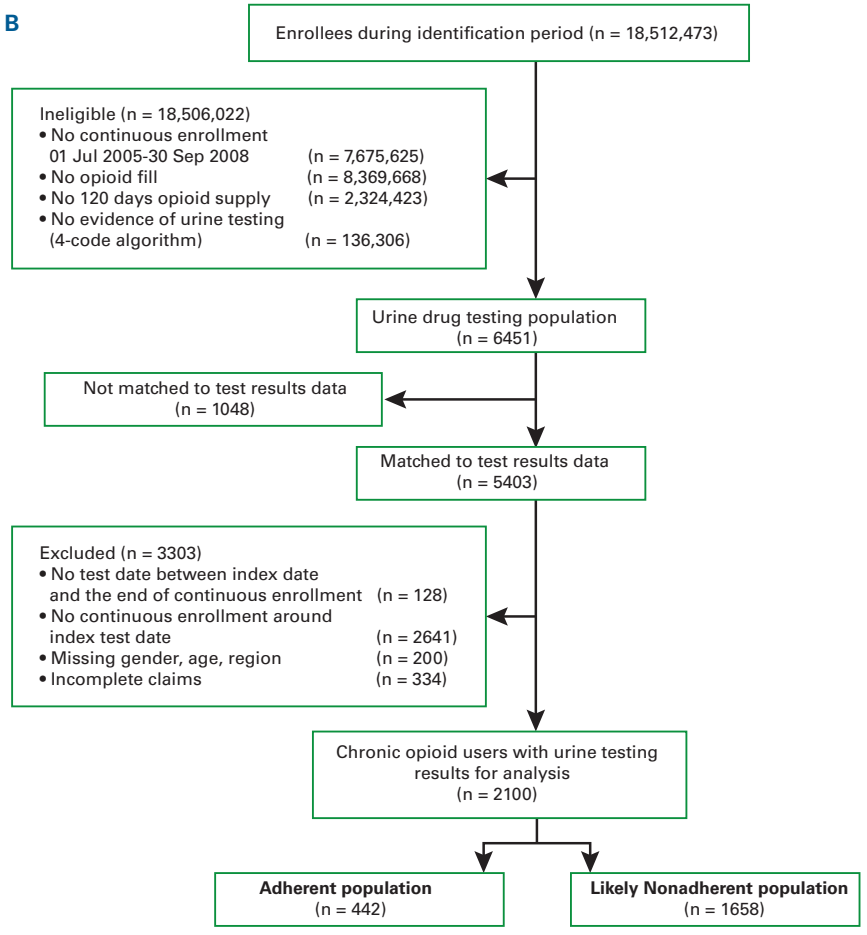
■ **eAppendix A.** Opioid Identification Codes[a]

Medication Class	Medication	HCPCS Code
Opioids, synthetic opioids, and other narcotic analgesics	Codeine	J0745 (inj)
	Dihydrocodeine	
	Morphine	J2270 (inj) J2271 (inj) J2275 (inj) S0093 (inf)
	Hydrocodone	
	Oxycodone	
	Hydromorphone	J1170 (inj) S0092 (inf)
	Oxymorphone	J2410 (inj)
	Levorphanol	J1960 (inj)
	Alfentanil	
	Remifentanil	
	Fentanyl	J3010 (inj) J1810 (inj)
	Meperidine	J2175 (inj) J2180 (inj)
	Levomethadyl	
	Methadone	J1230 (inj) S0109 (or)
	Propoxyphene	
	Buprenorphine	J0592 (inj)
	Nalbuphine	J2300 (inj)
	Butorphanol	J0595 (inj) S0012 (na)
	Pentazocine	J3070 (inj)
Exclusionary opioids for the control population	Sufentanil	
	Dezocine	
	Tramadol	
	Opium	

HCPCS indicates Healthcare Common Procedure Coding System; inf, infusion; inj, injectable; na, nasal spray; or, oral.
[a]Opioid use as indicated by HCPCS codes on medical claims or pharmacy claims for opioids in injectable, ampule, or suppository form were not included as part of the chronic opioid population selection criteria, but were included as part of the exclusion criteria for the non–chronic opioid population.

eAppendix B. Selection of Patients on Chronic Opioid Therapy[a]





[a](A) Chronic opioid users and matched control patients; (B) patients with urine drug monitoring results comprising adherent and likely nonadherent cohorts.

eAppendix C. Codes for Descriptive Conditions

Condition	*ICD-9-CM* Diagnosis Code
Alcoholism and selected drug abuse (excluding opioid abuse)	303.xx 304.1x-304.6x, 304.8x-304.9x 305.0x-305.4x, 305.6x-305.9x, V11.3
Depression	296.2x, 296.3x, 296.5x (excluding 296.x4) 296.82 300.4 309.0, 309.1, 309.28 311
Anxiety	293.84 300.0x, 300.2x , 300.3, 300.6 309.24 313.0
Opioid abuse/dependence	304.0x, 304.7x, 305.5x, 965.0x
Opioid overdose/poisoning	E850.0-E850.2

ICD-9-CM indicates *International Classification of Diseases, Ninth Revision, Clinical Modification*.

eAppendix D. Codes for Pain-Related Services and Procedures

Major Procedure	Subprocedure	CPT/HCPCS	*ICD-9-CM* Procedure	*ICD-9-CM* Diagnosis
Diagnostic imaging related to bone (including CT and MRI scans of the spine)	Bone x-rays	70100-70130 70140-70160 70190-70200 70210-70240 70250-70260 70328-70330 71100-71130 72010-72120 72170-72190 72200-72220 73000-73030 73050-73080 73090-73110 73120-73140 73500-73520 73530-73540 73550-73565 73590-73610 73620-73660 74710	87.16-87.17 87.22-87.29 87.43 88.2x-88.31 88.33	
	Bone CT/MRI scans	70336 72125-72158 73200-73202 73218-73223 73700-73702 73718-73723	88.93-88.94	
	Bone density measurement	76070-76071 76075-76078 76977 77078-77083 78350-78351 G0130-G0132	88.98	
	Other bone imaging	76880-76886 77072-77077 78300-78320 78399		
Surgery of the spine		22100-22226 22325-22328 22520-22849 22851 22856-22862 63001-63621 63709-63710 0092T 0096T 0098T 0163T 0165T 0195T-0196T	03.0x 03.1x 03.2x 03.4x 03.53 03.59 3.6x 80.5x 81.0x 81.3x 81.6x 84.51 84.59 84.6x 84.8x	
Spinal and peripheral nerve neurostimulator implantation and maintenance		63650-63688 64550-64595 95970-95973	03.93-03.94 04.92-04.93 86.94-86.98	
Intrathecal or epidural drug infusion pump implantation and maintenance		62350-62368 95990-95991	86.06	

(Continued)

eAppendix D. Codes for Pain-Related Services and Procedures *(Continued)*

Major Procedure	Subprocedure	CPT/HCPCS	*ICD-9-CM* Procedure	*ICD-9-CM* Diagnosis
Nerve blocks		64400-64425 64445-64449 64455 64600-64610 (neurolytic) 64620 (neurolytic)	04.2 (neurolytic) 04.8x 05.31	
Epidural steroids and other pain-associated spinal injections		62281-62282 (neurolytic) 62310-62319 64470-64476 64479-64484 64622-64627 (neurolytic) 64632-64640 (neurolytic)	03.8 (neurolytic) 03.91 03.92	
Electromyography and nerve conduction studies	Electromyography	95860 95861 95863 95864 95867 95868 95869 95870 95872	93.08	
	Nerve conduction tests	95900 95903 95904 S3905	89.15	
Attempted suicide and/or self-inflicted injury				E950.x-E958.x, E959 E980.x-E988.x, E989
Accidental poisoning/ accidental overdose				960.x-979.x

CPT indicates Current Procedural Terminology; CT, computed tomography; HCPCS, Healthcare Common Procedure Coding System; *ICD-9-CM*, *International Classification of Diseases, Ninth Revision, Clinical Modification*; MRI, magnetic resonance imaging.

eAppendix E. Percentage of Patients With Selected Comorbidities in the Baseline Period

Condition	Chronic Opioid Users, % (n = 49,425)	Nonusers, % (n = 49,425)	*P*[a]	Adherent, % (n = 442)	Likely Nonadherent, % (n = 1658)	*P*[a]
Comorbidity						
Spondylosis, intervertebral disc disorders, other back problems[b]	47.1	8.9	<.001	83.7	85.6	.324
Nontraumatic joint disorders[b]	36.9	10.2	<.001	40.1	43.4	.202
Mood disorders[b]	16.4	4.8	<.001	22.6	27.6	.037
Anxiety disorders[b]	—	—		12.4	19.5	<.001
Anxiety[c]	9.8	3.0	<.001	11.8	18.3	.001
Depression[c]	16.3	5.1	<.001	23.1	26.9	.104
Other nervous system disorders[b]	—	—		32.8	28.0	.047
Alcoholism/drug abuse[c,d]	8.1	2.2	<.001	11.8	15.9	.032
Opioid-related conditions[c]						
Opioid abuse/dependence[e]	0.86	0.03	<.001	2.7	3.1	.647
Opioid overdose/poisoning	0.12	0.01	<.001	0.2	0.6	.329

[a] χ^2 test.
[b] Selected from among the 20 most common comorbidities identified for the cohorts with Healthcare Cost and Utilization Project Comorbidity Software, version 3.2.
[c] Indicator variable.
[d] Excluding heroin.
[e] Including heroin.

eAppendix F. Baseline Distribution of Pain Medications Among Chronic Opioid Users With Urine Monitoring Results

			Distribution Within Cohorts, %		Distribution Between Cohorts, %		
Pain Medication	No.	Percentage of All Tested Patients (n = 2100) With Use of Specified Medication	Percentage of Patients in the Adherent Cohort (n = 442) With Use of Specified Medication	Percentage of Patients in the Likely Nonadherent Cohort[a] (n = 1658) With Use of Specified Medication	Percentage of Patients With Medication Use Who Are in the Adherent Cohort	Percentage of Patients With Medication Use Who Are in the Likely Nonadherent Cohort[a]	*P*[b]
Hydrocodone	1258	59.9	55.2	61.2	19.4	80.6	.023
Oxycodone	1127	53.7	46.4	55.6	18.2	81.8	<.001
Fentanyl	412	19.6	23.8	18.5	25.5	74.5	.014
Morphine	404	19.2	14.0	20.6	15.3	84.7	.002
Tramadol[c]	286	13.6	15.8	13.0	24.5	75.5	.126
Methadone	261	12.4	7.5	13.8	12.6	87.4	<.001
Propoxyphene	181	8.6	8.6	8.6	21.0	79.0	.985
Hydromorphone	127	6.0	6.6	5.9	22.8	77.2	.610
Codeine	98	4.7	3.6	5.0	16.3	83.7	.240
Others[d]	91	4.3	3.6	4.5	17.6	82.4	.407
Meperidine	69	3.3	2.5	3.5	15.9	84.1	.290

[a]Inclusion in the likely nonadherent cohort does not imply nonadherence for every specified medication (ie, a patient who was adherent to 1 opioid but nonadherent to another would be in the likely nonadherent cohort).
[b]χ^2 test comparing prevalence of medication use between adherent and likely nonadherent patients.
[c]Not included as part of the sample selection criteria; patients also had evidence of opioid use.
[d]Included buprenorphine, butorphanol, dihydrocodeine, levorphanol, nalbuphine, opium, oxymorphone, pentazocine, Suboxone, and Talwin.