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Long-acting Opioid Use and the Risk of Serious Infections: A Retrospective Cohort Study

Andrew D. Wiese,[1] Marie R. Griffin,[1,2,3] William Schaffner,[1,2] C. Michael Stein,[2] Robert A. Greevy,[3,4] Edward F. Mitchel Jr,[1] and Carlos G. Grijalva[1,3]

[1]Department of Health Policy and [2]Department of Medicine, Vanderbilt University Medical Center, [3]Mid-South Geriatric Research Education and Clinical Center, VA Tennessee Valley Health Care System, and [4]Department of Biostatistics, Vanderbilt University Medical Center, Nashville, Tennessee

Background. Although evidence from animal and human studies indicates opioid analgesics increase susceptibility to infections, it is unclear whether the risk varies by specific opioid. We compared the risk of serious infection among patients initiating long-acting opioid analgesics with and without previously reported immunosuppressive properties.

Methods. We conducted a retrospective cohort study of Tennessee Medicaid enrollees age ≥18 years initiating long-acting opioids (1995–2015). Hospitalizations for serious infection were identified using validated coding algorithms. We used multivariable Poisson regression models to calculate adjusted incidence rate ratios (aIRR) and 95% confidence intervals (CI) to compare the infection risk among patients using long-acting opioids with known immunosuppressive properties (morphine, fentanyl, methadone) to the infection risk among patients using long-acting opioids without known immunosuppressive properties (oxycodone, oxymorphone, tramadol) accounting for demographics, opioid dose, comorbidities and pain conditions, medication use, frailty indicators, and healthcare encounter history using exposure propensity scores. We further compared users of individual long-acting opioids to long-acting morphine users (considered the prototypical immunosuppressive opioid).

Results. Among the 61 240 patients initiating opioids with immunosuppressive properties and 22 811 patients initiating opioids without immunosuppressive properties, we identified 1906 serious infections. Nonimmunosuppressive opioid users had a lower rate of infections than immunosuppressive opioid users (aIRR:0.78 [CI: 0.66–0.91]). Among individual opioids, oxycodone users had a lower rate of infection than morphine users (aIRR:0.73 [CI: 0.60–0.89]). There were no significant differences in the infection risk between other opioids and morphine.

Conclusion. The risk of serious infections among long-acting opioid users varies by opioid type. Providers should carefully consider the risk of serious infections when making pain management decisions.

Keywords. opioid analgesics; serious infections.

The opioid epidemic in the United States was recently declared a public health emergency [1, 2]. Opioid use is associated with increased morbidity and mortality due to overdose, adverse respiratory outcomes, cardiovascular events, as well as serious infections [3–10].

Evidence from animal and in vitro experimental studies indicates that certain opioids (ie, morphine, methadone, and fentanyl) can disrupt immune responses and increase susceptibility to infections [11–14]. However, similar effects have not been documented with other opioids, including oxycodone, oxymorphone, and tramadol [11, 12, 15]. Existing evidence from randomized controlled trials is insufficient to elucidate the relevance of this opioid-induced immunosuppression on clinical outcomes due to limited sample sizes and incomplete reporting of infections [11, 14, 16]. Thus, whether the risk of serious infection varies by specific opioid formulation remains unclear.

The risk of opioid-related adverse outcomes is particularly worrisome among users of long-acting opioid formulations, typically prescribed for chronic pain, due to their potency and increased toxicity [5, 17, 18]. As multiple formulations of long-acting opioids are available, determining if the risk of serious infections varies by specific formulation could inform pain pharmacotherapy. Therefore, we conducted a retrospective cohort study to compare the risk of serious infection among patients initiating the use of different long-acting opioid analgesics, specifically those with and without previously reported immunosuppressive properties.

METHODS

Study Population

We conducted a retrospective cohort study among Tennessee Medicaid (TennCare) enrollees initiating the use of long-acting opioids from 1 January 1995 through 30 September 2015 (Supplement Section 1). The study was approved by the institutional review boards of Vanderbilt University and the Tennessee Department of Health, and by the Division of TennCare.

The cohort included adults aged ≥18 years initiating use of long-acting opioids, defined as filling a prescription for a long-acting opioid after 180 days with no long-acting opioid use. We required continuous enrollment in TennCare during the 366-day baseline period before the qualifying prescription fill and ≥ 1 clinical healthcare encounter during baseline. We excluded patients with conditions likely to reduce follow-up, increase the risk of infection independent of opioid use, or increase the possibility of misclassification of the opioid exposure (ie, patients with cancer, cystic fibrosis, chronic liver, lung and respiratory disease, end-stage renal disease, human immunodeficiency virus, immune disorders, organ transplantation, stroke, substance abuse, overdose and those using nonstudy opioids; Supplement Section 1; Supplementary Table S1). Patients could not enter the cohort until at least 30 days post-discharge from the most recent hospitalization. Patients who filled 2 different long-acting study opioids on the same qualifying date were excluded.

Exposure and Covariates

Study opioids consisted of oral and transdermal formulations of long-acting opioid analgesics (Supplement Section 1). For the primary analysis, opioids were classified based on experimental animal and in vitro studies as those with immunosuppressive properties (fentanyl, methadone, and morphine) and those without previously recognized immunosuppressive properties (oxycodone, oxymorphone, and tramadol) [11, 13, 15]. Secondary analyses focused on individual opioid formulations using morphine as the reference (the prototypical opioid with immunosuppressive properties) [11, 13, 15]. The daily dose of opioid use (in morphine milligram equivalents [MME]) was calculated using standard conversion factors (Supplementary Table S2).

We measured covariates in the 366-day baseline period including and before t_0 for all episodes of a filled long-acting opioid prescription. Covariates included demographics (age, sex, and race/ethnicity), pain conditions, comorbidities, and medication use (including short-acting opioid use), frailty indicators, and healthcare use history (Supplementary Table S1). Because only individuals enrolled with full benefits that demonstrated active use of healthcare services were eligible, lack of evidence for a covariate was counted as not present, rather than missing.

Follow-up

Patients entered the cohort on the earliest qualifying prescription fill date (t_0) for a long-acting study opioid that met all the above requirements. Follow-up continued from t_0 through the earliest of the end of the study (30 September 2015), identification of a serious condition or substance abuse diagnosis, loss of enrollment, a prescription fill for a non-study opioid or a different long-acting opioid, the 180th day without availability of a long-acting study opioid, date of death, or the date of hospitalization for serious infection (Supplementary Table S1). We characterized each person-day of follow-up according to the prescribed days supply of filled long-acting opioids, based on pharmacy records. We classified follow-up person-time covered by filled medication prescriptions as current use, person-time from 1 to 90 days after the most recent end of opioid supply as recent use, and all other person-time as past use. Current use in the first 30 days after t_0 was further classified as new use. Additional follow-up details are summarized in Supplement Section 1.

Outcome

Hospitalizations for serious infection were identified using an algorithm based on International Classifications of Diseases-Clinical Modification 9th-revision (ICD9-CM) diagnosis codes previously validated in the study population with a positive predictive value of 90.2% [19]. Infections identified included pneumonia, bacteremia/sepsis, pyelonephritis, meningitis/encephalitis, osteomyelitis/septic arthritis, endocarditis, and cellulitis (Supplementary Table S1) [10, 20, 21].

Statistical Analysis

Primary and Secondary Analyses

We used a multivariable Poisson regression model with robust standard errors to compare the relative incidence of hospitalizations for serious infection during periods of current use between those using opioids with and without previous evidence of immunosuppression [22, 23]. We calculated incidence rate ratios (IRR) and 95% confidence intervals (CIs) accounting for study covariates using exposure propensity scores, calendar year of the episode, and restricted cubic splines of patient age and opioid dose. Calculated propensity scores were included in the outcome regression model using restricted cubic splines to relax the assumption of the correct specification of the summary covariate's functional form [24, 25]. Secondary analyses compared the risk of serious infections between the current use of morphine and other opioids (fentanyl, oxycodone, methadone, and oxymorphone). We calculated separate propensity scores for each of these assessments.

Sensitivity and Exploratory Analyses

Details of additional sensitivity analyses are described in Supplement Section 1. In summary, we used inverse-probability of treatment weighting (IPTW) based on the propensity score as a different covariate balancing strategy, compared the risk of infections during periods of current use to past use by immunosuppressive properties of the opioid using the Centers for Disease Control and Prevention (CDC)-defined opioid dose categories (<50 MME/day, 50–90 MME/day, and ≥90 MME/day) [4], assessed the possibility of protopathic bias, and repeated the primary analysis excluding tramadol users. We conducted post-hoc sensitivity analyses accounting for cumulative dose of past glucocorticoid use, characteristics of the patient's geographical setting, and the potential interaction between treatment groups and opioid dose (Supplement Section 1). Statistical analyses and

manuscript preparation were performed using SAS version 9.4 (SAS Institute), Stata Version 15.1 (StataCorp LP), and StatTag (Northwestern University) [26].

RESULTS

Study Population and Episodes of Long-acting Opioid Use

After selection criteria were applied, we identified 69 128 unique patients who contributed 84 051 new episodes of long-acting study opioid use (Figure 1). Major reasons for exclusion among eligible long-acting opioid users (n = 164 876) were the presence of serious/life-threatening conditions and substance abuse, prevalent opioid use and nonstudy opioid use (Figure 1).

The majority of patients initiated the use of long-acting morphine (45.2%), followed by fentanyl (20.9%), oxycodone (19.7%), methadone (6.7%), oxymorphone (4.6%), and tramadol (2.9%) (Supplementary Table S3a). The most common conditions associated with pain were trauma, back, and musculoskeletal pain. The most common comorbidities were hypertension, chronic obstructive pulmonary disease, diabetes, prior infections, lipid disorders, and peripheral artery disease. The most common medications used during baseline were short-acting opioids, antibiotics, antidepressants, anticonvulsants, benzodiazepines, bronchodilators, glucocorticoids, proton-pump inhibitors and nonsteroidal anti-inflammatory drugs (Table 1 and Supplementary Table S4). The full list of conditions and medication use is reported in Supplementary Table S4.

A total of 1906 hospitalizations for serious infections were identified during 55 663 person-years of follow-up (3.42 hospitalizations for serious infections per 100 person-years). The most common infections were pneumonia (56.1%), cellulitis (17.9%), bacteremia without pneumonia (15.3%), pyelonephritis (6.1%), and septic arthritis/osteomyelitis (3.8%).

Comparison of Opioids With and Without Previously Reported Immunosuppressive Properties

Patients initiating immunosuppressive opioids were slightly older and more likely to be female compared to those initiating opioids without known immunosuppressive properties (Table 1). The mean starting dose of the opioids was similar among those initiating with immunosuppressive versus non-immunosuppressive opioids (72.6 MME/day versus 75.9 MME/day, respectively). The distribution of the propensity score had substantial overlap between the opioid groups (Supplementary Figure 1).

The crude incidence rate of infection-related hospitalizations was higher among patients using immunosuppressive opioids compared to those using opioids without known immunosuppression. In the adjusted analysis, the current use of opioids without known immunosuppressive properties was associated with a 22% lower rate of serious infections compared to the current use of immunosuppressive opioids (IRR: 0.78 [95% CI: 0.66–0.91]) (Table 2).

Infection-related hospitalization rates were higher during periods of current compared to past use (IRR:1.50 [95% CI: 1.29–1.74]) and was highest in the first 30 days after opioid initiation (new current use) (IRR:1.70 [95% CI: 1.50–1.94]) compared to prevalent current use. There were no statistically significant differences in the risk of hospitalization for infections between those initiating nonimmunosuppressive opioids
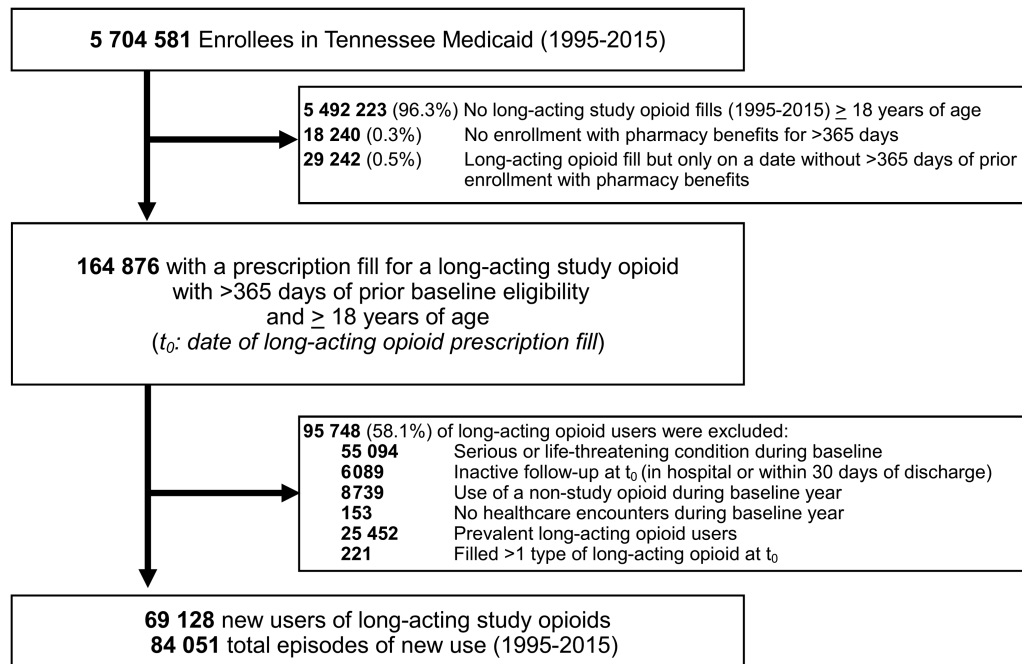

Figure 1. Identifying a retrospective cohort of patients initiating long-acting opioids, Tennessee Medicaid (1995–2015).

Table 1. Baseline Characteristics of New Long-acting Opioid Users for Selected Variables of Interest[a] by Treatment Group, Tennessee Medicaid (1995–2015)

	Nonimmunosuppressive (N = 22 811)		Immunosuppressive (N = 61 240)	
Age, y				
Mean (SD)	49.1	(15.3)	53.7	(17.3)
Median (IQR)	48.0	(21.0)	51.0	(23.0)
Characteristics	No.	(%)	No.	(%)
Sex				
Female	13 760	(60.3)	39 233	(64.1)
Race				
White	18 134	(79.5)	49 090	(80.2)
Black	2109	(9.3)	5818	(9.5)
Hispanic/Asian/Other	2568	(11.3)	6332	(10.3)
Selected comorbidities				
Cardiovascular disease[b]	2237	(9.8)	7162	(11.7)
Chronic obstructive pulmonary disease	3156	(13.8)	9835	(16.1)
Diabetes	3315	(14.5)	9857	(16.1)
Hypertension	6266	(27.5)	18 965	(31.0)
Infection history	8269	(36.3)	23 755	(38.8)
Lipid disorders	2119	(9.3)	6501	(10.6)
Peripheral artery disease	2305	(10.1)	7003	(11.4)
Tobacco use	732	(3.2)	1835	(3.0)
Selected pain or pain-inducing conditions				
Abdominal pain	1549	(6.8)	4391	(7.2)
Back pain	8356	(36.6)	25 342	(41.4)
Dental pain	259	(1.1)	519	(0.8)
External causes of injury	882	(3.9)	2253	(3.7)
Musculoskeletal pain	7402	(32.4)	21 516	(35.1)
Neuropathic pain	1805	(7.9)	5716	(9.3)
Pain not specified	1349	(5.9)	3649	(6.0)
Trauma	2857	(12.5)	6840	(11.2)
Selected medication use history				
Short-acting hydrocodone	5667	(24.8)	19 082	(31.2)
Short-acting oxycodone	3323	(14.6)	6724	(11.0)
Other short-acting opioids	5294	(23.2)	12 606	(20.6)
More than one short-acting opioid	8527	(37.4)	22 828	(37.3)
Antibiotics	16 252	(91.2)	45 231	(73.9)
Antifungals	2795	(12.3)	8266	(13.5)
Antipsychotics	2493	(10.9)	9902	(16.2)
Benzodiazepines	10 842	(47.5)	30 335	(49.5)
Bronchodilators, beta agonist	5444	(23.9)	15 682	(25.6)
Bronchodilators, other	2822	(12.4)	9297	(15.2)
Diabetes, hypoglycemic medications	3253	(14.3)	9634	(15.7)
Diabetes, insulin	1728	(7.6)	5708	(9.3)
Disease-modifying antirheumatic drugs	440	(1.9)	1214	(2.0)
Influenza vaccine	3230	(14.2)	10 041	(16.4)
Glucocorticoids	9826	(43.1)	27 859	(45.5)
Nonsteroidal anti-inflammatory drugs	13 361	(58.6)	35 402	(57.8)
Pneumococcal vaccine	534	(2.3)	1657	(2.7)
Proton pump inhibitors	6675	(29.3)	21 566	(35.2)
Sedatives	2982	(13.1)	9114	(14.9)
Selected frailty indicators				
Ambulation devices	1553	(6.8)	5080	(8.3)
Continuous/bilevel positive airway pressure	738	(3.2)	2303	(3.8)
Decubitus/pressure ulcers	719	(3.2)	2929	(4.8)
Enteral and parenteral nutrition	235	(1.0)	1234	(2.0)
Impaired mobility	321	(1.4)	895	(1.5)
Incontinence	530	(2.3)	1982	(3.2)

Table 1. Continued

	Nonimmunosuppressive (N = 22 811)		Immunosuppressive (N = 61 240)	
Oxygen supplementation	1316	(5.8)	4445	(7.3)
Rehabilitation	909	(4.0)	2177	(3.6)
Healthcare utilization				
ED visits in prior year				
0	10 172	(44.6)	27 984	(45.7)
1	5566	(24.4)	15 096	(24.7)
2	2837	(12.4)	7361	(12.0)
≥ 3	4236	(18.6)	10 799	(17.6)
Outpatient visits in past year				
0	10 270	(45.0)	26 095	(42.6)
1	4166	(18.3)	10 798	(17.6)
2	4135	(18.1)	11 812	(19.3)
≥ 3	4240	(18.6)	12 535	(20.5)
Hospitalizations in past year				
0	18 297	(80.2)	46 788	(76.4)
1	3944	(17.3)	12 364	(20.2)
≥ 2	570	(2.5)	2088	(3.4)

Abbreviations: ED, emergency department; IQR, interquartile range; PS, propensity-score; SD, standard deviation.

[a]Full list of covariates is included in Supplementary Table S4.

[b]Cardiovascular disease is an indication of at least one of the following: heart failure, acute myocardial infarction, carotid revascularization, coronary heart disease (ie, angina, coronary revascularization, stents, use of long-acting nitrates), cor pulmonale, and congenital heart defects.

compared to immunosuppressive opioids during periods of recent and past opioid use (IRR:0.87 [95% CI: 0.69–1.08] and IRR:0.79 [95% CI: 0.55–1.12], respectively). Additionally, the risk of infection associated with the new use versus past use was higher for immunosuppressive opioids (IRR: 2.51 [95% CI: 2.09–3.02]) compared to non-immunosuppressive opioids (IRR: 1.55 [95% CI: 1.12–2.14]). Similar findings were observed when comparing prevalent to past use for immunosuppressive and non-immunosuppressive opioids (IRR: 1.39 [95% CI: 1.19–1.62] and IRR: 1.14 [95% CI: 0.92–1.41], respectively).

Individual Opioids

Baseline patients' characteristics differed according to opioid type. Of note, fentanyl users were older and more likely to be female compared to those using morphine (Supplementary Table S6). Oxycodone users were similar in age and sex compared to

morphine users (Supplementary Table S6). Morphine and oxycodone users had the most follow-up in the study compared to fentanyl, methadone, and oxymorphone users, whereas tramadol users had the least follow-up in the study (Supplementary Table S3a). Oxycodone and tramadol users the most likely to end follow-up due to opioid discontinuation, whereas fentanyl users were the most likely to die during follow-up (Supplementary Table S5a and S5b). Because tramadol users only had 7 serious infections during periods of current use, this group was not compared to morphine users.

The propensity score distribution overlap for each opioid relative to morphine is shown in Supplementary Figure 2. In the adjusted analyses, the rates during periods of current fentanyl and methadone (both immunosuppressive) use compared to current morphine use were not statistically significantly different (Table 3), whereas oxycodone (without known

Table 2. Crude and Adjusted Incidence Rate Ratios for Serious Infections by Immunosuppressive Properties of the Long-acting Opioid Among Tennessee Medicaid Enrollees (1995–2015)

Opioid Type	Infections During Current Use (n)	Incidence per 100 Person-years of Current Use	Crude IRR (95% CI)		PS Spline-adjusted IRR (95% CI)[a]		IPTW-adjusted IRR (95% CI)[b]	
Previously described immunosuppressive properties								
Immunosuppressive[c]	1012	4.28	1.00	(reference)	1.00	(reference)	1.00	(reference)
Nonimmunosuppressive[d]	205	2.46	0.58	(0.49, 0.67)	0.78	(0.66, 0.91)	0.79	(0.67, 0.92)

Abbreviations: CI, confidence interval; IPTW, inverse-probability of treatment weighting; IRR, incidence rate ratio.

[a]Adjusted for cubic spline of the propensity score for treatment with non-immunosuppressive opioids, cubic spline of the cumulative opioid dose, and cubic spline of age, and calendar year.

[b]Adjusted for cubic spline of the cumulative dose, cubic spline of age, calendar year, and using IPTW with the propensity score for treatment with nonimmunosuppressive opioids.

[c]Opioids with evidence of immunosuppressive properties in experimental studies: morphine, fentanyl, methadone.

[d]Opioids without evidence or weak evidence of immunosuppressive properties in experimental studies: oxycodone, oxymorphone, tramadol.

Table 3. Crude and Adjusted Incidence Rate Ratios for Serious Infections by Individual Opioids Among Tennessee Medicaid Enrollees (1995–2015)

Opioid Type	Infections During Current Use (n)	Incidence per 100 Person-years of Current Use	Crude IRR	(95% CI)	Spline-adjusted IRR[a]	(95% CI)	IPTW-adjusted IRR[b]	(95% CI)
Opioids with previously recognized immunosuppressive properties								
Morphine	459	2.91	1.00	(reference)	1.00	(reference)	1.00	(reference)
Fentanyl	501	8.95	3.08	(2.71, 3.50)	1.06	(0.88, 1.28)	0.89	(0.73, 1.08)
Methadone	52	2.30	0.79	(0.59, 1.06)	0.83	(0.61, 1.13)	0.82	(0.60, 1.11)
Opioids without previously recognized immunosuppressive properties								
Oxycodone	179	2.84	0.98	(0.82, 1.16)	0.73	(0.60, 0.89)	0.72	(0.59, 0.87)
Oxymorphone	19	1.17	0.40	(0.25, 0.64)	0.95	(0.58, 1.56)	1.05	(0.56, 1.97)

Abbreviations: CI, confidence interval; IPTW, inverse-probability of treatment weighting; IRR, incidence rate ratio.

[a]Adjusted for cubic spline of the propensity score for treatment with each opioid, cubic spline of the cumulative opioid dose, and cubic spline of age and calendar year (2-year intervals).

[b]Adjusted for cubic spline of the cumulative dose, cubic spline of age, calendar year (2-year intervals), and using IPTW with the propensity score for treatment with each opioid.

immunosuppressive properties) users had a significantly lower rate of infections compared to morphine (immunosuppressive) users (IRR: 0.73 [95% CI: 0.60–0.89]). The rate of serious infections was similar among oxymorphone users compared to morphine users (Table 3).

Sensitivity Analyses (Described in Supplement Section 2)
The results of the IPTW analysis were consistent with the propensity score analyses for the primary comparison and the individual opioid comparisons (Tables 2 and 3). In the sensitivity analysis using CDC-defined opioid dosing categories, the risk of infection was higher for immunosuppressive opioids within each dosing category, and the association increased as the dose increased for immunosuppressive opioids. In contrast, this was not consistently observed for opioids without previously described immunosuppressive properties (Supplementary Table S7). The results from the sensitivity analyses accounting for the cumulative dose of past glucocorticoid use, possible protopathic bias, excluding tramadol users and accounting for residence county and rurality characteristics were similar to those from the primary analysis (Supplementary Table S8), and no interaction was observed between dose and opioid type (P = .28).

DISCUSSION

Prescription opioid use is a risk factor for infections among humans, with the greatest risk reported among users of long-acting opioids [8–10]. Experimental evidence from animal models and human studies suggest that different opioids exhibit different immunosuppressive properties [11, 13, 27]. However, whether the risk of serious infections differs for individual opioids among humans remained unclear. Our findings demonstrate that among patients initiating long-acting opioid analgesic use, patients using opioids without previously reported immunosuppressive properties had a lower risk of hospitalization for serious infections compared to immunosuppressive opioids. Furthermore, oxycodone users had a significantly lower risk of hospitalization for serious infection relative to morphine users, whereas no differences in risk were observed for other opioids.

Morphine, as the prototypical opioid used in experimental and in vitro studies, has well-recognized immunosuppressive properties, with only limited evidence of immunosuppression for methadone and fentanyl (Supplement Section 3) [11, 13, 27]. Immunosuppressive effects have not been observed in experimental studies among other opioid analgesics (eg, oxycodone, oxymorphone, hydrocodone, tramadol) [11, 13, 27]. As the precise immunosuppressive mechanism of opioids requires further study, our group of "nonimmunosuppressive" opioids may include some opioids with previously unrecognized immunosuppressive properties [11, 13, 15]. Importantly, our study could not directly evaluate the mechanism for the higher risk of infections associated with use of immunosuppressive opioids.

Although previous studies have demonstrated that the immunosuppressive properties of certain opioids are associated with an increased risk of serious infections in humans, few studies have assessed whether the use of different opioids is associated with a different risk of infection [8–10, 27–29]. In a study among community-dwelling older adults, the association between opioid use and pneumonia was stronger among users of immunosuppressive opioids (odds ratio [OR]:1.88 [95% CI: 1.26–2.79]) than users of nonimmunosuppressive opioids (OR: 1.23 [95% CI: 0.89–1.69]) compared to nonusers [8]. Among patients with rheumatoid arthritis, the strongest association between opioid use and the risk of infections was observed among periods of immunosuppressive opioid use compared to nonuse (IRR: 1.72 [95% CI: 1.33–2.23]), with a more modest association during periods of non-immunosuppressive opioid use (IRR: 1.37 [95% CI: 1.15–1.62]) [10]. Furthermore, among Tennessee Medicaid enrollees, opioids with known immunosuppressive properties had the strongest association with laboratory-confirmed invasive pneumococcal disease([OR: 1.74 [95% CI: 1.20–2.53]) compared to opioids without known immunosuppressive properties (OR: 1.55 [95% CI: 1.27–1.88]) [9]. Unlike those previous studies that used unexposed

groups as reference for comparisons, our study compared patients using different long-acting opioids and demonstrated that the risk of hospitalization for serious infection was 22% lower among those initiating opioids without previously reported immunosuppressive properties compared to those with such properties. Importantly, we also observed that the risk of serious infections associated with the current use of immunosuppressive opioids increased as the dose increased, but that the risk did not increase as the dose of nonimmunosuppressive opioids increased.

An important strength of this study was the use of validated definitions for identifying hospitalizations for serious infection using administrative data in the TennCare population. These definitions have a high positive predictive value (90.2%) compared with medical chart reviews [19]. When the incidence of the outcome is low, as in our study, the PPV approximates the specificity, such that the ICD9 coding algorithms had a high specificity for the identification of hospitalizations for serious infections. Nondifferential outcome misclassification between the exposure groups (ie, immunosuppressive vs nonimmunosuppressive opioid users) in this setting will bias the risk ratio estimate toward the null [27–29].

We focused this study on comparisons of long-acting opioid formulations only, rather than including comparisons with short-acting formulations, as previous evidence indicated that use of long-acting opioid formulations was associated with the highest risk of infection and due to concerns of comparability between those using long-acting and short-acting opioids. Additionally, by excluding individuals with serious life-threatening conditions and with evidence of opioid use disorders, we were able to focus the comparisons among individuals using long-acting opioid analgesics for chronic pain conditions. We observed consistent results when we applied several different analytical strategies to control for confounding, including the use of exposure propensity scores, to help balance out any differences in the large number of covariates between comparison groups. The new-user design helped with the comparability of study groups by equalizing the beginning of follow-up and ensuring all events that occurred after initiation of opioid use were appropriately classified [30]. Nevertheless, in spite of the use of active comparator groups and the use of propensity scores, we cannot completely rule out the possibility of residual confounding.

An important limitation in our study was that prescription opioid use was defined based on filled pharmacy prescriptions but not directly observed. It is possible that patients did not complete their full prescription or did not take their opioids as prescribed. To reduce this potential misclassification, we classified intervals covered by prescription days of supply as current use (representing the periods with highest likelihood of prescription opioid exposure) and compared the rate of infections during periods of current use in the primary analysis. Although we excluded patients with evidence of substance or alcohol use disorders, we were unable to account for illicit opioid use. We

were also unable to examine the risk for individual infection types (ie, bacterial, viral, or fungal) due to the challenge of accurately determining disease etiology in routine clinical practice or in research studies [31]. Although some reports have reported an association between conditions or procedures that induce pain with immunosuppression, we specifically accounted for pain-inducing conditions in our analyses to reduce concerns of residual confounding due to pain. Furthermore, although differences in pain control could theoretically contribute to the risk of infection among different opioid users, there is no evidence to suggest that the efficacy of pain control is different for patients using opioids with and without previously recognized immunosuppressive properties.

The selection of one of the multiple long-acting opioids available needs to consider both the safety and effectiveness of each formulation. In head-to-head randomized controlled trials, few differences in effectiveness or safety have been observed among different long-acting opioids, although small sample sizes likely limited the detection of differences in these trials [31]. Although not reported in every study, some trials suggest a lower rate of gastrointestinal complications associated with the use of long-acting oxycodone and fentanyl compared to long-acting morphine [31–34]. In addition, a retrospective observational study found that long-acting oxycodone users had a lower risk of all-cause hospitalizations and all-cause mortality than users of long-acting morphine, though morphine had a lower risk of hospitalizations and overdose compared to fentanyl and methadone, respectively [35]. Other studies have offered conflicting evidence regarding an increased risk of all-cause mortality among methadone users compared to morphine users [36, 37]. Our observations of differential infection risk with different opioid formulations should be considered among other safety and effectiveness concerns by clinicians and patients when making pain management decisions [28].

In conclusion, patients using long-acting opioids previously described as immunosuppressive had a higher risk of serious infections compared with patients using nonimmunosuppressive long-acting opioids. In addition, patients using long-acting oxycodone had a significantly lower risk of serious infection compared with those using long-acting morphine, the prototypical immunosuppressive opioid. These findings are consistent with results from animal and in vitro experimental studies showing immunosuppressive properties only in certain opioids, and provide further evidence that cautious, judicious and informed opioid selection for pain management is of utmost importance.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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