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ORIGINAL RESEARCH

National Cohort Study of Opioid Analgesic Dose and Risk of Future Hospitalization

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BACKGROUND: High daily and total doses of opioid analgesics (OAs) increase the risk for drug overdose and may be risks for all-cause hospitalization.

OBJECTIVE: To examine the association of OA dose measures with future all-cause hospitalization.

DESIGN/PATIENTS: Cohort study of 87,688 national health maintenance organization enrollees aged 45 to 64 years with noncancer pain who filled ≥2 OA prescriptions from January 2009 to July 2012.

METHODS: Outcomes were all-cause hospitalization and hospital days in 6-month intervals after the first OA was filled. In generalized linear mixed models, we examined interactions of 5 daily OA dose categories and 5 total dose categories in each 6-month interval adjusted for demographics, clinical conditions, psychotropic drugs, and current hospitalization. For high total OA doses, percentage of days covered by OA prescriptions in 6 months was examined.

RESULTS: Over 3 years, an average of 12% of subjects were hospitalized yearly for a mean 6.5 (standard deviation = 8.5) days. Compared with no OAs, adjusted odds of future hospitalization for high total opioid dose (>1830 mg) were 35% to 44% greater depending on daily dose category (all $P < 0.05$), but total OA dose ≤1830 mg had weak or no association with future hospitalization regardless of daily OA dose. For high total OA doses, odds of hospitalization were 41% to 51% greater for categories of percentage of time on OAs above >50% (>3 months) versus no OAs (all $P < 0.05$). Similar effects were observed for hospital days.

CONCLUSIONS: Higher total OA doses for >3 months within a 6-month period significantly increased the risk for all-cause hospitalization and longer inpatient stays in the next 6 months. *Journal of Hospital Medicine* 2015;10:425–431. © 2015 Society of Hospital Medicine

Longer term and higher doses of opioid analgesics (OAs) have been associated with multiple adverse outcomes such as loss of work, cognitive decline, and poor function.[1–4] One of the most widely reported complications of opioid therapy is drug overdose.[5–9] In population-based studies, daily morphine equivalent doses >100 mg have been associated with significantly increased risk of drug overdose.[5–10] Among health maintenance organization (HMO) enrollees filling at least 2 prescriptions for opioids, our group reported that daily opioid doses ≥100 mg were associated with approximately threefold greater adjusted odds of drug overdose.[10] We also observed over a twofold increase in odds of drug overdose for lower daily doses of 50 to 99 mg if the patient also received a high total opioid dose (>1830 mg) over a 6-month period. This analysis suggests that clinicians may need to monitor not only daily dose but also total dose of opioids to reduce the risk of drug overdose.

Yet drug overdose represents only a small subset of all hospitalizations for persons receiving long-term or higher doses of opioids for noncancer pain. These patients have significant demand for urgent care services, including hospitalization, for diverse reasons such as adverse effects of opioids, underlying cause of chronic pain, and comorbidities such as mental health disorders.[11] In a cohort of elderly primary care patients who were high hospital utilizers, Freund and colleagues reported that chronic pain and depression were the most common conditions co-occurring with their other comorbidities.[12] However, little is known about the association of opioid dose with the risk of all-cause hospitalization for patients with noncancer pain.

In this article we examined hospitalizations for a national cohort of HMO enrollees with noncancer pain who filled at least 2 prescriptions for schedule II or III opioids over a 3.5-year timeframe. This retrospective cohort analysis aims to identify clinically useful opioid dose measures for clinicians, administrators, and policymakers to use in identifying patients at increased risk of future hospitalization who may warrant interventions to reduce this risk.

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METHODS

Study Sample

From Aetna administrative databases including enrollment files and paid claims for services, we identified 261,528 subjects aged 18 to 64 years who had at least 2 paid claims for schedule II or III noninjectable OA prescriptions from January 2009 through July 2012.[10] For individuals meeting these criteria, study cohort eligibility required at least 12 months of enrollment and complete data on demographics and OA prescriptions as well as clinical conditions from at least 1 encounter (see Supporting Information, Appendix 1, in the online version of this article).[10] We excluded subjects with a cancer diagnosis who have high hospital utilization and those younger than 45 years because of a higher likelihood of pregnancy-related hospitalization. To afford sufficient observation time for outcomes, subjects with <12 months follow-up after the first opioid prescription were excluded. The resultant study cohort totaled 87,688 subjects.

To capture the changing nature of medication utilization and clinical conditions in this longitudinal study, we divided the study timeframe into 6-month intervals starting with the first opioid prescription and ending with the subject's last enrollment or end of the study (see Supporting Information, Appendix 2, in the online version of this article). Six-month intervals were studied because this is the maximum duration of benefit from randomized trials of opioid therapy for noncancer pain.[13] This study was approved by the University of Texas Health Science Center at San Antonio's institutional review board.

Outcome Variables

Study outcomes were all-cause hospitalization (binary) and hospital days (discrete) per 6-month interval and were measured repeatedly for up to 6, 6-month intervals.

Primary Independent Variables

We examined 2 opioid dose measures within a 6-month interval and hospitalization outcomes in the next 6 months (see Supporting Information, Appendix 2, in the online version of this article). We did not examine OA use in the last 6 months of the study timeframe because subsequent hospitalization outcomes were not available. We defined the total morphine equivalent dose of OA prescriptions filled within a 6-month interval based on the method used by Edlund et al.[14] and adapted by our group.[10] We also defined the daily dose of OAs that is a widely used metric used in chronic pain management guidelines.[10,15]

To calculate the total opioid dose, all filled schedule II or III OA prescriptions (noninjectable formulations) were identified from claims for filled prescriptions for each 6-month interval. The morphine equivalent dose for each opioid prescription was calculated from the number of pills dispensed multiplied by strength (in milligrams) and by a morphine equivalent conversion factor derived from several sources including published data,[16,17] conversion tables from Internet sources, and drug information resources.[18,19] A clinical pharmacist reviewed and finalized conversions. When an opioid prescription spanned two, 6-month intervals, the dose was divided proportionate to time in each interval. The total dose for all opioid prescriptions within an interval was summed and categorized by quartile of nonzero total dose as: 1 to 190, 191 to 450, 451 to 1830, and >1830 mg.[10]

To calculate the daily opioid dose in each interval, the total dose was divided by total nonoverlapping days' supply covered by all prescriptions. The average daily dose was categorized as in other studies: 1 to 19, 20 to 49, 50 to 99, and ≥100 mg.[5,6,10] In each 6-month interval, the percentage of days covered by filled prescriptions was calculated as total days' supply/180.

Other Independent Variables

Demographic data included age as of July 2012, sex, and US region. From available diagnosis codes for encounters, pain-related conditions were identified including: back pain, other osteoarthritis, neuropathic pain, chronic pain unspecified, or chronic headache (International Classification of Diseases, Ninth Revision, Clinical Modification codes available from authors). Mental health/substance use disorders were similarly identified: anxiety or post-traumatic stress disorder (PTSD), depression, psychosis, drug abuse, and alcohol abuse. Once a psychiatric condition or substance use disorder was diagnosed, it was considered to persist because these are usually not transient. We examined filled prescriptions for psychoactive drugs in 6-month intervals including: benzodiazepines (i.e., clonazepam, alprazolam, lorazepam, diazepam, chlordiazepine, temazepam, flurazepam), antidepressants (i.e., selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, tricyclics [complete list available from authors]), and sedatives (i.e., zolpidem, eszopiclone). For these drugs, time-varying variables were created as follows: benzodiazepines (0, 1–30, 31–90, 91–180 days), sedatives (0, 1–30, 31–90, 91–180 days), and antidepressants (0, 1–60, 61–180 days). Categories for duration of antidepressants differed because a clinical response can take up to 6 to 8 weeks.

Statistical Analyses

Descriptive statistics were examined for study cohort characteristics. For the binary all-cause hospitalization outcome, repeated measures logistic regression models were estimated using generalized estimating equations (GEE) to examine associations of daily opioid dose, total opioid dose, and their interaction with all-cause hospitalization. The fully adjusted model includes

TABLE 1. Patient Characteristics at Baseline*

Characteristics	Total, N = 87,688
Demographics	
Women, n (%)	48,077 (54.8)
Age, mean (SD)	53.8 (5.5)
US region, n (%)	
Midwest	4,609 (5.3)
Northeast	27,568 (31.4)
South	40,767 (46.5)
West	14,744 (16.8)
Clinical conditions, n (%)†	
Noncancer pain conditions	
Back pain	24,767 (28.2)
Large joint arthritis, other musculoskeletal‡	33,689 (38.4)
Neuropathy	1,519 (1.7)
Chronic pain (unspecified)	3,229 (3.7)
Headache	2,837 (3.2)
Mental health and substance use disorders	
Anxiety or post-traumatic stress disorder	6,006 (6.9)
Depression	6,111 (7.0)
Psychosis	1,259 (1.4)
Alcohol abuse	877 (1.0)
Other substance abuse	615 (0.7)
Current hospitalization, n (%)	11,165 (12.7)
Opioid measures, n (%)	
Daily MED dose, mg	
0	—
1–19	9,870 (11.3)
20–49	50,050 (57.1)
50–99	21,188 (24.2)
≥100	6,580 (7.5)
Total MED dose, mg	
0	—
1–190	20,276 (23.1)
191–450	26,000 (29.7)
451–1,830	23,551 (26.9)
>1,830	17,861 (20.4)
Percent time exposed to opioid therapy, median (Q1, Q3)	
Among any total MED	6.7 (2.8, 22.2)
Among total MED >1,830 mg	70 (42.8, 93.9)

NOTE: **Abbreviations:** MED, morphine equivalent dose; SD, standard deviation.

*The first 6-month interval started with the date of the first opioid prescription.

†Clinical conditions diagnosed at the baseline 6-month interval. International Classification of Diseases, Ninth Revision, Clinical Modification codes are available from the authors.

‡Arthritis, arthralgia, fracture, sprains.

demographics, chronic pain conditions, mental health conditions, substance use disorders, other psychoactive drugs, and current hospitalization (yes/no). For the hospital days per 6-month outcome, a series of repeated measures Poisson regressions were estimated using the GEE approach.

In a post hoc sensitivity analysis, we examined the association of the percentage of days covered by prescribed opioids, categorized based on approximate quartiles and clinical judgment, with hospitalization among subjects with a high total dose (>1830 mg). For this analysis, we created a composite measure of opioid treatment for each 6-month interval that has 6 categories: (1) none, (2) low total dose 1 to 1830 mg, (3) high total dose >1830 mg with ≤50% of days on opioids, (4) total dose >1830 mg with >50% to 75% of days on opioids, (5) total dose >1830 mg with >75% to 90% of days on opioids, and (6) total dose >1830 mg and >90% of days on opioids. Adjusted regression analyses described above were repeated for both outcomes and included this composite measure. All statistical tests were performed with a 2-sided significance level of 0.05, and analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

Of 87,688 study subjects, 54.8% were women, and the mean age was 53.8 years (standard deviation [SD] = 5.5). Nearly half of the cohort resided in Southern states (Table 1). In the baseline 6-month interval, the most common chronic noncancer pain conditions were musculoskeletal involving large joint arthritis/arthralgia (38.4%) and back pain (28.2%). In regard to mental health and substance use conditions, both anxiety/PTSD and depression were diagnosed in approximately 7% of the cohort, whereas psychosis, and alcohol and other substance use disorders were each diagnosed in <2%. In the baseline interval, 12.7% of subjects were hospitalized. The majority of patients received a daily opioid dose of 20 to 49 mg, and the median total dose was 450 mg. The median percent of time exposed to opioids was 6.7% among all study subjects and 70% for those with a high total dose (>1830 mg).

In the 3 study years, an average of 12% of the cohort was hospitalized yearly (Table 2), or 1120 hospitalizations per 10,000 person-years. Among those who were hospitalized, inpatient days averaged 6.5 (SD = 8.5). The highest proportion of hospitalized subjects was 6.5%, occurring in the 6-month interval immediately following the first opioid treatment interval. In subsequent 6-month intervals, hospitalization rates were relatively stable, ranging from 5.2% to 6.1% (Table 2). As shown, future hospitalization rates increased monotonically, with increasing total or daily dose within each 6-month interval.

In unadjusted analyses, a significant interaction between daily dose and total dose ($P < 0.001$) revealed that, within each daily dose category, the odds of hospitalization differed by total dose (all $P < 0.05$, Table 3). When the total dose was >1830 mg, the odds of future hospitalization rose monotonically with increasing daily dose (i.e., <20, 20–49, 50–99, ≥100 mg): 1.33, 1.84, 1.96, and 2.08 ($P < 0.05$ for all comparisons vs no opioids). On the other hand, when the total dose was 450 mg or less, all daily dose categories including a very high daily dose (≥100 mg) were not associated with future hospitalization (all $P > 0.05$ vs no opioids). When the total dose was 451 to 1830 mg, a nonlinear association with hospitalization appeared with higher odds for lower daily doses. For the outcome of hospital days per 6-month interval, increasing daily dose was also associated with more hospital days per 6-month interval when the total

TABLE 2. Opioid Dose Measures and Proportion of Hospitalized Subjects in Next Six-Month Interval

	6-Month Interval					
Subjects	1 (Baseline), N = 87,688	2, N = 65,835	3, N = 46,041	4, N = 31,550	5, N = 18,915	6, N = 3,502
Overall (%)	6.5	5.9	5.9	5.4	5.2	6.1
Opioid dose measure						
Daily dose (%)						
0 mg	—	4.8	4.4	4.0	3.6	3.2
1–19 mg	5.9	5.6	6.0	5.6	5.6	4.4
20–49 mg	6.2	6.5	7.1	6.6	6.1	6.1
50–99 mg	6.8	7.9	7.5	7.6	7.6	9.8
≥100 mg	9.0	9.3	10.3	9.2	9.5	9.5
Total dose (%) *						
0 mg	—	4.8	4.4	4.0	3.6	3.2
1–190 mg	5.5	4.7	5.0	4.1	4.0	2.7
191–450 mg	5.1	5.1	6.3	6.7	5.0	3.2
451–1,830 mg	6.5	7.4	7.9	7.2	7.1	7.0
>1,830 mg	9.8	9.6	9.6	8.9	8.8	9.0

NOTE: Entries are percent of future hospitalizations. For example, 6.5% (= 5,704/87,688) of patients at baseline were hospitalized in the subsequent 6-month interval.

*Quartiles for total dose among opioid users.

dose was high (>1830 mg), whereas for lower total doses, daily dose was weakly positive or even protective versus no opioids.

In the model adjusting for all covariates (Table 4), the interaction between total dose and daily dose was also significant ($P = 0.002$). When the total dose was high (>1830 mg), the adjusted odds of future hospitalization were significantly increased by 35% to 44% for daily doses of 20 to 49 mg or greater versus no opioids ($P < 0.05$ for all comparisons). When the total dose was <1830 mg, the majority of daily dose categories were not significantly associated with hospitalization. Similarly, in the fully adjusted analysis of hospital days, the number of inpatient days were increased by 28% to 48% when the total dose was >1830 mg and daily dose was >20 mg, but these associations were nonsignificant or protective when the total dose was lower.

In a sensitivity analysis, we examined the percentage of days covered by filled opioid prescriptions within a 6-month interval for subjects receiving high-dose therapy (Table 5). Compared with no opioid

TABLE 3. Unadjusted Associations of the Interaction of Total Opioid Dose and Daily Dose With Hospitalization Outcomes

	All-Cause Hospitalization (Yes/No), Odds Ratio (95% CI)				
	Daily Morphine Equivalent Dose, mg				
Total Morphine Equivalent Dose, mg	0	1–9	20–49	50–99	≥100
0	1	—	—	—	—
1–190	—	1.06 (0.95-1.19)	1.01 (0.95-1.08)	1.07 (0.95-1.19)	0.73 (0.44-1.21)
191–450	—	1.08 (0.96-1.22)	1.03 (0.96-1.10)	0.99 (0.9-1.10)	0.88 (0.67-1.15)
451–1,830	—	1.34 (1.21-1.48)*	1.37 (1.28-1.46)*	1.16 (1.05-1.27)*	1.25 (0.98-1.59)
>1,830	—	1.33 (1.09-1.62)*	1.84 (1.73-1.97)*	1.96 (1.82-2.11)*	2.08 (1.93-2.24)*
	Hospital Days per 6-Month, Incident Rate Ratio (95% CI)				
	Daily Morphine Equivalent Dose, mg				
Total Morphine Equivalent Dose, mg	0	1–19	20–49	50–99	≥100
0	1	—	—	—	—
1–190	—	0.95 (0.79-1.14)	0.90 (0.82-0.99)*	1.03 (0.87-1.23)	0.63 (0.36-1.12)
191–450	—	0.92 (0.77-1.10)	0.93 (0.84-1.02)	0.79 (0.69-0.91)*	0.69 (0.49-0.98)*
451–1,830	—	1.31 (1.10-1.57)*	1.26 (1.13-1.40)*	1.01 (0.86-1.19)	0.99 (0.71-1.37)
>1,830	—	1.32 (0.93-1.89)	1.79 (1.60-2.01)*	1.76 (1.54-2.01)*	2.09 (1.85-2.36)*

NOTE: Logistic regression was used for all-cause hospitalization, and odds ratios (95% CI) were reported with no opioid therapy as the reference group. Poisson regression was used for hospital days per 6-month, and incident rate ratio (95% CI) was reported with the no opioid therapy as the reference. **Abbreviations:** CI, confidence interval.

*$P < 0.05$ compared with no opioid therapy.

TABLE 4. Adjusted Association for the Interaction of Total Opioid Dose and Daily Dose With Hospitalization Outcomes*

	All-Cause Hospitalization (Yes/No), Odds Ratio (95% CI)				
	Daily Morphine Equivalent Dose, mg				
Total Morphine Equivalent Dose, mg	0	1–19	20–49	50–99	≥100
0	1	—	—	—	—
1–190	—	1.09 (0.97-1.23)	1.07 (1.00–1.14)	1.12 (1.00–1.26)†	0.75 (0.45-1.23)
191–450	—	1.00 (0.88-1.13)	0.99 (0.92-1.06)	0.97 (0.88-1.08)	0.87 (0.68-1.12)
451–1,830	—	1.16 (1.04-1.29)†	1.14 (1.07-1.22)†	0.94 (0.85-1.03)	1.08 (0.85-1.35)
>1,830	—	1.10 (0.90-1.34)	1.41 (1.32-1.51)†	1.35 (1.25-1.46)†	1.44 (1.34-1.55)†
	Hospital Days per 6-Month, Incident Rate Ratio (95% CI)				
	Daily Morphine Equivalent Dose, mg				
Total Morphine Equivalent Dose, mg	0	1–19	20–49	50–99	≥100
0	1	—	—	—	—
1–190	—	0.97 (0.8-1.18)	0.94 (0.85-1.04)	1.06 (0.88-1.27)	0.60 (0.33-1.1)
191–450	—	0.85 (0.71-1.02)	0.88 (0.79-0.98)†	0.75 (0.65-0.86)†	0.65 (0.46-0.92)†
451–1,830	—	1.16 (0.97-1.4)	1.09 (0.97-1.22)	0.83 (0.71-0.98)†	0.81 (0.59-1.13)
>1,830	—	1.12 (0.77-1.63)	1.41 (1.25-1.58)†	1.28 (1.12-1.46)†	1.48 (1.29-1.69)†

NOTE: **Abbreviations:** CI, confidence interval.

*Adjusted for time interval, age, gender, region, 5 noncancer pain condition indicators, anxiety, depression, psychotic disorder, alcohol abuse, substance abuse, duration of antidepressants per 6-month interval (3 levels: none, 1–60 days, 61–180 days), duration of benzodiazepines per 6-month interval (4 levels: none, 1–30 days, 31–90 days, 91–180 days), duration of sedatives per 6-month interval (4 levels: none, 1–30 days, 31–90 days, 91–180 days), and current hospitalization.

†$P < 0.05$ compared with no opioid therapy.

therapy, the adjusted odds of future hospitalization were 5% greater for low total opioid dose (1–1830 mg) and 21% greater for high total dose (>1830 mg) when the duration of treatment was shorter (≤50% of the 6-month interval). However, the odds were increased by 41% to 51% for a high total dose (>1830 mg), with longer periods of treatment (>50% of the interval). For hospital days as the outcome, subjects with high total doses (>1830 mg) and longer periods of treatment (>50% of the interval) had 41% to 71% more hospital days per 6-month interval than those with no opioid therapy.

TABLE 5. Adjusted Associations of Opioid Analgesic Dose and Duration With Hospitalization Outcomes*

	All-Cause Hospitalization	Hospital Days per 6 Months
Opioid Analgesic Category	Odds Ratio (95% CI)	Incident Rate Ratio (95% CI)
0 mg	1	1
1–1,830 mg	1.05 (1.00–1.10)†	0.94 (0.87-1.01)
>1,830 mg and ≤50% days on opioids	1.21 (1.11-1.31)†	1.10 (0.96-1.26)
>1,830 mg and >50 to ≤75% days on opioids	1.51 (1.40-1.64)†	1.45 (1.26-1.67)†
>1,830 mg and >75 to ≤90% days on opioids	1.50 (1.38-1.64)†	1.71 (1.46-1.99)†
>1,830 mg and >90% days on opioids	1.41 (1.31-1.52)†	1.41 (1.26-1.58)†

NOTE: **Abbreviations:** CI, confidence interval.

*Adjusted for time interval, age, gender, region, 5 noncancer pain condition indicators, anxiety, depression, psychotic disorder, alcohol abuse, substance abuse, duration of antidepressants per 6-month interval (3 levels: none, 1–60 days, 61–180 days), duration of benzodiazepines per 6-month interval (4 levels: none, 1–30 days, 31–90 days, 91–180 days), duration of sedatives per 6-month interval (4 levels: none, 1–30 days, 31–90 days, 91–180 days), and current hospitalization.

†$P < 0.05$ compared with no opioid therapy.

DISCUSSION

In a national cohort of HMO enrollees who filled at least 2 prescriptions for OAs, 12% were hospitalized annually. Other studies of opioid users have focused on only a fraction of these hospitalizations. For example, a recent Agency for Healthcare Research and Quality study reported that the rate of hospitalization for complications from accidental or deliberate overuse of opioids more than doubled from 11.7/10,000 in 1993 to 29.5/10,000 in 2010.[20] However, in our cohort, the all-cause hospitalization rate was 1120 per 10,000 person-years, or over 40 times greater than the rate for complications from overuse of opioids. By comparison, hospitalization for heart failure was only 32.8/10,000 nationally in 2010.[21] Thus, our study confirms the significant demand for hospital care by patients treated with opioids. A novel finding of our study is that the total dose of prescriptions filled over 6 months is significantly associated with an increased risk of future hospitalization. When the total dose within 6 months was in the top quartile (>1830 mg in our cohort), the adjusted odds of future hospitalization ranged from 35% to 44% greater than no opioids for daily opioid doses above 20 mg/day. On the other hand, when the total dose was ≤1830 mg, the daily opioid dose was only weakly associated with future hospitalization. These associations were

similar for hospital days per 6-month interval as the outcome.

Edlund and colleagues examined the total dose of opioids in a national cohort of veterans with chronic noncancer pain who filled at least 1 opioid prescription.[22] In 2011, the 60th percentile for the total opioid dose for these veterans was 3610 mg within a year, which is roughly equivalent to our top quartile (1830 mg) over a 6-month interval. These data support replicating our study in veterans to evaluate whether a similarly increased risk of hospitalization appears for those with high total opioid doses. In support of a concern among veterans, a population-based, cross-sectional study of hospitalized veterans reported a high rate of chronic opioid therapy (≥90 days) in the 6 months prior to hospitalization.[23]

Other studies have reported increased risk of hospitalization with chronic opioid therapy. Among 1045 patients followed up to 1-year post-transplantation, long-term opioids were associated with up to a sixfold greater risk of at least 4 admissions within that year.[24] Among 13,127 Danish adults on opioid therapy, the odds of future hospitalization from injuries were increased by 74% for long-term therapy and 46% for short-term therapy versus no opioids and by threefold and 1.6-fold, respectively, for hospitalization due to toxicity/poisoning.[9] However, none of these studies examined the dose of opioids.

In a sensitivity analysis, we found that when a subject received a high total opioid dose within 6 months, treatment for more than 50% of the interval (i.e., >3 months) was associated with a significantly increased risk of future hospitalization and significantly more hospital days. Because the strongest evidence for the benefit of opioids for chronic noncancer pain comes from trials of <3 months,[25] these data lend additional support to recommendations to minimize both dose and duration of opioid therapy.

Our study has several limitations. First, we did not assess the immediate risk of hospitalization after starting opioid therapy. Second, our outcome of hospitalization represents only 1 measure of risk. Thus, our data should not be regarded as supporting short-term use of high-dose opioids over 100 to 120 mg per day.[26] In an earlier study, we reported that either a high daily dose (≥100 mg) or a moderately high daily dose (50–99 mg) plus a high total dose (>1830 mg) increased the risk of drug overdose.[10] Third, we could not examine the reason for hospitalizations in this analysis. Therefore, we cannot presume that opioid therapy caused these hospitalizations, but it likely serves as a proxy for other factors such as disability and mental health disorders that increase risk of hospitalization. However, we did adjust for pain conditions as well as mental health and substance abuse disorders that are known to increase the risk of hospitalization in other cohorts.[27–30] In a national veterans study, the most common clinical conditions associated with long-term opioid therapy were major depression and PTSD.[22] Last, we did also not consider the number of prescribers of opioids. In a Medicare study, 1 versus 4 prescribers of OAs increased patients' annual hospitalization rate from 1.6% to 4.8%, respectively.[31]

Although the total opioid dose categories observed for our study population may differ from those in other cohorts, these data offer additional evidence for clinicians to consider this measure when assessing risk for hospitalization, and among subjects on high total doses, the percentage of time on opioids offers an additional measure of risk. Because opioid users with noncancer pain are heavy consumers of healthcare services,[32,33] public health benefits and reductions in costs of care may be substantial if opportunities can be identified to reduce hospital utilization by persons treated with higher doses of OAs.

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