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# Opioid Prescriptions and Short-Term Mortality: a U.S. National Study

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**BACKGROUND:** Opioid-related mortality continues to rise. Though risks of prescription opioid misuse and abuse are well known, short-term mortality across a range of prescription opioid exposure is unclear.

**OBJECTIVE:** This study was conducted in order to assess the short-term mortality associated with quantity of reported opioid prescriptions.

**DESIGN:** An observational analysis was performed using data from the Medical Expenditure Panel Survey, years 2005–2015, a population-based, nationally representative household survey.

**PARTICIPANTS:** This study included adults (age 18+) with prescription data and death status reported during their 2-year survey participation.

**MAIN MEASURES:** Key exposure is the number of opioid prescriptions (0, 1–5, 6 or more) in year 1 of survey participation. The main outcome is all-cause mortality reported during the 2-year survey participation.

**KEY RESULTS:** Of 90,622 participants, 14% reported at least 1 opioid prescription. There were 774 (0.9%) deaths during the survey period, 551 (0.7%) among those not reporting opioids, 127 (1.2%) among those reporting 1–5 opioid prescriptions, and 96 (3.9%) among those reporting 6 or more opioid prescriptions. After adjusting for sociodemographics, health status, and utilization, there was no significant association between category of opioid prescriptions and death during the study period; adjusted odds ratios = 0.86 (95% CI = 0.66, 1.22,  $p = 0.27$ ) and 0.99 (95% CI = 0.74, 1.34,  $p = 0.96$ ), respectively, for 1–5 prescriptions and 6 or more prescriptions.

**CONCLUSIONS:** In a nationally representative sample, opioid prescriptions were associated with increased short-term mortality only without adjustment for sociodemographics, health status, or utilization. The relationship between prescription opioid use and mortality risk is more complex than previously reported, meriting further examination.

**KEY WORDS:** opioids; mortality; pain; health status; United States.

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The United States (U.S.) faces a growing epidemic of opioid-related mortality,<sup>1–3</sup> which has triggered a wholesale re-examination of the safety of prescription opioid analgesics. The risks of misuse and abuse of prescription opioids are well-known, including overdose and opioid use disorder,<sup>4</sup> prompting initiatives to reduce initial prescribing and encourage “deprescribing” among patients receiving long-term prescription opioids.<sup>5,6</sup>

In possible contrast to the known mortality risks of misused and nonprescribed opioids, the extent to which receiving prescription opioids is associated with mortality remains understudied.<sup>7,8</sup> Prior studies of patients with chronic noncancer pain have found long-term or chronic opioid therapy (commonly defined as at least 3 months of continuous use) to be associated with lower health-related quality of life, more disability, more healthcare utilization, and greater risk of opioid use disorder.<sup>9,10</sup> Some studies similarly indicate a relationship between short-term use of prescription opioids and deleterious outcomes.<sup>11–13</sup> However, the causal direction of these relationships remains uncertain. Given the growing concerns about prescription opioid safety and possible adverse unintended consequences of restricting and deprescribing opioids (e.g., patient dissatisfaction, worse clinician–patient relationships, and increased illicit drug use),<sup>14</sup> there is an urgent need to better characterize prescription opioid-related mortality risk.

We analyzed data from individuals enrolled for 2 years in the 2005–2015 U.S. Medical Expenditure Panel Survey (MEPS) to examine the relationship between the number of opioid analgesic prescriptions received in participation year 1 and all-cause mortality during survey participation and to explore how patient sociodemographic factors and health status may affect the relationship. Given what is known about the risks associated with opioid misuse, we hypothesized that short-term mortality would be higher among the opioid-exposed in the sample.

## METHODS

### Data Source

MEPS is a nationally representative survey of healthcare use and costs in the U.S. civilian and noninstitutionalized

population. The survey is conducted by the Agency for Healthcare Research and Quality (AHRQ) as a subset of the National Health Interview Survey and employs an overlapping panel design. Data are collected for individuals over a 2-year period through baseline and follow-up interviews.<sup>15</sup> The MEPS Household Component collects information on interview language, country of origin, sociodemographic information, usual source of care, and health insurance coverage. Two additional survey components were also examined. The MEPS Prescribed Medicines file is a subcomponent detailing prescription drug information for all survey participants during each of the follow-up interviews. The Medical Conditions file documents all conditions reported by respondents at each follow-up survey. We utilized MEPS data from these three components for the years 2005–2015. Response rates declined from 61.3 to 47.7% during the study years.<sup>16</sup>

The analytic sample for this study included all participants aged 18 or older who provided baseline data and for whom mortality data was available within their 2-year study participation period. We utilized the overlapping panel design to assess prospectively the association between opioid prescription exposure and other factors (sociodemographic characteristics, markers of health status, and healthcare utilization) in participation year 1 with mortality during survey participation.

## Measures

**Opioid Prescriptions.** We categorized year 1 prescription opioid exposure using the number of discrete opioid prescriptions reported in the Prescribed Medicines file. Opioid prescriptions were categorized as none (analytic reference), 1–5, and 6 or more. These categories were chosen to account for incidental, short-term exposure (1–5 prescriptions in the year) and longer-term use (6 or more prescriptions).

**Mortality.** We assessed short-term all-cause mortality as death occurring during the 2 years of MEPS enrollment. Mortality was counted if death was reported by a household proxy respondent as the person's disposition status in any of the survey rounds.

**Covariates.** We included key variables to account for sociodemographic characteristics, health status, health behaviors, and healthcare utilization. Sociodemographic covariates included age (in years), sex, self-reported race/ethnicity (White, Hispanic, Black, Other), U.S. census region (Northeast, Midwest, South, West), education level (less than high school, some high school, high school graduate, some college, college graduate), household income level (< 100, 100–124, 125–199, 200–399, or  $\geq$  400% of the federal poverty level), and health insurance status (uninsured, privately insured, or publicly insured). Measures of health status in year 1 included the 12-item Short-Form Health Survey (SF-12), utilizing both the Mental Component Summary (MCS-12) and Physical Component Summary (PCS-12). Separately, we

assessed responses to the single question “In general, would you say your health is: excellent, very good, good, fair, or poor?” Both health status measures have been shown to independently predict mortality.<sup>16,17</sup> We further assessed morbidity using a count of eight self-reported chronic conditions (diabetes, hypertension, coronary heart disease, myocardial infarction, cerebrovascular disease, asthma, emphysema, and arthritis). Separately, persons reporting any visit with a diagnosis of any cancer (excluding only nonmelanoma skin cancer) were coded as having cancer. Self-reported smoking status (nonsmoker vs current smoker) was also assessed. To measure healthcare utilization, a potential marker for morbidity as well as propensity to seek care, we included variables for total year 1 healthcare expenditures and number of physician office visits.

## Statistical Analyses

We analyzed data using Stata version 15.1 in 2017–2018. We utilized longitudinal strata and primary sampling unit identifiers, with survey weights to account for the complex survey design and sampling design of successive waves of the MEPS. We performed a sequence of logistic regression analyses to assess the association between year 1 prescription opioids and death during the study period and to explore how that association varied according to categories of covariates. The key independent variable was opioid prescriptions, assessed as no opioids (reference), 1–5 opioid prescriptions, or 6 or more opioid prescriptions. The initial analysis included no covariates. Next, sociodemographic characteristics (age, sex, race/ethnicity, census region, education level, household income level, and health insurance status) were added as covariates. Next, health status–related covariates were added (mental health status [MCS-12], physical health status [PCS-12], the single question self-rated health), as well as health conditions [count of eight chronic conditions], the presence or absence a cancer diagnosis, and smoking status. Finally, utilization variables (total health expenditures (as the natural log of [actual expenditures + 1]) and number of physician office visits) were added. All analyses also adjusted for MEPS panel year to account for potential secular temporal trends. Secular trends were explored further by adding an interaction term between opioid prescription category and time period.

## RESULTS

The analytic sample included 90,622 adult MEPS participants between the years 2005 and 2015 with year 1 baseline and health data and mortality status data.

Table 1 summarizes the characteristics of the analytic sample comparing individuals in each of the opioid prescription categories. In total, 14% ( $n = 12,780$ ) of the sample reported at least 1 opioid prescription, with the majority of those (80.6%) receiving fewer than 6 prescriptions. Only 2480 patients (2.7%

Table 1 Patient Characteristics by Category of Opioid Prescriptions

Characteristic	Total	No opioids	1–5 prescriptions	≥ 6 prescriptions	<i>p</i> value (sample)
<i>N</i>	90,622	77,842	10,300	2480	
Age, mean (SD)	45.8 (17.4)	45.4 (17.5)	47.0 (17.2)	55.4 (14.5)	< 0.001
Sex, female	49,377 (54.5%)	41,354 (53.1%)	6455 (62.7%)	1568 (63.2%)	< 0.001
Race					
White	43,385 (47.9%)	36,002 (46.3%)	5786 (56.2%)	1597 (64.4%)	< 0.001
Hispanic	22,642 (25.0%)	20,638 (26.5%)	1736 (16.9%)	268 (10.8%)	
Black	16,873 (18.6%)	14,171 (18.2%)	2191 (21.3%)	511 (20.6%)	
Other	7722 (8.5%)	7031 (9.0%)	587 (5.7%)	104 (4.2%)	
Education					
<High school	8144 (9.0%)	7189 (9.2%)	685 (6.7%)	270 (10.9%)	< 0.001
Some high school	12,239 (13.5%)	10,268 (13.2%)	1489 (14.5%)	482 (19.4%)	
HS graduate	27,785 (30.7%)	23,664 (30.4%)	3250 (31.6%)	871 (35.1%)	
Some college	21,886 (24.2%)	18,452 (23.7%)	2851 (27.7%)	583 (23.5%)	
College graduate	20,568 (22.7%)	18,269 (23.5%)	2025 (19.7%)	274 (11.0%)	
Household income, % federal poverty level					
< 100	16,277 (18.0%)	13,368 (17.2%)	2131 (20.7%)	778 (31.4%)	< 0.001
< 125	5480 (6.0%)	4626 (5.9%)	616 (6.0%)	238 (9.6%)	
< 200	15,043 (16.6%)	12,950 (16.6%)	1626 (15.8%)	467 (18.8%)	
< 400	27,128 (29.9%)	23,507 (30.2%)	3021 (29.3%)	600 (24.2%)	
400+	26,694 (29.5%)	23,391 (30.0%)	2906 (28.2%)	397 (16.0%)	
Census region					
Northeast	13,870 (15.3%)	12,312 (15.8%)	1269 (12.3%)	289 (11.7%)	< 0.001
Midwest	18,008 (19.9%)	15,062 (19.3%)	2361 (22.9%)	585 (23.6%)	
South	34,518 (38.1%)	29,284 (37.6%)	4133 (40.1%)	1101 (44.4%)	
West	24,226 (26.7%)	21,184 (27.2%)	2537 (24.6%)	505 (20.4%)	
Insurance status					
Private	53,440 (59.0%)	46,125 (59.3%)	6342 (61.6%)	973 (39.2%)	< 0.001
Public	19,603 (21.6%)	15,469 (19.9%)	2815 (27.3%)	1319 (53.2%)	
None	17,579 (19.4%)	16,248 (20.9%)	1143 (11.1%)	188 (7.6%)	
12-Item Short Form Health Survey component, mean (SD)					
PCS	49.0 (10.8)	50.2 (9.8)	44.4 (12.3)	30.1 (11.1)	< 0.001
MCS	50.6 (10.2)	51.1 (9.8)	48.6 (11.2)	42.0 (12.7)	< 0.001
Self-rated health					
Excellent	20,565 (22.7%)	19,055 (24.5%)	1449 (14.1%)	61 (2.5%)	< 0.001
Very good	28,889 (31.9%)	25,812 (33.2%)	2818 (27.4%)	259 (10.4%)	
Good	26,718 (29.5%)	22,683 (29.1%)	3441 (33.4%)	594 (24.0%)	
Fair	11,129 (12.3%)	8387 (10.8%)	1888 (18.3%)	854 (34.4%)	
Poor	3321 (3.7%)	1905 (2.4%)	704 (6.8%)	712 (28.7%)	
Current smoker	16,620 (18.3%)	13,251 (17.0%)	2432 (23.6%)	937 (37.8%)	< 0.001
Count of chronic diseases, median (IQR)	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	1.00 (0.00, 2.00)	2.00 (1.00, 3.00)	< 0.001
Count of chronic diseases, mean (SD)	0.89 (1.21)	0.80 (1.14)	1.24 (1.36)	2.36 (1.53)	< 0.001
Any cancer diagnosis	3164 (3.5%)	2258 (2.9%)	645 (6.3%)	261 (10.5%)	< 0.001
Year 1 total healthcare expenditures, median (IQR)	983.0 (136.0, 3853.0)	703.0 (79.0, 2779.0)	4566.0 (1564.5, 11,379.0)	9473.0 (4255.5, 20,688.0)	< 0.001
Office visits, median (IQR)	1.0 (0.0, 4.0)	1.0 (0.0, 3.0)	4.0 (1.0, 8.5)	8.0 (4.0, 15.0)	< 0.001
Opioid prescriptions, year 1					
None	77,842 (85.9%)	77,842 (100.0%)	–	–	< 0.001
1–5	10,300 (11.4%)	–	10,300 (100.0%)	–	
≥ 6	2480 (2.7%)	–	–	2480 (100.0%)	
Died during survey period	774 (0.9%)	551 (0.7%)	127 (1.2%)	96 (3.9%)	< 0.001

Table 1 data are sample-based and have not been adjusted for survey characteristics. *p* values are based on the sample and are not survey-adjusted. SD = standard deviation, IQR = interquartile range, PCS = Physical Component Summary of Short-Form Health Survey, MCS = Mental Component Summary of Short-Form Health Survey

of the total sample) reported 6 or more opioid prescriptions. Patients receiving opioids were more likely to be older, female, White, and of lower income; to live in the Midwest or South census regions; and to be publicly insured. They were also more likely to have poor health status, with lower average PCS and MCS scores, lower self-rated health, and higher rates of smoking and cancer diagnoses. Persons reporting more opioid prescriptions were also more likely to die during their 2-year MEPS participation period (Table 1): Among individuals reporting 6 or more opioid prescriptions, 3.9% died during the survey period, compared to 1.2% of the category reporting 1–5 opioid prescriptions and 0.9% of those reporting no opioids.

In Table 2, the results of sequential regression models are shown that examined how the unadjusted association between prescription opioids and short-term mortality was affected by adjusting for different categories of covariates. Model 1, the unadjusted model, yielded an odds ratio of mortality of 1.53 (95% CI = 1.20–1.94, *p* < 0.01) for the 1–5 opioid prescription category and an odds ratio of 5.48 (95% CI = 4.23–7.11, *p* < 0.01) for the category of 6 or more opioid prescriptions, both as compared to the statistical reference of no opioids. In model 2, which included adjustment for key sociodemographic variables (age, sex, race, education level, household income, census region, and insurance status), the odds ratio for the 1–5 opioid prescription category remained essentially unchanged

**Table 2 Unadjusted and Adjusted Odds of Mortality by Opioid Prescription Category (with 95% Confidence Intervals)**

Logistic regression model	1–5 prescriptions	p value	≥ 6 prescriptions	p value
1. Unadjusted	1.53 (1.20, 1.94)	0.001	5.48 (4.23, 7.11)	<0.001
2. Sociodemographics	1.51 (1.18, 1.92)	0.001	3.20 (2.39, 4.29)	<0.001
3. Sociodemographics + Health status related	0.99 (0.77, 1.29)	0.965	1.14 (0.85, 1.53)	0.395
4. Sociodemographics, health status related + utilization	0.86 (0.66, 1.12)	0.269	0.99 (0.74, 1.34)	0.963

Reference group for all odds ratios: no opioid prescriptions. Model 1 is unadjusted. Model 2 adjusted for sociodemographic variables: age, sex, race, education level, household income, census region, and insurance status. Model 3 included all covariates in model 2 plus additional markers of health status: SF-12 Physical and Mental components (PCS, MCS), self-rated health, count of eight key comorbidities, cancer diagnosis, and smoking status. Model 4 included all covariates in model 3 plus additional markers of healthcare utilization: total year 1 healthcare expenditures (log[expenditures + 1]) and number of doctor's office visits

(adjusted odds ratio (aOR) = 1.51, 95% CI = 1.18–1.92,  $p < 0.01$ ). The aOR for 6 or more opioid prescriptions decreased to 3.20 (95% CI = 2.39–4.92,  $p < 0.01$ ). In model 3, which added additional adjustment for health status, the odds ratios were no longer significant: for 1–5 opioid prescriptions, mortality aOR = 0.99 (95% CI = 0.77–1.29,  $p = 0.96$ ), and for 6 or more

opioids, aOR = 1.14 (95% CI = 0.85–1.53,  $p = 0.40$ ). The final model (model 4) added adjustment for healthcare utilization (total healthcare expenditures and doctor's office visits) and also demonstrated no statistical difference in mortality risk between the categories of opioid prescriptions and those prescribed no opioids.

The analysis including an interaction term between opioid prescription category and time period did not demonstrate a significant interaction ( $F(10, 436) = 0.78, p = 0.65$ ).

Table 3 shows the results of the final regression analysis assessing this relationship between opioid category and short-term mortality after adjustment for all key covariates. In the final model, as compared to the reference category of no opioids, the aOR for death in the 1–5 opioid prescription category was 0.86 (95% CI = 0.66–1.12,  $p = 0.27$ ), and the aOR in the 6 or more category was 0.99 (95% CI = 0.74–1.34,  $p = 0.96$ ). The most significant predictors of short-term mortality in the fully adjusted model included higher age, male sex, Black race, no insurance, smoking, cancer, and higher total health expenditures.

**Table 3 Adjusted Odds of Short-Term Mortality by Patient Characteristics**

Factor	Adjusted odds of death	p value
Opioid category (ref = none)		
1–5 opioid prescriptions	0.86 (0.66, 1.12)	0.269
≥ 6 opioid prescriptions	0.99 (0.74, 1.34)	0.963
Age	1.07 (1.06, 1.08)	0.000
Sex, female	0.57 (0.48, 0.67)	0.000
Race (ref = White)		
Hispanic	0.67 (0.50, 0.90)	0.009
Black	1.35 (1.09, 1.67)	0.006
Other	0.96 (0.67, 1.38)	0.843
Education (ref = less than high school)		
Some high school	1.35 (0.99, 1.84)	0.058
High school graduate	1.15 (0.88, 1.49)	0.301
Some college	0.93 (0.68, 1.28)	0.674
College graduate	0.81 (0.57, 1.16)	0.248
Household income (ref = < 100% FPL)		
100–124% FPL	1.14 (0.82, 1.57)	0.444
125–199% FPL	0.97 (0.74, 1.26)	0.805
200–399% FPL	1.05 (0.80, 1.39)	0.710
400% + FPL	0.75 (0.53, 1.08)	0.118
Census region (ref = Northeast)		
Midwest	1.07 (0.80, 1.42)	0.645
South	0.96 (0.75, 1.24)	0.762
West	0.95 (0.71, 1.28)	0.745
Insurance status (ref = private)		
Public	1.20 (0.98, 1.48)	0.075
None	1.55 (1.10, 2.17)	0.012
Panel	1.02 (0.99, 1.04)	0.236
12-Item Short Form Health Survey component		
Physical component score	0.96 (0.95, 0.97)	0.000
Mental component score	0.98 (0.97, 0.99)	0.000
Self-rated health (ref = excellent)		
Very good	1.27 (0.84, 1.93)	0.259
Good	1.00 (0.65, 1.53)	0.982
Fair	1.48 (0.93, 2.35)	0.095
Poor	3.47 (2.07, 5.80)	0.000
Current smoker	1.51 (1.18, 1.94)	0.001
Count of chronic diseases	0.96 (0.89, 1.03)	0.208
Any cancer diagnosis	2.70 (2.20, 3.31)	0.000
Year 1 total healthcare expenditures	1.13 (1.03, 1.24)	0.007
Office visits	0.99 (0.98, 1.01)	0.435

Table 3 data have also been adjusted for survey characteristics and panel year

Ref = reference category, FPL = federal poverty level, PCS = Physical Component Summary of Short-Form Health Survey, MCS = Mental Component Summary of Short-Form Health Survey, Year 1 total healthcare expenditures = log[expenditures + 1]

**DISCUSSION**

In a nationally representative U.S. sample of individuals enrolled in the MEPS for two consecutive years, we found that receipt of opioid prescriptions in participation year 1 was not associated with increased risk of death during the 2-year survey period, after adjusting for sociodemographic factors, health status, and healthcare utilization. This was true both for participants receiving incident and/or short-term prescriptions as well as those receiving longer-term prescriptions. Unadjusted analysis, as well as the sociodemographically adjusted analysis, revealed an increased mortality risk associated with both categories of opioid prescriptions. That increased risk was eliminated with further adjustment for health status. Finally, additional adjustment for healthcare utilization produced no further significant change in the opioid mortality association.

Though opioid overdose mortality in the U.S. has increased notably over the past 15 years, likely due to misuse of opioids and transition to heroin (and, more recently, fentanyl and other synthetic analogs), the impact of prescribed opioids on all-cause mortality has received less attention.<sup>18</sup> Our findings

indicated no increase in short-term mortality associated with receiving prescription opioids after adjustment for health status, even among the patients who likely received them for longer-term therapy.

Our study found there were substantial sociodemographic and health differences between individuals reporting and those not reporting prescribed opioids. Those prescribed opioids were, on average, older, more likely women, poorer, and less healthy than others. These findings are consistent with previous surveillance studies.<sup>19,20</sup> The combination of sociodemographic and health status differences likely explains the opioid prescription–mortality association we observed in the unadjusted analysis.

The attenuation of the unadjusted mortality association with opioid prescribing occurred primarily after adjusting for health status. There are at least two potential explanations for this observation. It may be that receiving opioids *leads one* to be in poorer health (as measured, for example, by lower self-rated health). If this were so, then there may be an increased mortality risk among patients receiving opioid prescriptions that is effectively “masked” in our adjusted model; in other words, the model is overadjusted. Alternatively, receipt of prescription opioids may be a consequence of patient factors (especially poorer health status) that confer increased mortality risk. While the observational nature of our analyses precludes drawing causal inferences, future appropriately designed studies to examine these hypotheses would be useful.

One potential conclusion to draw from these results is that most patients who are prescribed opioids use them as prescribed and do not experience the risks known to be associated with opioid misuse or use of illicit opioids. This is an important distinction considering the sweeping policies and practice changes aimed at restricting opioid prescribing; however, evidence suggests the current opioid epidemic is driven by illicit and synthetically derived opioids.<sup>2</sup> Our findings suggest a need for greater attention to individual risks for opioid-related adversity, balanced against the necessary objectives of safely and effectively managing pain.

The strengths of our study included the use of a nationally representative sample and the examination of the associations with different categories of prescription use. The existing literature has often conflated opioid abuse and misuse with all use of opioids. Additionally, examining short-term mortality is important. Though we are unable to assess any longer-term association between opioid prescriptions and mortality, the short-term outcome allowed us to assess a more direct link between the exposure and the outcome with less opportunity for exogenous events to confound the relationship during follow-up.

Our study also has certain limitations. Though prior work has shown associations between prescription opioids and other outcomes including nonfatal overdose and dependence, we were unable to examine these potential harms in our analysis.<sup>21–23</sup> Secondly, nonresponse to the MEPS may also have introduced bias, as it is unknown whether opioid-related risk

behaviors differ among responders and nonresponders. We also acknowledge that, though designed to be nationally representative of the general household U.S. population, MEPS excludes certain populations that may be at higher risk for opioid misuse and related mortality, such as hospitalized and institutionalized persons. Our study also lacked information regarding the doses (e.g., morphine-equivalent units) of prescribed opioids. Many prior studies have demonstrated greater risks associated with higher prescription opioid doses. Nonetheless, examining the risk associated with duration of receipt of prescription opioids, independent of dosage, is still worthwhile given studies suggesting greater harms resulting from greater duration of use.<sup>24</sup> Finally, it is possible that continuous opioid exposure is associated with greater risk of harm, but there were relatively few respondents with higher quantities (e.g., 12 or more) of opioid prescriptions reported in year 1 of their MEPS participation to be able to meaningfully subanalyze this group.

In conclusion, this analysis found that individuals reporting opioid prescriptions had no greater short-term mortality than those reporting no exposure to opioids after sociodemographic and health status adjustment. These findings highlight the need for further work to understand the risk of opioid analgesic prescriptions in the general population. As these risks are likely highly variable, future efforts should attempt to better clarify individual risk predictors of morbidity and mortality among patients prescribed opioids for pain.

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#### Compliance with Ethical Standards:

**Conflict of Interest:** The authors declare that they do not have a conflict of interest.

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