Opioid Analgesics and the Risk of Serious Infections

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To my amazing parents, Brian and Denise, for their guidance and support

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CHAPTER 1

INTRODUCTION

Overview

Opioid analgesics are commonly used for the treatment of pain.[1,2] As prescription opioid use has increased over the past several decades so too has the evidence that opioid use is associated with an increased risk of opioid use disorders, overdose, and an excess morbidity and mortality from serious adverse respiratory, cardiovascular events, and other causes.[3-11] There is a long-standing evidence from animal and *in-vitro* studies that certain opioids induce immunosuppression and facilitate the development of serious infections. Nevertheless, the clinical implications of opioid analgesic use and the risk of infections among humans have remained understudied.[12-16] Recent evidence suggests that prescription opioid use may be associated with an excess of serious infections.[17-20] Furthermore, although there are multiple opioid formulations available for use, not all opioids are thought to have the same effect on the immune system. Identifying potentially problematic opioid formulations could inform pain management guidelines, especially among vulnerable populations at high risk of serious infections. Therefore, we conducted a sequence of epidemiological studies to examine and characterize the association between opioid analgesic use and the risk of serious infections.

Since the 1990s, there has been a well-documented increase in opioid analgesic in the U.S.[5,21,22] Even though the number of filled opioid prescriptions has decreased nationally since 2010, prescription opioid use in 2015 was still 3 times as high as in 1999.[23] In addition, opioid use has increased during that time in certain geographical regions of the U.S.[23] Estimates from

the U.S. National Survey on Drug Use and Health indicated that nearly 92 million U.S. adults were prescribed an opioid analgesic in 2015, representing over one-third of the U.S. adult population.[24] Even though the increasing trend of opioid prescribing has slowed in recent years, the prevalence of prescription opioid use in the U.S. will likely continue to remain high for years to come, providing further importance to characterizing the side effects and adverse outcomes associated with opioid analgesic use.

Commonly described side effects of prescription opioid analgesic use include feelings of sedation, dizziness, nausea, vomiting, and constipation, as well as more rare instances of hyperalgesia, muscle rigidity, and hormonal imbalances.[25] However, the association between prescription opioid use and the risk of more severe adverse outcomes (e.g., opioid use disorders, overdose, and associated-mortality) has also been reported.[3-7,9,10,17] More recently, studies have demonstrated previously unrecognized associations between opioid use and cardiovascular and all-cause mortality. However, the necessary understanding of the safety profile of these commonly used medications remains incomplete.[5,26,27]

Opioid-induced immunosuppression: experimental evidence

An excess of infections has been previously documented among opioid users (both prescription and illicit use).[16-20,28-32] Although high-risk behaviors cause infections among illicit opioid users, evidence from animal and *in-vitro* studies also suggests that opioid-induced immunosuppression is another potential cause of infections.[13-16,33-48] Experimental studies have provided clear evidence that opioids can negatively impact immune responses by downregulating the response of both innate and acquired immunity processes (specific pathways highlighted in Table 1.1 for individual opioids).[32,34] Morphine is the de-facto opioid of choice for the study of opioid-induced immunosuppression due to its strong affinity for binding to cellular receptors and

its primordial opioid chemical structure. It is also an active metabolite of other commonly used opioids. Thus, the majority of the existing experimental evidence has focused on the examination of the effects of morphine exposure.[37,49,50]

Molecular basis of opioid-induced immunosuppression

The primary mechanism for the downregulation of both adaptive and innate immunity is through the binding of exogenous opioids to the mu opiate receptor (MOP or μ receptor) found on T lymphocytes, macrophages, and immature immune cells.[14,34,49] Morphine, specifically, has been linked to the reduction in the production of macrophage and lymphocyte cells, macrophage migration in response to infection, the ability of neutrophils and macrophages to facilitate pathogen destruction through phagocytosis and the release of chemical intermediates, and a reduction in natural killer cells' activity.[14,32,40,51] Regarding T-lymphocyte production, morphine interacts with intermediate factors that control interleukin-2 (IL-2) and interferon-gamma activity, two important cytokines necessary in the adaptive immune response.[34,52-54] As some of these intermediate factors (nuclear factor cytokines and micro-ribonucleic acids) are also involved in the activation of certain macrophage functions, morphine's impact on macrophage function may be compounded by this interaction, along with a direct interaction with MOP receptors on macrophages.[14,34,52] High doses of morphine have also been shown to induce apoptosis in macrophages.[14] Morphine, in addition to fentanyl, has also been shown to suppress the response of mast cells and dendritic cells, while the binding of morphine to opioid receptors in the central nervous system has been shown to impair natural killer cells' activity.[14,43,55]

Morphine can also impact the adaptive immune response, mainly by impairing T cell activity. Morphine impairs T cell activation and proliferation through the reduction of major histocompatibility complex class II (MHC-II) receptor expression on immune cells and by

binding to T cell MOP receptors to initiate the production of only specific T cell phenotypes.[14] Morphine also activates the production of specific immunomodulatory intermediates (such as glucocorticoids and noradrenalin) through direct activation of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system.[56] It is important to note that the described morphine-induced immunosuppression may be dependent on the administered dose and type of animal model so that caution is warranted in generalizing these findings directly to human exposure to morphine.[14,57-59]

Variability of immunosuppressive effects of opioids

One limitation in the experimental literature on opioid-induced immunosuppression is that the majority of studies have focused primarily on exposure to morphine. Fewer studies have characterized the immunosuppressive effects of other opioids. One such study among male Swiss mice comparing naturally-occurring opiates (morphine and codeine) against synthetic opioids (e.g., hydromorphone and oxycodone) reported a strong immunosuppressive effect associated with morphine, a weak effect for codeine, and no measurable immunosuppressive effects related to hydromorphone and oxycodone exposure.[12] The different chemical structure of morphine and codeine ($C_{7\text{-}8}$ double bond) compared to hydromorphone and oxycodone ($C_{7\text{-}8}$ single bond and C_6 carbonyl substitution relative to morphine) is the hypothesized reason for this difference in effect.[12] Buprenorphine (a synthetic derivative of morphine with a $C_{7\text{-}8}$ single bond and C_6 carbonyl substitution), an opioid also not structurally similar to morphine, is not associated with the immunosuppression observed for morphine when administered at equianalgesic doses in mouse and rat models, although studies at higher doses have provided conflicting information.[36,60-62]

In studies comparing buprenorphine and fentanyl, acute fentanyl administration decreases lymphocyte proliferation compared to acute buprenorphine administration, and to the chronic use of either opioid.[36,62] Fentanyl also reduced natural killer cell proliferation and movement in a small study of healthy humans compared to placebo.[63]

Tramadol activates the immune response though through increased lymphocyte production, natural killer activity, and cytokine activation.[64-66] Tramadol use enhanced natural killer cell activity in mice after surgery and among human cancer patients compared to both morphine and no opioid use.[64-66] The immunosuppressive effects of methadone are less clear, but methadone has been shown to interact with opioid receptors on lymphocytes (same receptors as morphine), to facilitate HIV infection relative to non-methadone users, and has been shown to induce apoptosis in cancer cells relative to nicotine exposure.[37,49,67,68] Thus, these observations suggest that methadone use can impair the immune response.

Opioid exposure increases risk of infections in animal models

Mechanisms of opioid-induced (mainly morphine) immunosuppression have been well characterized, but so has the association between opioid analgesic use and the susceptibility to infections in experimental animal models. In several studies, Wang et al. used murine models to demonstrate that mice exposed to morphine had an increased susceptibility to infection by *Streptococcus pneumoniae* [due to reduced lymphocyte and natural killer cell activity] compared with non-morphine exposed mice.[40,41,43] Morphine treatment was also associated with an increased susceptibility to infection by *Listeria monocytogenes, Salmonella enterica*, *Acetinobacter baumannii* and reactivation of latent Herpes Simplex viruses in mice.[44-46,69] In addition, a recent study reported that mice exposed to morphine experience a greater reduction in phagocytosis of gram-positive bacteria compared to gram-negative bacteria, indicating that

morphine-induced immunosuppression might inhibit the response to infection differently dependent on the pathogen type.[70]

Summary of experimental evidence for opioid-induced immunosuppression

In summary, the existing experimental literature has demonstrated that opioids (especially morphine) induce immunosuppression through multiple cellular and immune pathways, and suggests that their immunosuppressive effect is dependent on the type and dose of the opioid. Morphine administration in mice is also associated with an increased risk of infection compared with non-morphine exposed mice, and this increased risk of infection correlated with measurable reductions in the immune response among mice in the same studies. We summarized the current understanding of the immunosuppressive effects of individual opioids from experimental studies in Table 1.1.

Table 1.1. Summary of existing evidence for the immunosuppressive effects of individual opioid types from animal and *in-vitro* experimental studies[14,34,49,59,71]

Specificity of evidence		**Type of Immunosuppression**
Experimental evidence	Buprenorphine	Neutral/immune-stimulatory effect[1]
	Tramado1	Neutral/immune-stimulatory effect[1]
	Hydrocodone	Weak/neutral immunosuppression[1]
	Hydromorphone	Weak/neutral immunosuppression[1]
	Oxycodone	Weak/neutral immunosuppression[1]
	Oxymorphone	Weak/neutral immunosuppression[1]
	Codeine	Weak immunosuppression[1]
	Fentanyl	Strong immunosuppression[1]
	Morphine	Strong immunosuppression[1,2]
Suggestive evidence	Dihydrocodeine	Strong immunosuppression[3]
	Methadone	Strong immunosuppression[3,4]
Not studied	Pentazocine	None
	Propoxyphene	None
	Tapentadol	None
	Levorphanol	None
	Meperidine	None

[1]Based on i*n-vitro* studies examining impact on immune system cells and response
[2]Based on animal studies examining impact on susceptibility to bacterial infections
[3]Chemical structure similar to morphine
[4]Suggestive due to known affinity for immune cell receptors, similar to opioids known to be immunosuppressive

Opioid-induced immunosuppression: clinically relevant?

In light of the extensive experimental evidence for opioid-induced immunosuppression and observed increase susceptibility to infections among exposed animals, the question arises whether or not the use of opioid analgesics could induce a clinically important increased risk of infection among humans. Available data from clinical trials are insufficient for assessing infectious disease risk associated with opioid use due to ethical concerns around enrolling patients with severe pain into a group without opioid treatment, the limited size and follow-up time in clinical trials, and the variability in reporting infectious outcomes (as infections have been considered unrelated adverse events in clinical trials of opioids).[14,16]

Using the evidence from the epidemiologic literature, patients with opioid use disorders have high rates of infections, but this increased risk is difficult to attribute directly to opioid-induced immunosuppression due to the presence of other existing risk factors for infection among these patients.[14] In the few studies that have focused on the effects of opioids on the risk of infections among humans, opioid use has also been associated with an increased risk of infection among post-surgical patients, burn and intensive-care unit patients, advanced cancer patients, community-dwelling older adults, hemodialysis patients, and patients with rheumatoid arthritis.[18-20,28,29,72] The small sample sizes and focus of these studies (specialized groups of hospitalized patients and healthcare-associated infections) limit their interpretability outside of these populations though. However, two studies conducted in the outpatient setting provide evidence of a clinically important increased risk of infections associated with prescription opioid analgesic use.[18,19] The first study was a case-control study conducted in a population of older adults living in a community-dwelling setting and identified 38% increased odds of opioid exposure among pneumonia cases compared with controls.[18] Our research group recently

completed another study among patients with rheumatoid arthritis that reported a 38% increased risk of serious infections during periods of opioid use compared with periods of non-use.[19] Both studies reported an increased risk of infection related to new opioid use compared to non-use and observed increased risks related to long-acting opioids and opioids previously identified as immunosuppressive in animal model studies. Both studies accounted for the possibility of confounding by indication (i.e., conditions that lead to opioid use also predisposes individuals to infection] by examining the association between other pain medications and the risk of infections. Also, both studies addressed the possibility of protopathic bias [i.e., opioids prescribed for symptoms related to the infection before the identification of the infection (e.g., to treat a pneumonia-related cough)] through sensitivity analyses that excluded opioid use initiated within three and seven days of the infection date. However, neither of those studies had sufficient sample size to compare the risk of infection across individual opioid types, controlling for dose, potency, and duration of action for the opioid. Thus, the differences in the risk of infection by opioid type while accounting for each of these factors remain unclear.

The feasibility of conducting retrospective pharmacoepidemiological studies of serious infections using administrative data

Serious infection outcomes identified from administrative databases have been used extensively in the previous literature.[73-77] However, few studies have described the validation and performance of specific coding algorithms to identify serious infections. Of those conducted previously, most have only assessed the performance of discharge diagnosis codes for the identification of common infections (e.g., pneumonia or sepsis), within specific populations (e.g., patients with rheumatoid arthritis), or focused solely on healthcare-associated or hospital-acquired infections.[78-86] The performance of discharge diagnosis codes has primarily been

assessed for codes from the International Classifications on Diseases-Clinical Modification 9th-revision (ICD9-CM), and primarily involved the validation of a convenience sample hospitalizations for possible infection.[78-86] Most prior studies only examined the positive predictive value of discharge diagnosis code with the rationale that a high positive predictive value will approximate a high specificity of the coding algorithm.[87-89] These studies also recognize that the low prevalence of infections makes it impractical to collect a truly random sample of records that do not fulfill the coding algorithms to calculate their sensitivity and negative predictive value.[87-89] In general, findings from several previous validation studies conducted in specific settings (e.g., Veterans Affairs database, large urban academic hospitals) have shown existing coding algorithms to have reasonable specificity and good positive predictive value for identifying hospitalizations for certain serious infections. However, the generalizability of these findings to other settings remains unclear.

Nevertheless, the identification and validation of coding algorithms to identify serious infections in a particular population of interest is an important methodological requirement in any study using administrative data to examine serious infections as outcomes using administrative data, as the performance of coding algorithms may vary across different populations and administrative datasets.[88] Using accurate coding algorithms to identify serious infections is important to reduce misclassification of the outcome and its impact on measures of association. A high positive predictive value and high specificity for outcome identification reduce the impact of misclassification on relative risk estimates in epidemiological studies.[89]

CHAPTER 2

MOTIVATION AND AIMS OF THE STUDY

MOTIVATION

The substantial increase in opioid use has fueled an interest in the characterization of the safety profile of these commonly used medications. Safety concerns related to opioid use have mainly focused on the potential for abuse, addiction, overdose and overdose related-deaths. Although evidence from animal and in-vitro human studies suggests that certain opioids impair immune function, the association between the use of certain opioids and the risk of infections in humans remained understudied. Given the widespread use of opioids, clarifying the clinical importance of opioid-induced immunosuppression is of great interest to public health.[14-16,34,90] As existing clinical trial data are insufficient to study this particular question, epidemiological studies can help to determine the importance of opioid-induced immunosuppression on the incidence of serious infections.[14,16]

The design and conduct of the proposed studies require careful consideration of methodological details. For example, validating hospitalizations for serious infections identified using coding algorithms and determining the extent that misclassification could influence an observed association is an important step for any epidemiological study using administrative data. The availability of laboratory-confirmed outcomes identified from other accessible sources at Vanderbilt provides an alternative to outcomes identified using coding algorithms alone, and is another way to reduce concerns about outcome misclassification. Using both validated coding

algorithms for serious infections and laboratory-confirmed infections as study outcomes will allow a the robustness examination of the associations of interest.

SPECIFIC AIMS

We proposed to conduct a sequence of retrospective studies among individuals enrolled in Tennessee Medicaid (TennCare) between 1995 and 2014. With the overarching goal of determining the clinical implications of exposure to opioids with previously described immunosuppressive properties in animal experimtents, we proposed the following specific aims: **Aim 1:** To test the hypothesis that outpatient prescription opioid analgesic use is associated with an increased risk of laboratory-confirmed invasive pneumococcal disease (IPD). Using a nested case-control study design in a retrospective cohort of individuals >5 years of age enrolled in TennCare, we evaluated whether individuals with IPD were more likely to have an opioid exposure compared to those without IPD. Using laboratory-confirmed cases reported to the Active Bacterial Core Surveillance System (ABCs) helped reduce the impact of potential outcome misclassification on our measures of association. However, these highly specific outcomes are rare and represent only a small fraction of all serious infections hospitalizations occurring among susceptible subjects.

To enable a more comprehensive assessment of other infections, we validated algorithms based on administrative codes to identify hospitalizations for serious infection hospitalizations in the Tennessee Medicaid population. Therefore, we proposed the operational aim: **Aim 2:** To determine the positive predictive value of different algorithms for identifying each type of hospitalization for serious infection based on diagnosis, procedure, and healthcare utilization

codes (ICD9-CM) in a cohort of TennCare patients. Validated algorithms for different serious infection types were used to identify outcomes for Aim 3.

As laboratory-confirmed infections represented only a small percentage of all hospitalizations for serious infection (Aim 1), we further proposed: **Aim 3:** To test the hypothesis that outpatient prescription opioid analgesic use is associated with an increased risk of hospitalization for serious infection in a retrospective cohort of individuals ≥18 years of age. We compared the risk of hospitalization for serious infections among different long-acting opioids in new users of long-acting opioids for chronic non-cancer pain.

CHAPTER 3

STUDY POPULATION

All patients and information used in this study were identified from existing data sources housed in the Division of Pharmacoepidemiology, Department of Health Policy at Vanderbilt University Medical Center. The main study population used in each aim is comprised of individuals enrolled in the Tennessee Medicaid (TennCare) program. TennCare is the Medicaid-managed program in Tennessee that provides healthcare insurance to those who are Medicaid eligible and to those who otherwise lack access to healthcare, therefore consisting of a largely low-income population. TennCare currently provides healthcare coverage to around 1.5 million individuals, which accounts for around 20% of Tennessee's overall population. In January 2016, the TennCare population was primarily female (57.9%) with an age distribution consisting mostly of those <20 years of age (57.6%), followed by those 21-64 years (37.8%), those >65 years (4.6%).[91,92] Although percentages of males and females were similar among those less than 20 years of age [<18 years (females 49% and males 51%) and 19-20 years (females 54% and males 46%)], females represented over 2/3 of the enrolled individuals among those 21-64 and ≥65 years of age (70% and 69%, respectively).[91] The race-ethnicity distribution of the TennCare population in 2016 was White (42.1%), Black (22.3%), Other (31.4%) and Hispanic (4.2%).[91]

The TennCare databases consist of a family of relational databases that encompass demographic information, healthcare encounter information and filled pharmacy prescriptions for enrollees. At our Division, the information in the TennCare databases is organized and formatted enabling its use for research purposes. These data are also supplemented with vital

records information (birth/mortality data) as well as hospital discharge information from the Tennessee Hospital Discharge Data System. In addition, the TennCare pharmacy information is supplemented with Medicare Part D pharmacy information (2006-2015) for those that were eligible for both programs. The Medicare Part D program was implemented on January 1, 2006. Our research group has extensive experience working with the TennCare databases over the past 30 years. The use of the Tennessee Medicaid databases allows for the use of a large cohort of enrolled individuals (n=~4,500,000) for which opioid prescription exposures and study outcomes can be reliably measured over a relatively long period (1995-2015). This combined data source has been used extensively for pharmacoepidemiological studies.[7,8,19,93,94]

Another source for the identification of outcomes in Aim 1 was the Active Bacterial Core surveillance system (ABCs), a surveillance system funded by the Centers for Disease Control and Prevention and established in 1995. The ABCs conducts active population and laboratory-based surveillance for detection of pathogens of public health relevance. The purpose of ABCs is to measure the incidence and identify risk factors for invasive disease from selected pathogens, including *Streptococcus pneumoniae.* In Tennessee, Vanderbilt University Medical Center collaborates with the Tennessee Department of Health and the Tennessee Emerging Infections Program to operate the surveillance system in Tennessee. Surveillance for *S. pneumoniae* in Tennessee has been conducted in various counties throughout the study period, including five urban counties from 1995-1999, 11 counties in 2000-2009, and 20 in 2010-2015. According to U.S. Census estimates from 2010, the ABCs surveillance catchment area included 57.6% of the Tennessee population.

The ABCs database consists of demographic information, healthcare encounter information, risk factor information, and specimen/pathogen information for every detected case.

Cases reported to ABCs are regularly audited to ensure the information reported to ABCs is valid. Our research group works closely with the ABCs staff at Vanderbilt University Medical Center and has an existing partnership to access these data files for the study period (1995 through 2014). Our research group has experience linking individuals who are enrolled in TennCare and are identified by the ABCs system.[95]

CHAPTER 4

OPIOID ANALGESIC USE AND THE RISK OF INVASIVE PNEUMOCOCCAL DISEASE*

*** Portions of this chapter have been provisionally accepted for publication**

INTRODUCTION

As opioid analgesic use has increased worldwide, the safety of prescription opioid use has come under further scrutiny.[90,96-98] Common safety concerns include the potential for opioid use disorders, overdose, and the development of serious adverse respiratory and cardiovascular events.[3-6] However, these known adverse effects only partially account for the excess morbidity and mortality observed among prescription opioid users.[7,9,10] There are also concerns about a potential excess of infections observed among prescription opioid users, but few studies have attempted to quantify the risk of infection among subjects using opioid analgesics.[17-19]

Certain opioids have known immunosuppressive properties, and their use may increase the risk of infections.[14,99] Animal and *in–vitro* experimental studies have demonstrated that some opioids disrupt lymphocyte and phagocyte proliferation, reduce innate immune cell activity, and inhibit cytokine expression and antibody production.[14,32,37] In animal models, opioid-induced immune disruption also led to an increased susceptibility to bacterial infection, including infections caused by common human pathogens such as *Streptococcus pneumoniae*.[40,41,45] However, the clinical implications of these observations for humans, including whether the risk differs by specific opioid properties or dose, remains unclear.

Invasive pneumococcal disease (IPD), caused by *S. pneumoniae,* includes serious illnesses such as bacteremia, meningitis and invasive pneumonia.[100] Known risk factors for IPD include age (young children and older adults), decreased immune function, chronic high–risk

medical conditions (e.g., lung, liver and kidney disease) and cigarette smoking.[100-103] Since IPD monitoring and prevention remains a public health priority, and opioid analgesic use represents a potentially novel and modifiable risk factor for serious infections including IPD, we sought to test the hypothesis that opioid analgesic use is an independent risk factor for laboratory-confirmed IPD.

METHODS

Data Sources

We conducted a nested case-control study among a retrospective cohort of persons enrolled in the Tennessee Medicaid (TennCare) program. TennCare, the managed Medicaid program in Tennessee, provides healthcare insurance to Tennessee residents who are Medicaid eligible. TennCare data provided information about enrollment, demographics, pharmacy use, healthcare encounters and comorbidities for each subject. These data were supplemented with State Vital Records information and hospital-based data from the Tennessee Hospital Discharge Data System. Pharmacy data were supplemented with Medicare Part D information for dual-eligible subjects. Laboratory-confirmed IPD cases were identified from the Tennessee Active Bacterial Core surveillance (ABCs) system. The ABCs system conducts active population and laboratory-based surveillance of IPD in 20 Tennessee counties.

This study was approved by the IRBs of Vanderbilt University and the Tennessee Department of Health, and the Bureau of TennCare.

Study Cohort

From 1995 through 2014, we identified all TennCare enrollees with at least one filled study opioid prescription (see **Exposure**) to exclude subjects with contraindications to opioids

and those who may not be eligible to receive opioids. These subjects entered the study cohort on the earliest date (t_0) when a study opioid prescription was filled, and the following criteria were met: >365 baseline days of continuous prior TennCare enrollment, age >5 years, documented access to pharmacy benefits, >1 healthcare encounter and no IPD identified during baseline, and free of non-study opioid (see **Exposure**) prescriptions during baseline or on t_0. Subjects were also required to have $\geq$1 day of residence in a Tennessee county that reported to the ABCs system during the study period (see **Case-Control Selection**). Follow-up continued from t_0 through the earliest of the following dates: end of the study (December 31, 2014), death, loss of enrollment, IPD, or first non-study opioid use. Subjects who ended follow-up due to loss of enrollment, IPD, or non-study opioid use were allowed to re-enter the cohort if they subsequently fulfilled all eligibility criteria as above.

Case-Control Selection

We used the ABCs system to identify laboratory-confirmed IPD among cohort members. IPD was defined by the isolation of *S. pneumoniae* from a normally sterile site (e.g., blood, cerebrospinal fluid).[101] The sample collection date was the index date for each case. We used incidence density sampling to randomly select up to 20 cohort members at risk but without laboratory-confirmed IPD (controls) per case. Controls were matched to their case on the index date, as well as on age (individual years) and county of residence on that date. A subject could serve as a control for multiple cases and could later become an IPD case.

Exposure

The use of prescribed study opioids was the exposure of interest. Study opioid analgesics were prescribed oral and transdermal formulations. Non-study opioids included antitussive and antidiarrheal formulations (non-pain indications), injectable formulations for which timing of use

and dose can be difficult to ascertain, and formulations used primarily for opioid use disorders (i.e., buprenorphine). Using pharmacy data, we defined four mutually exclusive exposure categories relative to the index date for cases and controls. Current users were subjects with a study opioid prescription overlapping the index date. To minimize exposure misclassification due to imperfect adherence or intermittent use, recent users were subjects whose most recent prescription ended 1-90 days prior to the index date, and past users were subjects whose most recent prescription ended 91-182 days before the index date. Remote users included all other scenarios with no opioid prescription that ended within 182 days before the index date. Also, new users were defined as a subset of current users whose prescription overlapping the index date was initiated after 182 days without an opioid prescription. Current opioid use, the main study exposure, was further classified according to the opioid duration of action (short or long-acting), potency (moderate or high), previously described immunosuppressive properties (immunosuppressive, non-immunosuppressive, unknown), and estimated daily dose in morphine milligram equivalents (MME) on the index date (<50mg, 50-90mg, ≥90mg) [Appendix Table A1].[5,104] To avoid misclassification, current users of ≥1 different opioid type were classified separately from those receiving only a single opioid type.

Covariates

Relevant demographics, comorbidities (including well-recognized risk factors for IPD), acute and chronic pain conditions, medication use and healthcare utilization, were measured during the 365 days prior to the index date and considered as potential confounders. Demographics included sex and race. Other covariates, including healthcare resources use, were defined using diagnosis and procedure codes. Medications were identified using national drug codes. Well-recognized risk factors for IPD, per the Advisory Committee on Immunization

Practices (ACIP), included alcohol/substance abuse, cardiovascular disease, serious hepatic and chronic lung disease, end-stage renal disease/hemodialysis, HIV, malignancy, immune disorders, diabetes, sickle-cell disease, and tobacco use.[102,103] Other comorbidities included surrogate markers for frailty (such as debility, pressure ulcers, impaired mobility, among others).[105] Acute and chronic pain conditions included abdominal or back pain, trauma, headache, arthritis, and neuropathic pain, among others. Healthcare resources use included nursing home residence and the baseline number of hospitalizations, outpatient, and emergency department visits (Appendix Table A2).

Statistical Analysis

We compared the odds of being a current opioid user versus a remote user between IPD cases and controls. Multivariable conditional logistic regression was used to calculate adjusted odds ratios (aOR) and 95% confidence intervals (CI) accounting for the matching design and adjusting for all well-recognized risk factors for IPD. To assess model fit and fulfillment of assumptions, we conducted standard regression diagnostics for conditional logistic regression.[106] Three plots were used to identify any outliers using diagnostic statistics for each observation visually. Outliers were identified as any observations with values that were very different from the distribution of values for the study population as a whole using scatterplots of the Hosmer-Lemeshow leverage statistic, change in Pearson chi-square statistic and the change in Deviance statistic versus the estimated probability from the fitted model for each observation.

Planned secondary analyses stratified current opioid use according to the duration of action, potency, previously described immunosuppressive properties, and estimated MME daily dose.[5,18,19,104] We also assessed IPD associated with pneumonia separately from non-pneumonia

IPD outcomes since opioid-related respiratory depression may facilitate aspiration and the development of pneumonia.

As a complementary method of assuring that current and remote opioid users were similar concerning IPD risk, we conducted a separate planned analysis by calculating an IPD risk score that included all study covariates, excluding the well-recognized risk factors for IPD that were included in the primary analysis (Appendix Table 3). Analogous to propensity scores for cohort studies, disease risk scores provide an efficient strategy to account for potential differences in the risk of IPD between exposure groups in case-control designs, especially when the number of covariates is large, the exposure consists of multiple categories and the number of cases is limited.[107-109] The IPD risk score was calculated among all non-current opioid users using a logistic regression model with IPD as the outcome and included 103 covariates assessed in the 365 days preceding the index date. The coefficients from this logistic regression model were then used to calculate the predicted probability of IPD for each subject in the entire study population independent of opioid exposure and the presence of well-recognized risk factors for IPD. We incorporated the IPD risk score, categorized as deciles of predictive probabilities, together with the well-recognized risk factors for IPD into the conditional logistic regression model for opioid use and IPD.[107]

Since some opioid use may be prescribed for the initial clinical manifestations of IPD (e.g., chest pain associated with pneumonia), a planned sensitivity analysis excluded new users that initiated current opioid use within four days (inclusive) of the index date to address possible protopathic bias. Our primary analysis accounted for the use of the pneumococcal polysaccharide vaccine in the 365 days prior to the index date. Since polysaccharide vaccine protects against IPD for at least 5 years,[102] we examined pneumococcal vaccination history among a subset of

cases and controls with >5 years of continuous enrollment preceding their index date. Since pneumococcal conjugate vaccine also provides long-term protection against IPD, we repeated our main analysis excluding data from 2012-2014, when this vaccine was recommended for use among adults.[102,103] Finally, we assessed the sensitivity of our estimates to the impact of a potential unmeasured confounder.[110] All analyses were performed in Stata-IC, version 15.1 (College Station, TX).

RESULTS

Among the retrospective cohort of TennCare enrollees who fulfilled all selection criteria (n=221,660), we identified 1,233 laboratory-confirmed IPD cases [73.9% (n=911) were invasive pneumonia] and 24,399 matched controls. Cases had a higher percentage of males and a higher prevalence of risk factors for IPD compared to controls, including cardiovascular and chronic lung disease, HIV, malignancy, and smoking. In addition, 25.2% of IPD cases were current users of opioids on the index date compared with 14.4% of controls (Table 4.1). Among current opioid users, a higher percentage of cases used long-acting and high potency opioids, and higher daily doses compared to controls (Table 4.2). Comparing characteristics between exposure groups, current opioid users had a higher prevalence of risk factors for IPD than remote users, including age $\geq$40 years, cardiovascular and chronic lung disease, malignancy, diabetes, smoking and higher prior levels of healthcare utilization. Vaccination with pneumococcal polysaccharide vaccine in the 365 days prior to the index date was more common among current users than remote users (Table 4.3).

Table 4.1. Characteristics of IPD cases and matched controls, Tennessee Medicaid enrollees (1995-2014)

Characteristic	IPD Cases (n=1,233)		Controls (n=24,399)	
Female sex - no. (%)	732	(59.4%)	16,731	(68.6%)
Race - no. (%)				
White	571	(46.3%)	11,378	(46.6%)
Black	534	(43.3%)	10,378	(42.5%)
Other	128	(10.4%)	2,643	(10.8%)
Age Category[a], years - no. (%)				
<18	44	(3.6%)	880	(3.6%)
18-39	262	(21.2%)	5,240	(21.5%)
40-64	636	(51.6%)	12,688	(52.0%)
65-74	159	(12.9%)	3,158	(12.9%)
≥75	132	(10.7%)	2,433	(10.0%)
Residence[a] - Type of County[b] - no. (%)				
Non-Metropolitan	177	(14.4%)	3,336	(13.7%)
Metropolitan	1,056	(85.6%)	21,063	(86.3%)
Comorbidities[c] - no. (%)				
Alcohol and Substance Abuse	165	(13.4%)	966	(4.0%)
Cardiovascular Disease	266	(21.6%)	2,761	(11.3%)
Serious hepatic disease	68	(5.5%)	213	(0.9%)
Chronic Lung Disease	354	(28.7%)	2,979	(12.2%)
End-stage renal disease	69	(5.6%)	388	(1.6%)
HIV	161	(13.1%)	296	(1.2%)
Malignancy	144	(11.7%)	948	(3.9%)
Immune Disorder/Transplant	22	(1.8%)	89	(0.4%)
Diabetes	253	(20.5%)	3,928	(16.1%)
Sickle Cell Disease	13	(1.1%)	37	(0.2%)
Smoking-related Diagnosis	272	(22.1%)	2,063	(8.5%)
Healthcare Utilization[c] - no. (%)				
Pneumococcal polysaccharide vaccination	43	(3.5%)	561	(2.3%)
Outpatient Clinic Visits				
0-4	565	(45.8%)	13,333	(54.6%)

5-9	284	(23.0%)	5,958	(24.4%)
10-19	276	(22.4%)	4,095	(16.8%)
≥ 20	108	(8.8%)	1,013	(4.2%)
ED Visits				
0	361	(29.3%)	11,973	(49.1%)
1-2	489	(39.7%)	8,728	(35.8%)
3-4	205	(16.6%)	2,270	(9.3%)
≥ 5	178	(14.4%)	1,428	(5.9%)
Hospitalizations				
0	578	(46.9%)	18,128	(74.3%)
1	297	(24.1%)	3,880	(15.9%)
2	157	(12.7%)	1,302	(5.3%)
≥ 3	201	(16.3%)	1,089	(4.5%)
Recent Nursing Home Stay- past 30 days	69	(5.6%)	1,132	(4.6%)
Opioid Use[d] - no. (%)				
Remote Users	492	(39.9%)	12,690	(52.0%)
Past Users	118	(9.6%)	2,705	(11.1%)
Recent Users	312	(25.3%)	5,483	(22.5%)
Current Users	311	(25.2%)	3,521	(14.4%)
IPD Syndrome - no. (%)				
Invasive Pneumonia	911	(73.9%)	n/a	
Other IPD syndromes[e]	322	(26.1%)	n/a	

[a]Controls were matched to cases on individual year of age, county of residence and eligibility on the index date (i.e., controls had to be eligible retrospective cohort members on the index date for the case)

[b]Metropolitan counties were defined as those under ABCs surveillance with at least one city with a population >100,000 according to 2015 Census estimates (Davidson, Hamilton, Knox, Rutherford, and Shelby)

[c]Comorbidities and healthcare utilization patterns were assessed in the 365-day period preceding the index date for cases and controls (with the exception of "Recent Nursing Home Stay")

[d]Opioid use (current, recent, past and remote) was assessed relative to the index date for cases and matched controls

[e]Other IPD syndromes included meningitis, primary bacteremia and bacteremia secondary to other conditions (e.g., cellulitis)

Table 4.2. Distribution of Opioid Characteristics in Current Opioid Users among IPD cases and matched controls, Tennessee Medicaid enrollees (1995-2014)

Characteristic[a]	IPD Cases (n=311)		Controls[b] (n=3,521)	
New Users - no (%)	21	(6.8%)	186	(5.3%)
Duration of Opioid Action - no. (%)				
Short-Acting (SA)	231	(74.3%)	2,869	(81.5%)
Long-Acting (LA)	37	(11.9%)	256	(7.3%)
Combination SA/LA	43	(13.8%)	396	(11.2%)
Previously described Immunosuppressive Properties[c]- no. (%)				
Unknown	35	(11.3%)	408	(11.6%)
Non-Immunosuppressive (NIS)	200	(64.3%)	2,446	(69.5%)
Immunosuppressive (IS)	44	(14.1%)	368	(10.5%)
Combination Unknown/NIS/IS	32	(10.3%)	299	(8.5%)
Potency of Opioid - no. (%)				
Medium	182	(58.5%)	2,479	(70.4%)
High	100	(32.2%)	813	(23.1%)
Combination Medium/High	29	(9.3%)	229	(6.5%)
Opioid Dose (MME)[d] - no. (%)				
<50mg	170	(54.7%)	2,220	(63.1%)
50-90mg	51	(16.4%)	509	(14.5%)
≥90mg	90	(28.9%)	792	(22.5%)

[a]All opioid characteristics were defined a priori (Appendix Table 1 in the supplement)

[b]Controls were matched to cases on individual year of age, county of residence and eligibility on the index date (i.e., controls had to be eligible retrospective cohort members on the index date for the case)

[c]Each opioid was categorized a priori as potentially immunosuppressive, non-immunosuppressive and unknown based on existing literature (Appendix Table 1 in the supplement)

[d]Categories of opioid dose were defined a priori according to morphine milligram equivalents (MME) per day based on categories outlined in the CDC chronic pain opioid prescribing guidelines that recommend careful assessment of opioid prescriptions 50-90 MME and ≥90 MME per day(6)

Table 4.3. Characteristics of current opioid users compared to remote opioid users, Tennessee Medicaid enrollees (1995-2014)[a]

Characteristic	Current Opioid Users[b] (n=3,832)		Remote Opioid Users[b] (n=13,182)	
Female sex - no. (%)	2,555	(66.7%)	8,757	(66.4%)
Race - no. (%)				
White	2,431	(63.4%)	5,385	(40.9%)
Black	951	(24.8%)	6,380	(48.4%)
Other	450	(11.7%)	1,417	(10.7%)
Age Category, years				
<18	17	(0.4%)	621	(4.7%)
18-39	361	(9.4%)	3,049	(23.1%)
40-64	2,334	(60.9%)	6,698	(50.8%)
65-74	642	(16.8%)	1,552	(11.8%)
≥75	478	(12.5%)	1,262	(9.6%)
Residence - Type of County[c]				
Non-Metropolitan	829	(21.6%)	1,542	(11.7%)
Metropolitan	3,003	(78.4%)	11,640	(88.3%)
Comorbidities[d] - no. (%)				
Alcohol and Substance Abuse	262	(6.8%)	418	(3.2%)
Cardiovascular Disease	724	(18.9%)	1,110	(8.4%)
Serious hepatic disease	69	(1.8%)	81	(0.6%)
Chronic Lung Disease	908	(23.7%)	1,167	(8.9%)
End-stage renal disease	91	(2.4%)	161	(1.2%)
HIV	93	(2.4%)	198	(1.5%)
Malignancy	293	(7.6%)	340	(2.6%)
Immune Disorder/Transplant	27	(0.7%)	36	(0.3%)
Diabetes	908	(23.7%)	1,696	(12.9%)
Sickle Cell Disease	12	(0.3%)	14	(0.1%)
Smoking-related Diagnosis	665	(17.4%)	703	(5.3%)
Healthcare Utilization[d] - no. (%)				
Pneumococcal polysaccharide vaccination	147	(3.8%)	234	(1.8%)
Outpatient Visits				
0-4	1,111	(29.0%)	8,781	(66.6%)

5-9	917	(23.9%)	2,895	(22.0%)
10-19	1,332	(34.8%)	1,276	(9.7%)
≥ 20	472	(12.3%)	230	(1.7%)
ED Visits				
0	1,603	(41.8%)	7,750	(58.8%)
1-2	1,393	(36.4%)	4,217	(32.0%)
3-4	466	(12.2%)	847	(6.4%)
≥ 5	370	(9.7%)	368	(2.8%)
Hospitalizations				
0	2,429	(63.4%)	10,682	(81.0%)
1	749	(19.5%)	1,631	(12.4%)
2	308	(8.0%)	515	(3.9%)
≥ 3	346	(9.0%)	354	(2.7%)
Recent Nursing Home Stay - Past 30 days	299	(7.8%)	503	(3.8%)
IPD Case Status - no. (%)				
Control	3,521	(91.9%)	12,690	(96.3%)
Case	311	(8.1%)	492	(3.7%)

[a]Counts within rows of each variable type will not total to the full study population, as totals for past users (n=2,823) and recent users (n=5,795) are not included in this table

[b]Opioid use (current, recent, past and remote) was assessed relative to the index date for cases and matched controls

[c]Metropolitan counties were defined as those under ABCs surveillance with at least one city with a population >100,000 according to 2015 Census estimates (Davidson, Hamilton, Knox, Rutherford, and Shelby)

[d]Comorbidities and healthcare utilization patterns were assessed in the 365-day period preceding the index date for cases and controls (with the exception of "Recent Nursing Home Stay")

Opioid use and risk of IPD

Current use of opioids was significantly associated with IPD compared with remote opioid use in the multivariable conditional logistic regression model, which adjusted for well-known risk factors for IPD [aOR: 1.62 (95% CI: 1.36 to 1.92)] (Table 4.4 and Appendix Table A5). When current use was classified based on opioid characteristics, current use of both long-acting [aOR: 1.87 (95% CI: 1.24 to 2.82)] and short-acting opioids [aOR: 1.58 (95% CI: 1.32 to 1.90)] was associated with IPD compared with remote use. The association was demonstrated across all daily opioid dose categories, with the highest aORs observed at MME doses $\geq$50mg [50-90mg aOR: 1.71 (95% CI: 1.22 to 2.39) and $\geq$90mg aOR: 1.75 (95% CI: 1.33 to 2.29)].

Additionally, the strongest associations were observed for the use of high potency opioids, and opioids with previously described immunosuppressive properties (Table 4 and Appendix Table 6). Importantly, the association between current opioid use and IPD was consistently demonstrated for both pneumonia IPD [aOR: 1.54 (95% CI: 1.26 to 1.88)] and non-pneumonia IPD [aOR: 1.94 (95% CI: 1.36 to 2.77)]. In the small subset of current users identified as new users (n=21 cases), the aOR was higher compared with remote users [aOR: 2.44 (95% CI: 1.49 to 4.00)] (Table 4.4).

The IPD risk score was calculated among non-current users [n=21,800 and 922 IPD cases (Appendix Table A3)]. Including the IPD risk score in the model yielded results that were very similar [aOR: 1.61 (95% CI: 1.35 to 1.91)] (Appendix Table A4) to findings of the main analysis. Few observations were identified as outliers based on the leverage and change in deviance statistic for each observation and matched group. among cases compared to controls in the plot of individual observations.

Table 4.4. Crude and Adjusted Odds Ratios (aOR) for Laboratory-Confirmed Invasive Pneumococcal Disease by Opioid Use Type among Tennessee Medicaid Enrollees (1995-2014)

Exposure[a]	Cases	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio[b] (95% CI)
Recency of Opioid Use			
Remote Users	492	1.00 (reference)	1.00 (reference)
Past Users	118	1.13 (0.92 to 1.39)	0.87 (0.70 to 1.08)
Recent Users	312	1.50 (1.29 to 1.73)	1.03 (0.87 to 1.21)
Current Users	311	2.47 (2.11 to 2.89)	1.62 (1.36 to 1.92)
New Users[c]	21	3.01 (1.90 to 4.78)	2.44 (1.49 to 4.00)
Duration of Opioid Action			
Remote Users	492	1.00 (reference)	1.00 (reference)
Short-Acting (SA) Opioid Users	231	2.24 (1.89 to 2.66)	1.58 (1.32 to 1.90)
Long-Acting (LA) Opioid Users	37	3.92 (2.73 to 5.61)	1.87 (1.24 to 2.82)
Combination SA/LA Opioid Users	43	3.15 (2.25 to 4.42)	1.64 (1.12 to 2.38)
Previously described Immunosuppressive Properties			
Remote Users	492	1.00 (reference)	1.00 (reference)
Unknown	35	2.26 (1.58 to 3.25)	1.79 (1.22 to 2.63)
Non-Immunosuppressive (NIS)	200	2.31 (1.93 to 2.77)	1.55 (1.27 to 1.88)
Immunosuppressive (IS)	44	3.23 (2.33 to 4.48)	1.74 (1.20 to 2.53)
Combination Unknown/NIS/IS	32	3.07 (2.09 to 4.50)	1.72 (1.12 to 2.63)
Potency of Opioid			
Remote Users	492	1.00 (reference)	1.00 (reference)
Medium	182	2.04 (1.70 to 2.45)	1.52 (1.25 to 1.85)
High	100	3.50 (2.77 to 4.43)	1.72 (1.32 to 2.25)
Combination Medium/High	29	3.62 (2.42 to 5.44)	2.20 (1.40 to 3.46)
Dose of Opioid (MME[d])			
Remote Users	492	1.00 (reference)	1.00 (reference)
<50mg	170	2.13 (1.77 to 2.58)	1.54 (1.26 to 1.88)
50-90mg	51	2.82 (2.07 to 3.83)	1.71 (1.22 to 2.39)
≥90mg	90	3.19 (2.50 to 4.06)	1.75 (1.33 to 2.29)

[a]Each set of opioid characteristics (recency, duration of action, immunosuppression, potency, and dose) were examined using a separate conditional logistic regression model including the same covariate sets (Appendix Table A6)

[b]Adjusted odds ratio are derived from the full model including sex, race, alcohol/substance abuse, cardiovascular disease, serious hepatic disease, chronic lung disease, hemodialysis, HIV, cancer, immune disorders, diabetes, sickle cell disease, smoking, nursing home residency, pneumococcal polysaccharide vaccination and numbers of healthcare encounters taking into account the study design where controls were matched to cases on individual year of age, county of residence and eligibility on the index date

[c]Subset of current users; [d]MME: Morphine milligram equivalent (MME) per day

No outlier observations were identified in the plot of the change in Pearson chi-square statistic for each observation and matched group, although calculated values were relatively high. In sensitivity analyses excluding observations with change-in-Pearson chi-square statistics >50, the association between current opioid use and IPD was consistent [aOR, 1.81 (95% CI, 1.51 to 2.17)] with the main study finding, though the point estimate was even higher.

Sensitivity analyses

In the planned sensitivity analysis that excluded cases and controls with an index date in the first four days of new use, the aOR for current users was relatively unchanged from the main analysis [aOR: 1.56 (95% CI:1.31 to 1.86)]. The aOR comparing the small subset of new users to remote users was reduced but had limited precision [aOR: 1.51 (95% CI: 0.66 to 3.45)].

As uncontrolled confounding is an important concern in epidemiological studies, especially residual confounding, we conducted a sensitivity analysis to explore the strength of association and distribution of a hypothetical binary unmeasured confounder that would be required in the association between opioid use and the risk of IPD to explain the observed adjusted odds ratio of 1.62 (95% CI, 1.36 to 1.92). To conduct this sensitivity analysis, we used an array approach to determine how different assumptions about an unmeasured confounder might explain the observed association in our primary analysis.[110] The analysis can be conducted using a worksheet freely available at www.drugepi.org.

For a conservative assessment, we focused on the lower bound of the 95% confidence interval from our main analysis, an adjusted odds ratio of 1.36. Considering that this approximated an observed relative risk of 1.36, we determined the "true" relative risk that would exist if a certain unmeasured confounder was accounted for that was not accounted for in our study. This assessment involved varying the prevalence of the hypothetical unmeasured

confounder in the exposed (current opioids users) and unexposed (remote opioid users) groups, as well as the strength of the association between the hypothetical unmeasured confounder and IPD. We examined different scenarios varying the prevalence of the confounder in current opioid users from 0 to 50% but holding the prevalence constant in remote opioid users at 10% and 20%, as well as varying the strength of the confounder-IPD association from 1.0 to 5.5.

Based on those assumptions, we estimated that an unmeasured confounder would need to be an independent, strong risk factor for IPD with a relative risk of 2 or higher, and need to have an absolute difference in prevalence of $\geq$35% between current opioid users compared to remote users to explain the observed adjusted odds ratio of 1.36 (Appendix Figure 4.1). At lower absolute differences in the prevalence (25%, 15%, and 10%), the unknown confounder would need to have a stronger, independent association with IPD (relative risks of 2.5, 3.5 and 5.5, respectively). Weaker confounders or those with lower exposure prevalence differences could only partially attenuate the observed association, but could not fully account for it (Appendix Figure 4.1). The estimations and Appendix Figure 1 can be replicated using a worksheet freely available at www.drugepi.org.[110]

Importantly, none of the measured covariates (including well-known risk factors for IPD) included in our study met any of the scenarios previously described (Table 4.3 and Appendix Table A5). The highest independent associations between a risk factor and IPD were for HIV, sickle-cell disease and serious hepatic disease (aOR, 10.22, aOR, 3.75 and aOR, 2.94, respectively). These conditions are rare with an absolute difference in prevalence between current and remote opioid users of 0.9%, 0.2% and 1.2 %, respectively (Table 3). The highest absolute prevalence differences between current and remote opioid users were race (23.6% difference in prevalence of Whites), number of outpatient visits (25.1% difference in those

visiting outpatient settings 10-19 times in the prior year), chronic lung disease (14.8%), smoking (11.9%), diabetes (10.8%), cardiovascular disease (10.5%), and age (10.1% difference in prevalence in adults 40 to 64 years). However, these covariates had aORs <1.83 for IPD and were all fully accounted for by our design and analyses.

In addition, the more comprehensive IPD risk score analysis found results that were virtually identical to the primary analysis. As the IPD risk score included all measured relevant covariates, it seems unlikely that unmeasured confounding could explain the entirety of the observed association between opioid use and the risk of IPD.

In the extended examination of pneumococcal polysaccharide vaccination history among cases and controls with five years of continuous enrollment before the index date, vaccination was higher among cases than controls (14.9% vs. 10.1%, n=18,354) and current opioid users compared to remote opioid users (16.4% vs. 8.5%). Therefore, due to the protective effect of polysaccharide vaccination observed in the study population, differences in polysaccharide vaccination history could not explain our findings, and our estimates may be conservative. Similarly, excluding individuals with an index date in years when pneumococcal conjugate vaccines were recommended for adults yielded results similar to the main findings [n=23,065; aOR: 1.64 (95% CI: 1.36 to 1.97)].

CONCLUSIONS

We report a strong association between use of prescribed opioids and the risk of laboratory-confirmed IPD. The association was strongest for current users of long-acting, high-potency, previously described as immunosuppressive and high-dose opioid formulations, and was consistent across clinical syndromes of IPD.

The immunosuppressive properties of certain opioid analgesics, including morphine and fentanyl, have been well established.[14,99] In animal models, exposure to certain opioids increased the risk of infections due to common pathogens, including *S. pneumoniae*.[40,41] Among humans, opioid use has been previously linked to an increased risk of infection among hospitalized surgical, burn and cancer patients.[20,28,29] Two previous smaller studies have also reported an association between outpatient prescription opioid use and the risk of serious infection in high-risk groups. One study, restricted to community-dwelling older adults enrolled in a private health insurance system, reported that patients with pneumonia had a 39% increased odds of opioid exposure compared to controls.[18] In another study of patients with rheumatoid arthritis, there was a 38% increased frequency of hospitalization for serious infection during periods of current opioid use compared to non-opioid use, and results were consistent across pneumonia and serious non-pneumonia infections.[19] In both previous studies, and consistent with our current findings, the occurrence of serious infections was highest during periods of exposure to long-acting opioids, high opioid doses, and opioids previously described as immunosuppressive.[18,19]

A unique strength of this study was the use of ABCs data to identify laboratory-confirmed IPD cases. We minimized misclassification by using only laboratory-confirmed outcomes. The specificity of laboratory-confirmed IPD is very high, supporting its use for assessment of relative measures of association. Furthermore, IPDs are prototypical community-acquired infections, and thus less affected by other factors (e.g., recent hospitalization, IV drug use) that may impact assessments of serious infections as a whole.[103] In context of the previous literature, our assessment of IPD complements previous studies and suggests that opioid analgesic use increases the risk of serious infections among humans.[18,19]

An important limitation of our study is that opioid use was based on pharmacy prescription fills, but actual use was not directly observed. We attempted to minimize misclassification of the exposure by defining recent and past use categories to ensure that the current use category represented periods with the highest likelihood of using opioid analgesics. Although we did account for evidence of alcohol/substance use disorders in the analysis, we were unable to assess illicit opioid use, as well as account for those that misuse/divert their opioid prescriptions. Another limitation was the inability to make direct comparisons across opioid types while accounting for duration of action, potency, and the dose of each opioid prescription. Although we observed the strongest associations for long-acting, high potency, immunosuppressive and high-dose opioids, laboratory-confirmed IPD were relatively rare, and we were underpowered to account for these factors simultaneously and to make direct comparisons among individual opioids. Because there are differences in the bioavailability, half-life, and amount of active metabolites among opioids, we would expect that the association between opioid use and serious infections might vary across opioids. Future studies will be important to characterize the role of individual opioids and inform prescribers and patients regarding appropriate opioid selection.

Our analyses accounted for a substantial number of relevant covariates. However, we cannot rule out the possibility of residual confounding. We estimated that a potential unmeasured confounder would need to fulfill two criteria: be a very strong risk factor for IPD and have a substantial distribution imbalance between exposure groups, to explain our findings. Nevertheless, the consistency of results in the more comprehensive IPD risk score analysis and the primary analysis should reduce concerns about residual confounding. Although our main analysis directly accounted for pneumococcal polysaccharide vaccination history during the year

preceding the index date, an extended assessment also examined the history of vaccination during the five years preceding the index date and considered this as a potentially unmeasured confounder. Since pneumococcal vaccination was more common among current than remote opioid users, accounting for the protective effect of this factor would result in a stronger association between opioid use and IPD. Similarly, we found that the availability of pneumococcal conjugate vaccine for adults starting in 2012 had no impact on our findings.

Our study findings complement the previous experimental evidence from animal models and the studies among humans and indicate that prescription opioid use is an independent, novel risk factor for IPD, and likely for other infections in humans as well. As the strongest associations were observed for opioids with certain characteristics (namely long-acting, high potency, formulations previously described as immunosuppressive, and high doses), these findings should be considered during the selection of opioid analgesics for pain management.

In conclusion, we found that current opioid use was strongly and consistently associated with the risk of IPD and that the association was strongest for the use of long-acting and high potency formulations, formulations previously described as immunosuppressive, and high dose opioids. Our results indicate that opioid use is an independent risk factor for IPD and that ongoing and future efforts to reduce opioid overuse may have an impact on these previously under-recognized associated infections.

CHAPTER 5

VALIDATION OF DISCHARGE DIAGNOSIS CODES TO IDENTIFY SERIOUS INFECTIONS AMONG OLDER ADULTS*

***Portions of this chapter have been submitted for publication**

INTRODUCTION

Infectious diseases remain a leading cause of morbidity and mortality in the U.S. and elsewhere.[111] Older adults, in particular, are at high risk for serious infections and their long-term consequences.[112,113] Among older adults, community-acquired serious infections (including pneumonia, sepsis, and meningitis) often require hospitalization and represent a substantial burden on the U.S. healthcare system.[114-117] Therefore, it is important to monitor the incidence of these infections, identify important risk factors, and determine the impact of preventative policies (e.g., vaccination) on these diseases among older adults.[118-120]

Large-scale epidemiological studies using administrative data often use serious infections as outcomes.[73-77] However, few studies have evaluated the performance of diagnosis codes to identify serious infections among older adults. Most previous studies that have assessed the performance of coded discharge diagnosis codes to identify serious infections have focused mainly on common infections (e.g., pneumonia or sepsis), specific populations (e.g., patients with rheumatoid arthritis), or on healthcare-associated or hospital-acquired infections.[78,80-87,121] Nevertheless, the performance of coded discharge diagnoses for accurately identifying hospitalizations due to serious infection among older adults is unclear. Therefore, we sought to determine the positive predictive value (PPV) of specific discharge diagnoses for identifying serious infections that required hospitalization among older adults.

METHODS

Data sources

TennCare is the managed Medicaid program in Tennessee that provides healthcare insurance to those who are Medicaid eligible. We used data from TennCare, supplemented with data from the Tennessee Hospital Discharge System (a registry for all hospitalizations in Tennessee) and pharmacy information from Medicare Part D for those that were dual eligible, to identify a retrospective cohort of TennCare enrollees ≥50 years of age with pharmacy benefits (2008-2013). Cohort members had at least 180 days of continuous baseline enrollment before cohort entry and to be free of certain life-threatening conditions known to increase the risk of infection (solid organ transplantation, end-stage renal disease, HIV/AIDS, malignancy and serious kidney, liver and respiratory disease). Cohort members were also required to have evidence of at least one pharmacy prescription fill and evidence of at least one healthcare encounter during baseline (to ensure detection of healthcare usage). Follow-up started on the earliest date the inclusion criteria were met and continued through the earliest of the following: study end date (December 31, 2013), the day before the diagnosis of a serious, life-threatening condition that would have precluded entry into the cohort, loss of enrollment, or date of death. From this retrospective cohort, we identified possible hospitalizations for serious infections (see **Identification of hospitalizations for serious infection**) for our validation study. To avoid including infections that may have originated during a previous hospitalization, we excluded hospitalizations for infections that occurred in the 30-day period after discharge from a previous hospitalization.

Identification of hospitalizations for serious infection

Clinical knowledge and literature review were used to identify discharge diagnosis codes used to identify serious infections that require hospitalization (**study infections**), including pneumonia (alone or with a primary diagnosis of bacteremia/sepsis), bacteremia/sepsis, pyelonephritis, meningitis/encephalitis, osteomyelitis/septic arthritis, endocarditis, and cellulitis.[19,87,93,122] Specific International Classifications of Diseases-Clinical Modification 9th-revision (ICD9-CM) diagnosis codes used to identify possible hospitalizations for each infection type are presented in Table 5.1.

Sampling Strategy

We used stratified random sampling to select a representative subset of study infection hospitalizations from among all possible cases identified in the retrospective cohort. To prevent an over-representation of larger hospitals and to identify any regional variability in coding practices and infection prevalence, we constructed a sampling framework that stratified hospitals based on their geographic region in Tennessee (West, Central, and East), and tertiles of reported discharge volume (Low, Medium, and High).[123-125] From this sampling framework, we randomly selected three hospitals from each of these nine sampling strata and retrieved their medical records for review and validation (Figure 5.1). This strategy, relative to a purely random sample, ensured better representation of infections identified in smaller hospitals and those in more rural regions of Tennessee. If a hospital refused to participate, we replaced it with another hospital randomly selected from the same sampling stratum.

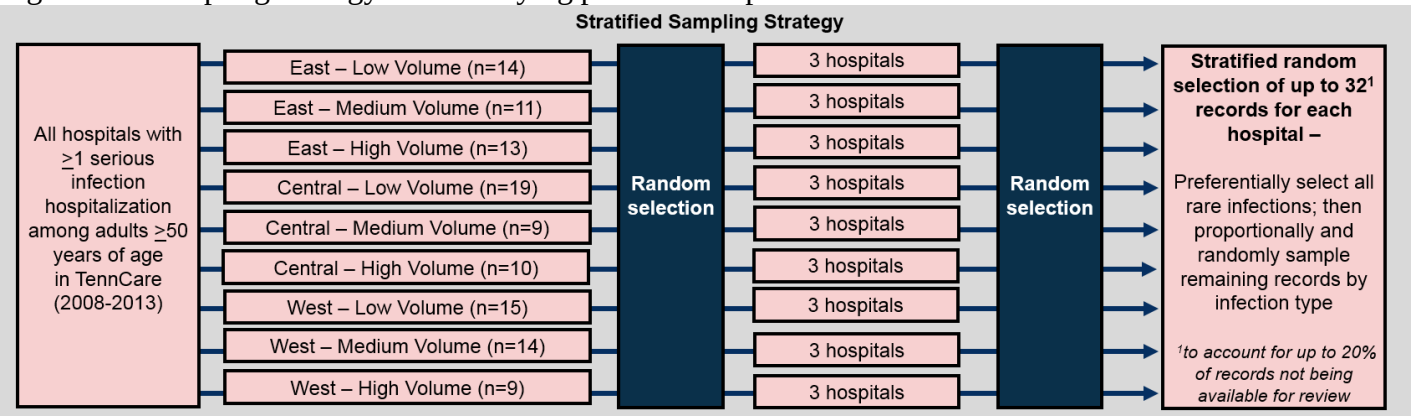
Table 5.1. Discharge diagnosis code definitions (ICD9-CM) for hospitalizations for serious infection

Serious Infection	Primary (first listed) discharge diagnosis code
Pneumonia-primary definition	003.22, 480.*‡, 481, 482.*, 483.*, 484.*, 485.*, 486.*, 487.0
Pneumonia-secondary definition (pneumonia diagnosis (above) in any other diagnosis field)	510.*, 038.*, 790.7, 995.91, 995.92
Meningitis/ Encephalitis	003.21, 036.0, 0.47*, 049.*, 053.0, 054.72, 072.1, 091.81, 094.2, 098.82, 100.81, 320.*, 036.1, 054.3, 056.01, 058.21, 058.29, 062.*, 063.*, 064.*, 066.41, 072.2, 094.81, 130.0, 323.*
Bacteremia/ Sepsis†	038.*, 790.7, 995.91, 995.92
Cellulitis/ Soft-tissue infections	035, 040.0, 569.61, 681.*, 682.*, 728.86, 785.4
Endocarditis	036.42, 074.22, 093.2*, 098.84, 421.*, 422.92
Pyelonephritis	590.*
Septic Arthritis/ Osteomyelitis	003.23, 056.71, 098.5*, 711.0, 711.00-711.07, 711.09, 711.9*, 003.24, 376.03, 526.4, 730.0*, 730.1*, 730.2*

† Without a diagnosis of pneumonia in any other diagnosis field
‡ A * indicates all numeric values [0-9]

The overall goal was to review and validate 675 hospitalizations for serious infection from 27 hospitals (25 hospitalizations for each of the three hospitals comprising a stratum, yielding 75 hospitalizations for each of the nine strata) (Table 5.2). We conservatively assumed that up to 80% of records requested would be available for review, and requested 32 records per hospital to receive an average of 25 records from each (Figure 5.1). To ensure that we reviewed sufficient rare infections, we preferentially selected possible hospitalizations for meningitis/encephalitis, osteomyelitis/septic arthritis and endocarditis from each hospital in the sample. We randomly selected the remaining set of possible hospitalizations for other serious infection based on the proportional distribution of common infections at each hospital (pneumonia, bacteremia/sepsis, pyelonephritis, and cellulitis) until we identified 32 infections. For hospitals with fewer than 32 infections during the study period, we requested all infections.

Figure 5.1. Sampling strategy for identifying potential hospitalizations for serious infection



Abstraction and Adjudication of Medical Records

Relevant clinical information was abstracted from each medical record (transfer notes, emergency room summary, admission summary, physical/history, pharmacy information, laboratory, microbiology, and radiology information, and discharge summary) using a

standardized and customized REDCap electronic data capture instrument hosted at Vanderbilt University.[126] In preparation for this study, the case report form was pilot-tested among a separate, convenience sample of 354 possible infections identified in the cohort from 3 hospitals in the same city as Vanderbilt University. This separate sample of hospitalizations was used only for pilot-testing the case report form, and so we did not include this pilot sample in the current study. One trained medical reviewer abstracted the relevant information for all selected records using the case report form. A second trained medical reviewer abstracted relevant information from a subset of selected records, which included all meningitis and endocarditis records, and a random selection of 10% of each of the remaining infection types, to assess the interrater reliability of the adjudication process. Each reviewer conducted the process independently and blinded from one another.

All records received were abstracted, reviewed and adjudicated. During the abstraction process, we treated the lack of a particular finding in the medical record as a lack of evidence for that finding, and so no information was considered missing after abstraction. Information abstracted from the medical record was compared to *a priori* definitions for each infection type to make the final determination of whether a hospitalization represented a confirmed infection or not (**Appendix B)**. Previous validation studies and expert clinical knowledge were used to define these specific *a priori* definitions for each infection type (**Appendix B**).[87,122,127]

Statistical analysis

We calculated the PPV of the ICD9-CM discharge diagnosis codes for identifying hospitalizations for serious infection using the results of the *a priori* definitions applied to the information abstracted from the medical records as the reference. Secondary analyses assessed whether the PPV for hospitalizations for serious infection differed across hospitals of different

sizes and in different geographical regions of Tennessee using a two-sample difference in proportion test. In addition, we assessed the impact on the PPV for all infections when requiring microbiological identification of a pathogen (excluding common contaminants) from a sterile site within two days before or after the hospitalization admission date. Among hospitalizations for possible pneumonia, we also assessed the PPV when radiological evidence of pneumonia was required [i.e., pneumonia, opacity, or infiltrate mentioned in a chest X-ray or computed tomography scan report] (**Appendix B**). We also assessed the impact of excluding hospitalizations that occurred after the individual was transferred from another healthcare facility since documentation and details of the infection could be missing or incomplete in the receiving hospital.[128] For the subset of records abstracted by both reviewers, inter-reviewer agreement for the adjudication of true or misidentified hospitalizations was assessed using the Gwet's first agreement coefficient (AC_1).[129-131] Since Cohen's kappa statistic can be unreliable when the prevalence of the event and the level of observer agreement are high in the study sample, we used Gwet's AC_1 as a reliability measure unlikely to be affected by these concerns.[131-133] We performed all analyses in Stata-IC, version 15.1 (College Station TX).

RESULTS

Cohort characteristics

Among a retrospective cohort of 129,465 adults ≥50 years of age enrolled in TennCare, 8,322 hospitalizations for serious infection were identified during the study period (2008-2013). Pneumonia, cellulitis and bacteremia/sepsis were the most common infections (54.3%, 20.5% and 18.4%, respectively), followed by pyelonephritis (3.8%) and septic arthritis/osteomyelitis (2.5%). Fewer than 1% of hospitalizations were due to meningitis/encephalitis (n=30) and

endocarditis (n=18). Cohort members were primarily female (57.8%) with a median age of 60 years and with residence outside of a nursing home (85.9%).

Collection, review, and adjudication of selected medical records

Of the 27 hospitals we selected for the sample initially, 21 (78%) were able to participate. We selected seven additional hospitals to replace the six non-participants to achieve the desired sample size, including an additional small hospital in the East region due to a large number of unavailable records from a single participating hospital.

We received 716 (89%) of 808 requested records from 28 participating hospitals [Table 5.2]. Record availability from participating hospitals was lower in medium size hospitals (81.8%) compared to small (93.5%) and large hospitals (91.7%) but did not differ by geographic region. Record availability by infection type was greater than 86% for all infection types, except hospitalizations for the rare endocarditis cases (57.1%; only 4 of 7 cases).

There was evidence of transfer for 21.8% of the hospitalizations for serious infection [highest percentage of transfers for bacteremia/sepsis (38.5%) and pneumonia (25.1%)]. The most common healthcare facility source was a nursing home/skilled nursing facility (84.6%), but also included group home sources (7.7%), other sources (4.5%) [assisted living facility, mental health center] and another acute care hospital (3.2%). There was evidence of an emergency department visit within seven days before admission date for the serious infection hospitalization in 4.8% of the records.

Performance of discharge diagnosis codes

A total of 646 [PPV: 90.2% (95% CI: 88.0-92.4)] of the hospitalizations for serious infection identified using ICD9-CM discharge diagnosis codes were confirmed by applying the *a priori* definitions to the abstracted data. The PPV was highest for pneumonia and cellulitis

[96.8% (95% CI: 94.5-98.4) and 91.1% (95% CI: 86.0-96.1), respectively], and was ≥75% for bacteremia/sepsis, pyelonephritis, septic arthritis/osteomyelitis, and endocarditis. The PPV was lowest for meningitis/encephalitis [50.0% (95% CI: 19.0-81.0)], although the precision was limited due to a low number of available records for review (Table 5.2).

When we evaluated the performance across stratification sampling parameters, no differences were observed in the PPV for records from hospitals in different geographical regions of Tennessee. Although the PPV was high for all three discharge volume groups, the PPV was significantly lower in large hospitals [84.6% (95% CI: 80.1-89.0)] compared to smaller hospitals [93.9% (95% CI: 90.8-97.0); comparison p=0.001] and medium hospitals [92.7% (95% CI: 89.4-96.0); comparison p= 0.005] (Table 5.2).

In the 82 records independently abstracted by two reviewers to assess reliability, there was 92.7% (95% CI: 86.9-98.4) agreement for identifying true hospitalizations for serious infection. The inter-rater agreement was also high when assessing reliability, independent of the outcome prevalence, with an AC_1 of 0.91 (95% CI: 0.84-0.99).

Sensitivity analysis

The PPV was unchanged when excluding the 21.8% of hospitalizations that occurred as transfers from another healthcare facility [90.1% (95% CI: 87.7-92.6)]. Microbiological evidence of the specific infection type was found in 47.6% of records, leading to reduced PPVs when requiring microbiological evidence [45.4% (95% CI: 41.7-49.0)]. Microbiological evidence of infection was highest in hospitalizations for suspected pyelonephritis (94.4%), but was ≤60% for every other infection type [pneumonia (42.7%); cellulitis/soft tissue infections (58.5%); bacteremia/sepsis (26.1%)]. When requiring radiological confirmation of pneumonia, the PPV for coded diagnoses was 78.8% (95% CI: 74.5-83.2).

Table 5.2. Positive predictive value (PPV) of coded discharge diagnosis definitions for hospitalizations for serious infections among older adults enrolled in Tennessee Medicaid, 2008-2013

Type	Expected Number of Records	Records Received	PPV (95 % CI)
Overall	675	716	90.2 (88.0, 92.4)
Region Specific			
West	225	195	91.3 (87.3, 95.2)
Central	225	225	88.9 (84.8, 93.0)
East	225	296	90.5 (87.2, 93.9)
Bed volume size specific			
Low	225	230	93.9 (90.8, 97.0)
Medium	225	233	92.7 (89.4, 96.0)
High	225	253	84.6 (80.1, 89.0)
Serious Infection			
Pneumonia	305	340	96.8 (94.5, 98.4)
Cellulitis/Soft-tissue infections	125	123	91.1 (86.0, 96.1)
Pyelonephritis	80	89	87.6 (80.8, 94.5)
Bacteremia/Sepsis	100	92	82.6 (74.9, 90.4)
Septic Arthritis/Osteomyelitis	50	58	75.9 (64.8, 86.9)
Meningitis/Encephalitis	10	10	50.0 (19.0, 81.0)
Endocarditis	5	4	75.0 (32.6, 100.0)

Approximately 95.6% of possible hospitalizations for pneumonia had at least one documented chest x-ray or CT-scan. Among those patients with a chest x-ray or CT-scan report available (n=325), 83.4% had a finding compatible with pneumonia. The main findings among the 54 patients with possible pneumonia and a radiological report available, but without radiological confirmation of pneumonia included atelectasis (n=6), interstitial pneumonitis (n=3), chronic heart failure with pulmonary edema (n=1), and no radiological findings of any kind (n=44).

CONCLUSIONS

Discharge diagnoses for identifying hospitalizations due to serious infections had a very high positive predictive value, especially for identifying common serious infections among older adults in our population. PPVs were consistently high across different hospital types and regions of Tennessee. Microbiological confirmation was available for fewer than 50% of those admitted with possible hospitalizations for serious infections, and as expected, such a requirement resulted in a lower PPV. Importantly, the PPV for pneumonia hospitalizations remained relatively high even when requiring radiological confirmation. In addition, including hospitalizations for serious infection that were the result of a transfer from another healthcare facility (e.g., acute care hospital, skilled nursing facility) did not change the PPV of hospitalizations for serious infection.

The PPV for hospitalizations for pneumonia in previous smaller validation studies has ranged from 72 to 86% in different healthcare systems, but those studies did not focus on older adults.[87,134-136] In our study of hospitalizations among older adults, we found that coded discharge diagnoses have a higher PPV for pneumonia compared to previous studies. The PPV for bacteremia/sepsis was also in the higher range of previously reported PPVs in other

populations (reported range from 45% to 97.7%), and for septic arthritis/osteomyelitis compared to a previous study conducted among patients with diabetes (63.9% versus 75.9% in our study).[121,137,138] Overall, the observed PPV for all infections in our study was comparable to two previous comprehensive validation studies of bacterial infections, one among patients with rheumatoid arthritis in a single hospital system and another among patients in one of the Veteran's Affairs integrated service networks.[122,127] Compared to the two previous comprehensive validation studies of ICD9 codes, we abstracted and adjudicated a larger number of records while using a more systematic sampling strategy to receive records for hospitalizations from multiple regions and hospital types as opposed to a single hospital or healthcare system. However, the PPVs for individual infections were less precise and less comparable, especially for rare infections, as would be expected due to the low numbers of rare infections across previous studies.[122,127] The results of our study are also similar to previous validation studies using ICD10 codes to identify hospitalizations for serious infection.[139,140]

One limitation to consider in our study was the inability to estimate the sensitivity and specificity of the coding definitions. Those determinations would have required collecting an extensive random sample of medical records without an infection identified from the administrative data to allow a precise estimation of those measures. However, the relatively low prevalence of hospitalizations for serious infection among the older adults population indicates that the PPV will approximate the specificity, and so we chose only to determine the PPV of the discharge diagnosis codes.[88] Of note, the high PPV observed in our study approximates a high specificity for the diagnosis codes. Importantly, any non-differential disease misclassification between exposure groups resulting from the use of highly-specific discharge diagnosis codes will be less prone to biased estimates of the relative risk.[89] Also, though caution is warranted in

generalizing these findings to a different population, coded discharge diagnoses for serious infections had a high PPV across hospitals of different sizes and across all geographical areas of Tennessee, which may have differences in the prevalence of hospitalizations for serious infection.[141]

Another limitation is the use of available clinical information to operationalize definitions for adjudication of true hospitalizations for infections. It is possible that procedures, laboratory findings and diagnoses of interest that informed the final diagnosis of infection were not fully recorded in the medical records, and thus, not available for our review. Also, although we used previous validation studies and clinical information to build pre-specified definitions for the adjudication of true infections, our reference criteria may be imperfect, considering the retrospective nature of our determinations and potential variability in clinical practice. Nevertheless, we also assessed how the availability of selected findings (i.e., microbiological and radiological information) in the medical record impacted the overall and infection-specific PPV. We demonstrated that relying on highly specific clinical diagnostics, such as microbiological and radiological information, to confirm true infections would result in lower PPVs for identification of infections in administrative data. Requiring microbiological confirmation to confirm true infections is challenging because of the known low sensitivity of culture-based diagnosis methods (most commonly used in clinical practice), which may lead to misclassification.[142,143] In addition, requiring radiological evidence compatible with pneumonia within two days of hospital admission did lower the observed PPV for pneumonia hospitalizations. Nevertheless, the observed PPV remained close to 80%, which should reduce concerns about using diagnosis codes to identify hospitalizations due to pneumonia. Another limitation to consider is that our diagnosis codes were based on the ICD9-coding system only. Although these findings will be

helpful for retrospective studies that encompass periods of ICD9 use, additional studies evaluating the performance of ICD10-based codes would be useful to complement our findings.

Our study demonstrated that discharge diagnosis codes could be used to identify hospitalizations for serious infections among older adults accurately. We observed the highest PPVs for the most common infections, and the PPV for pneumonia remained high when requiring radiological confirmation. The PPV was poor when microbiological confirmation of infection was required to identify a true hospitalization for serious infection. This information supports the use of discharge diagnosis codes for infections as outcomes in ongoing and future studies among older adults.

CHAPTER 6

LONG-ACTING OPIOID USE AND THE RISK OF SERIOUS INFECTIONS IN PATIENTS WITH NON-CANCER PAIN

INTRODUCTION

The extent of prescription opioid analgesic use in the United States is recognized as a public health emergency, specifically related to the increasing evidence of safety concerns associated with opioid use.[96,97] In addition to concerns about opioid use disorders and the risk of overdose, opioid analgesic users have an increased morbidity and mortality due to adverse respiratory outcomes, cardiovascular events, and the development of serious infections.[3,5,7,9,10,17-20] The risk of these adverse outcomes associated with opioid use is particularly worrisome among users of long-acting opioid analgesics, due to their potency and potential increased toxicity.[7,144,145]

Evidence from animal and *in-vitro* experimental studies indicate that certain opioids (specifically morphine, methadone, fentanyl, and codeine) can disrupt the immune response and increase susceptibility to certain bacterial infections.[12-14,51,70] In some experiments, certain opioids structurally different from morphine were shown to have neutral (specifically oxycodone and hydromorphone) or neutral/positive effects (e.g., tramadol) on the immune response towards a potential infection compared with no opioid exposure.[13,14,49] However, studies conducted in humans are very limited, and it remains unclear whether different opioids might differentially impact the clinical risk of serious infection among opioid analgesic users. Importantly, existing data from randomized controlled trials are unable to elucidate the clinical importance of opioid-induced immunosuppression with regards to risk of infections, due to limited sample sizes and

incomplete reporting of infectious outcomes.[14-16] As multiple formulations of strong, long-acting opioids are available in the market, determining if all opioids confer a similar risk of serious infections could inform pain pharmacotherapy. Therefore, we conducted an observational study to compare the risk of serious infection among patients initiating therapy with different long-acting opioid analgesics, specifically those with and without previously reported immunosuppressive properties.

METHODS

Data sources

We conducted a retrospective cohort study among Tennessee Medicaid (TennCare) enrollees initiating the use of long-acting opioids from 1995 through 2014. TennCare provides healthcare insurance to Tennessee residents who are Medicaid eligible. The TennCare data provided information about enrollment, demographics, pharmacy use, healthcare encounters and comorbidities for each subject. State Vital Records information and hospital encounter data from the Tennessee Hospital Discharge Data System were used to supplement the TennCare data. In addition, Medicare Part D information supplemented the pharmacy data for those that were dual-eligible. The study was reviewed and approved by the institutional review boards of Vanderbilt University, the Tennessee Department of Health, and by the Bureau of TennCare.

Study Population

The cohort included adults aged >18 years initiating the use of long-acting opioids with continuous enrollment in TennCare (gaps of < 7 days allowed) and without evidence of a serious or life-threatening condition at baseline that could reduce follow-up or substantially increase the risk of serious infections (Appendix Table C1). The baseline period was defined as the 366-day

period prior to the initiation of a long-acting opioid prescription. To ensure patients used their benefits and had access to healthcare, we excluded patients without at least one coded healthcare encounter (e.g., inpatient/outpatient visit, 23-hour stay, emergency department visit) during baseline. We also specifically excluded patients with a diagnosis of substance abuse and those individuals with at least one filled prescription for a non-study opioid during baseline (see below). Recently discharged patients were not allowed to enter the cohort until at least 30 days post-discharge from the hospital. Qualified patients entered the cohort upon filling a new long-acting study opioid prescription (i.e., no long-acting opioid use in prior 180 days) after having filled a short-acting study opioid prescription in the prior 180 days. We required that qualified patients have filled a short-acting study opioid prescription in the prior 180 days to further limit the cohort to individuals with chronic pain transitioning from short-acting opioid analgesic use to long-acting opioid analgesic use for the first time (new users). Patients were excluded if they filled two different long-acting study opioids on the same qualifying date.

Exposure

Study opioids consisted of oral and transdermal formulations of long-acting opioid analgesics identified at the national drug code classification level (Appendix Table A1) including morphine, fentanyl, oxycodone, methadone, oxymorphone, and tramadol. Other cough and anti-diarrheal opioid formulations not indicated for pain management, and formulations for which exposure can be difficult to track, (e.g., intravenous and injectable formulations) were considered non-study opioids. For each long-acting opioid prescription, the daily dose of opioid use calculated was based on the morphine milligram equivalents (MME) using standard conversion factors shown in Appendix Table A1. For the primary analysis, opioids were identified as those with previously recognized immunosuppressive properties (fentanyl, methadone, and morphine)

and those without known immunosuppressive properties from experimental animal and *in-vitro* studies (oxycodone, oxymorphone, and tramadol).[14,34,49]

Follow-up

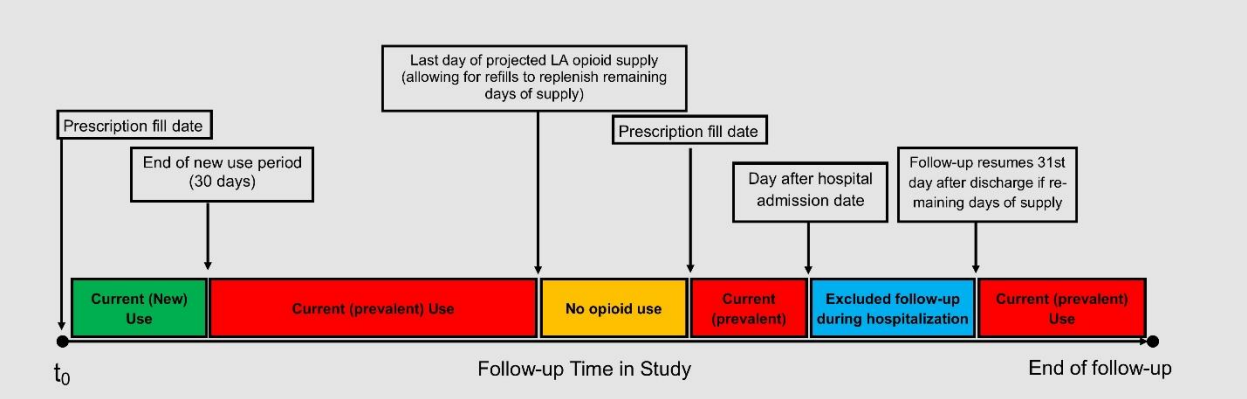
Patients entered the cohort on the earliest qualifying prescription fill date for a new long-acting study opioid prescription that met all the above requirements at baseline (t_0). Patients continued follow-up through the earliest of the end of the study (December 31, 2014), identification of a serious life-threatening condition or substance abuse diagnosis (Appendix Table C1), loss of enrollment (>7 days without evidence of enrollment), a prescription fill for a non-study opioid, a prescription for a different long-acting opioid, completing 180 days without availability of a long-acting study opioid (i.e. after exhaustion of days of supply), date of death, or the date of hospitalization for serious infection (Appendix Table C3). Patients who left the cohort could reenter the cohort later if they subsequently fulfilled all eligibility criteria.

Each person-day of follow-up was characterized according to the probability of study medication exposure. We defined current use based on the days of dispensed long-acting opioid therapy determined from the prescription fill date, number of pills and days of supply (Figure 6.1). We classified any non-current use person time as non-use to minimize the potential misclassification of the exposure. To examine if the risk of infection was different in the period immediately after initiating a long-acting study opioid, we classified the first 30 days of current use after initiating a long-acting study opioid prescription as new use.

We also tracked person-time in the hospital and the 30-day post-discharge period. Medication use (including opioid use) could not be assessed during person-time in the hospital and so this person-time was excluded from follow-up (Figure 6.1). This period encompassed the person-time from the day after admission to a hospital or 23-hour observational stay for any

casue other than a serious infection through the date of discharge. We also excluded the 30-day post-discharge period as this is a high-risk period for developing healthcare-associated serious infections and for which medication exposure assessment can be difficult to ascertain for prescriptions received during the hospital stay. Any opioid prescription remaining (determined by remaining days of supply) at the time of a hospitalization or 23-hour observational stay was assumed to be kept, with use resuming on the day after the hospital discharge date. Filled opioid prescriptions during the 30-day discharge period were assessed to inform exposure definitions (see below) during subsequent follow-up periods.

Figure 6.1 Definition of follow-up based on opioid exposure classifications



Outcome

Hospitalizations for serious infection were identified using specific algorithms of International Classifications of Diseases-Clinical Modification 9th-revision (ICD9-CM) diagnosis codes validated in the study described in Chapter 5. Specific infections identified included pneumonia (alone or with a primary diagnosis of bacteremia/sepsis), bacteremia/sepsis, pyelonephritis, meningitis/encephalitis, osteomyelitis/septic arthritis, endocarditis and cellulitis

(Appendix Table C3).[19,87,93,122] These definitions had a PPV of 90.2% (95% CI: 88.0, 92.4) using medical chart review as reference (Chapter 5).

Covariates

We measured relevant covariates in the 366-day baseline period prior to t_0 for all episodes of long-acting opioid therapy. We assessed demographics (age, sex, and race/ethnicity), the type of short-acting opioids used before long-acting opioid initiation, the presence of different chronic pain indications, comorbidities, medication use, frailty indicators, and healthcare encounter history (Appendix Tables C1 and C2). Per our selection criteria, only individuals enrolled with full benefits and that demonstrated access to those services were included. Therefore, lack of evidence for a diagnosis or medication meant the individual was without a history of that condition or medication use, and so this information was not considered missing.

Statistical Analysis

We compared the risk of hospitalization for serious infection between periods of current use of opioids without previous evidence of immunosuppression (oxycodone, oxymorphone, and tramadol) compared to opioids with previous evidence of immunosuppression (fentanyl, methadone, and morphine). The incidence rates of hospitalization for serious infection were calculated per 100 person-years of current use of opioids with and without evidence of immunosuppression, as well as for each opioid type. A multivariable Poisson regression model was used to compare the current use of opioids based on previously reported immunosuppressive properties. Additionally, separate multivariable Poisson models were used to make individual comparisons of current use of each opioid (fentanyl, oxycodone, methadone, oxymorphone, and tramadol) versus current use of morphine as the common referent. In a pre-planned analysis, we

also further stratified current use based on new use (first 30 days after long-acting opioid initiation) and prevalent use (all current use not classified as new).[18,19]

In the regression models, we calculated incidence rate ratios [with 95% confidence intervals (CI)] using robust standard errors and accounting for 132 covariates using exposure propensity scores, calendar year of the episode, and restricted cubic splines of patient age and dose of the opioid (calculated as MME/day). The propensity score was calculated using probit regression models to determine the predicted probability of receiving non-immunosuppressive opioids relative to immunosuppressive opioids accounting for the duration of each episode of current use. For the assessment of individual opioids, a separate propensity score was calculated for each opioid relative to morphine. All available covariates were included in the propensity score calculation, except for age and calendar year, which were accounted for directly in the final outcome model. We visually explored the distributional overlap of the propensity score across treatment groups. Propensity scores were included as a covariate in each Poisson regression model using restricted cubic splines to relax the assumption of the correct specification of the covariate function form.[146-149]

In addition, we conducted a sensitivity analysis using inverse-probability of treatment weighting (IPTW) with the propensity score for each analysis to assess the robustness of our findings to a different covariate balancing strategy. As a part of this sensitivity analysis, we calculated standardized mean differences (SMD) between treatment groups with and without IPTW to assess the balance of individual covariates before and after weighting and accounting for the duration of each observed current use episode. An additional sensitivity analysis to assess the possibility of protopathic bias on the associations of interest (i.e., the possibility that opioid use was triggered by early manifestations of an infection) was also conducted by excluding

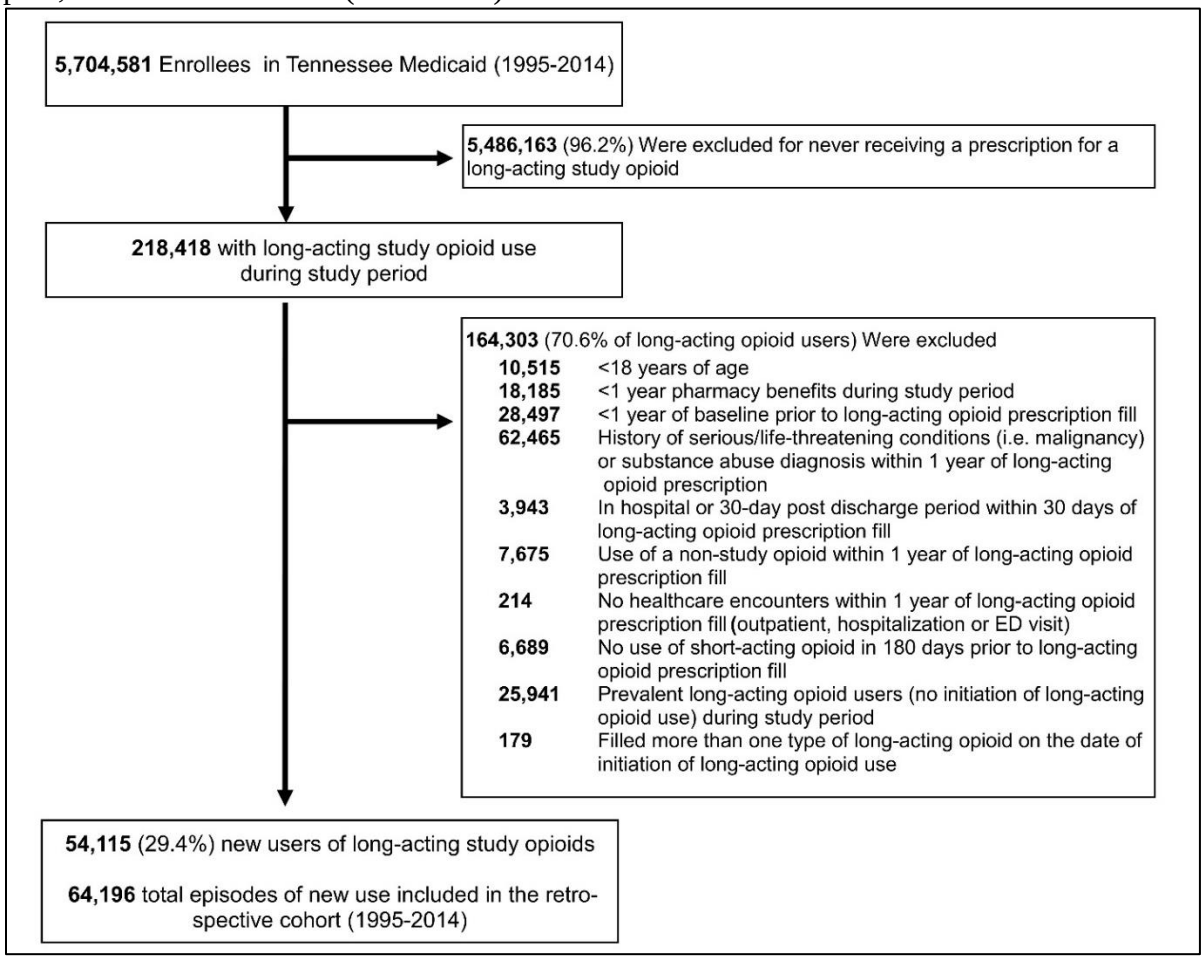
patients that developed an infection during the first four days following initiation of opioid use. Also, an exploratory analysis assessed for potential interaction between treatment groups and dose using the likelihood ratio test. Statistical analyses were performed using SAS version 9.4 (SAS Institute) and Stata Version 15.1 (StataCorp LP).

RESULTS

From 1995 to 2014, 54,115 patients contributing 64,196 new episodes of long-acting study opioid use were identified from an underlying retrospective cohort of 218,418 eligible TennCare enrollees (Figure 6.2). Major reasons for the exclusion of long-acting opioid users from the retrospective cohort were the presence of exclusionary criterion (28.6% of eligible enrollees due to serious/life-threatening conditions and substance abuse), less than 1 year of available baseline information (13.1%), less than 1 year of pharmacy eligibility prior to the long-acting opioid prescription fill (8.3%), a history of prevalent opioid use (11.9%), and for being <18 years of age (4.8%) [Figure 6.2].

We identified a total of 794 hospitalizations for serious infection among subjects in the retrospective cohort (n=494 during periods of current use). Hospitalization for pneumonia was the most commonly identified infection (55.3%), followed by cellulitis (19.9%), bacteremia (9.9%), pyelonephritis (9.2%), septic arthritis/osteomyelitis (5.0%) and meningitis/encephalitis (0.8%). No cases of endocarditis were identified in the retrospective cohort during the study period. Most individuals use of a long-acting opioid with previous evidence of immunosuppressive properties (n=46,870) relative to opioids without previous evidence of immunosuppressive properties (n=17,221).

Figure 6.2. Identifying a retrospective cohort of patients initiating long-acting opioids for chronic pain, Tennessee Medicaid (1995-2014)



A small number initiated other long-acting opioid types (n=105), including levorphanol and tapentadol. Individuals initiating immunosuppressive opioids were slightly older and more likely to be female (median age: 51 years; 63.8% female) compared to those initiating non-immunosuppressive opioids (median: 47 years; 60.8% female) [Table 6.1 and Appendix Table C4]. The distribution of the starting opioid dose was very similar between the two treatment groups (median dose: 60 MME/day in both groups).

The majority of patients initiated with long-acting morphine (47.9%), followed by oxycodone (19.5%), fentanyl (18.8%), methadone (6.4%), oxymorphone (4.6%), tramadol

(2.7%) and other opioids (0.2%) [Appendix Table C5]. Baseline characteristics of these patients differed according to opioid type. Of note, fentanyl users were older (median: 66 years) and more likely to be female (71.6%) compared to those using morphine (median age: 48 years; 61.4% female) [Appendix Table C5]. Tramadol users were also more likely to be female (73.7%) but were younger (median: 45 years) relative to morphine users (Appendix Table C5). Total follow-up was similar regardless of the type of long-acting opioid initiated (Appendix Table C6).

The most common pain indications were back pain and musculoskeletal pain, although neuropathic and trauma-related pain were also common [Table 6.1]. The most common comorbidities were essential hypertension, chronic bronchitis, diabetes, prior infections, and peripheral artery disease (Table 6.1). The most common medications used in the year before long-acting opioid initiation were hydrocodone, antibiotics, antidepressants, anticonvulsants, glucocorticoids, and non-steroidal anti-inflammatory drugs (Table 6.1). Indicators of frailty were relatively rare in the study population, except for ambulation devices (Table 6.1). No apparent differences in the reason for the end of follow-up were observed across opioid types, except that tramadol users were more likely to be censored due to 180 days without a subsequent long-acting opioid prescription (Appendix Table C7).

In the primary analysis, the propensity score model included 132 covariates, as drug overdose and hepatic disease were omitted for collinearity with other variables. The distribution of the propensity score had substantial overlap between the immunosuppressive and non-immunosuppressive opioid treatment groups (Appendix Figure C1). In the sensitivity analysis using IPTW with the propensity score, only very few and minor differences in covariates

remained after weighting, as all absolute standardized mean differences were less than 0.03 for covariates included in the propensity score model.

In pairwise comparisons, the distribution of the propensity score had some overlap for each opioid relative to morphine, except for tramadol (Appendix Figure C2). In the sensitivity analysis using IPTW, differences between those initiating with morphine and the other opioids were reduced in each of the pairwise comparisons, except tramadol (Appendix Table C8). Morphine and oxycodone users were the most comparable (SMD less than or equal to 0.01 for all covariates) treatment groups after weighting. Fentanyl users were different from morphine users, yet standardized differences were reduced after weighting (Appendix Table C8). Due to the low number of infections observed in tramadol users (n=2) and extreme differences at baseline between tramadol and morphine users, we did not compare tramadol to morphine users in the set of individual secondary analyses (although tramadol users were not excluded from the primary analysis).

A total of 794 hospitalizations for serious infections were identified during 39,784 person-years of follow-up (1.99 serious infections per 100 person-years). Of these, 496 infections were identified during periods of current opioid use (2.11 serious infections per 100 person-years) and 298 infections during periods of non-use (1.83 per 100 person-years). The majority of hospitalizations for serious infection were due to pneumonia (n=440; 55.3%), followed by cellulitis (19.9%), bacteremia without pneumonia (9.9%), pyelonephritis (9.2%) and septic arthritis/osteomyelitis (5.0%). Meningitis was rare (0.8%), and no cases of endocarditis were observed in the cohort.

The crude incidence rate was higher among those patients using immunosuppressive opioids compared to opioids without known immunosuppressive properties (Table 6.2).

Table 6.1. Baseline characteristics and standardized mean differences for selected variables by treatment group before and after inverse-probability treatment weighting using the propensity score

	Immunosuppressive N=46,870		Non-immunosuppressive N=17,221		Absolute standardized mean differences	
					Before weighting	After weighting
Selected comorbidities						
Chronic Bronchitis	6742	(14.4%)	2225	(12.9%)	0.02	0
Depression	3722	(7.9%)	1174	(6.8%)	0.05	0
Diabetes	6639	(14.2%)	2227	(12.9%)	0.02	0.01
Essential hypertension	13439	(28.7%)	4495	(26.1%)	0.03	0.01
Hemolytic anemia	107	(0.2%)	25	(0.1%)	0.01	0
Infections	17658	(37.7%)	6313	(36.7%)	0.04	0
Lipid disorders	4626	(9.9%)	1514	(8.8%)	0.03	0
Obesity	1568	(3.3%)	565	(3.3%)	0	0
Obstructive coronary artery disease	2735	(5.8%)	950	(5.5%)	0.01	0
Osteoporosis-related BMD testing	1905	(4.1%)	531	(3.1%)	0.07	0.01
Parkinson's Disease	2329	(5.0%)	708	(4.1%)	0.08	0
Peripheral artery disease	4993	(10.7%)	1647	(9.6%)	0.04	0
Peripheral neuropathy	2390	(5.1%)	783	(4.5%)	0.02	0
Seizures	1173	(2.5%)	379	(2.2%)	0.05	0
Sepsis/Bacteremia	225	(0.5%)	54	(0.3%)	0.04	0
Sickle-cell disease	98	(0.2%)	25	(0.1%)	0.01	0
Thyroid disease	1838	(3.9%)	581	(3.4%)	0.02	0
Tobacco use	1261	(2.7%)	497	(2.9%)	0.05	0
Pain indications						
Abdominal Pain	3270	(7.0%)	1214	(7.0%)	0	0
Arthritis/SLE	1346	(2.9%)	505	(2.9%)	0.02	0.01
Back pain	21715	(46.3%)	7071	(41.1%)	0.02	0.01
External causes of injury	1724	(3.7%)	735	(4.3%)	0	0
Headache	2126	(4.5%)	771	(4.5%)	0.02	0
Musculoskeletal Pain	17512	(37.4%)	6044	(35.1%)	-0.02	0.01
Neuropathic Pain	4695	(10.0%)	1491	(8.7%)	0.03	0
Pain Not Specified	2529	(5.4%)	963	(5.6%)	0.03	0
Trauma	5453	(11.6%)	2356	(13.7%)	0.04	0
Short-acting opioid use in prior 180 days						
Hydrocodone alone	17103	(36.5%)	5223	(30.3%)	0.16	0.01
Oxycodone alone	5845	(12.5%)	2918	(16.9%)	0.22	0
Other opioids alone	3552	(7.6%)	1327	(7.7%)	0.07	0
More than one short-acting opioid	20370	(43.5%)	7753	(45.0%)	0.03	0
Medication use history						
Angiotensin-converting enzyme inhibitor/angiotensin receptor blockers	16178	(34.5%)	5458	(31.7%)	0.04	0.01
Anti-arrhythmic	3486	(7.4%)	965	(5.6%)	0.09	0

	Immunosuppressive N=46,870		Non-immunosuppressive N=17,221		Absolute standardized mean differences	
					Before weighting	After weighting
Antibiotics	35782	(76.3%)	12902	(74.9%)	0.02	0
Anticonvulsants	18705	(39.9%)	5694	(33.1%)	0.15	0.01
Antidepressants	30523	(65.1%)	10286	(59.7%)	0.13	0.01
Antifungals	6531	(13.9%)	2236	(13.0%)	0.03	0
Antipsychotics	7466	(15.9%)	1954	(11.3%)	0.18	0
Beta-blockers	10083	(21.5%)	3335	(19.4%)	0.07	0
Bronchodilators, beta agonists	12243	(26.1%)	4295	(24.9%)	0.01	0.01
Bronchodilators, other	7078	(15.1%)	2180	(12.7%)	0.06	0
Calcium-channel blockers	8749	(18.7%)	2937	(17.1%)	0.05	0
Disease modifying anti-rheumatic drugs	983	(2.1%)	367	(2.1%)	0.02	0
Glucocorticoids	22953	(49.0%)	8033	(46.6%)	0.06	0.01
Hypoglycemic medications	7121	(15.2%)	2363	(13.7%)	0.04	0
Influenza vaccine	7657	(16.3%)	2378	(13.8%)	0.08	0
Loop diuretics	9039	(19.3%)	2710	(15.7%)	0.1	0.01
Minor tranquilizers/barbiturates	2048	(4.4%)	682	(4.0%)	0.02	0
Non-steroidal anti-inflammatory drugs	29480	(62.9%)	10878	(63.2%)	0.01	0
Other anti-hypertensives	3424	(7.3%)	1100	(6.4%)	0.06	0.01
Pneumococcal vaccine	1228	(2.6%)	383	(2.2%)	0	0.01
Proton Pump Inhibitors	16861	(36.0%)	5239	(30.4%)	0.11	0
Sedatives	7536	(16.1%)	2433	(14.1%)	0.05	0.01
Statins	11954	(25.5%)	3999	(23.2%)	0.03	0
Thyroid Hormones	5184	(11.1%)	1716	(10.0%)	0.04	0
Frailty markers						
Urinary tract infection	2437	(5.2%)	722	(4.2%)	0.09	0
Ambulation devices	3564	(7.6%)	1085	(6.3%)	0.05	0
Decubitus/pressure ulcers	1533	(3.3%)	417	(2.4%)	0.07	0
Incontinence	1295	(2.8%)	357	(2.1%)	0.08	0
Oxygen supplementation	2958	(6.3%)	895	(5.2%)	0.03	0.01
Rehabilitation	1570	(3.3%)	713	(4.1%)	0.03	0
Healthcare utilization						
Nursing facility setting	522	(1.5%)	98	(0.8%)	0.23	0
ED visits in prior year[1]						
0	13435	(39.2%)	4663	(38.2%)	0	0.01
1	8375	(24.5%)	2882	(23.6%)	0.02	0.02
2	4447	(13.0%)	1658	(13.6%)	0.04	0.03
$\geq$ 3	7982	(23.3%)	3003	(24.6%)	0.01	0.02
Hospitalizations in past year[1]						
0	26805	(78.3%)	9693	(79.4%)	0.07	0
1	6696	(19.6%)	2266	(18.6%)	0.07	0
$\geq$ 2	738	(2.2%)	247	(2.0%)	0.02	0.01
Demographics						

	Immunosuppressive N=46,870		Non-immunosuppressive N=17,221		Absolute standardized mean differences	
					Before weighting	After weighting
Sex						
Male	16947	(36.2%)	6757	(39.2%)	0.14	0
Female	29923	(63.8%)	10464	(60.8%)	0.14	0
Race						
White	37771	(80.6%)	13874	(80.6%)	0.02	0
Black/Other	9099	(19.4%)	3347	(19.4%)	0.02	0
Demographics (not included in the propensity score calculation)						
Year of cohort entry[2]						
1995	202	(0.4%)	0	(0.0%)	0.05	0.06
1996	271	(0.6%)	17	(0.1%)	0.07	0.08
1997	436	(0.9%)	39	(0.2%)	0.09	0.11
1998	791	(1.7%)	156	(0.9%)	0.1	0.12
1999	1333	(2.8%)	383	(2.2%)	-0.12	0.14
2000	2130	(4.5%)	1726	(10.0%)	0.01	0.01
2001	2869	(6.1%)	2380	(13.8%)	0.26	0.23
2002	3930	(8.4%)	1657	(9.6%)	0.2	0.19
2003	4839	(10.3%)	1592	(9.2%)	0.08	0.09
2004	5725	(12.2%)	815	(4.7%)	0.13	0.11
2005	4307	(9.2%)	817	(4.7%)	0.14	0.11
2006	2882	(6.1%)	1009	(5.9%)	0.09	0.07
2007	2625	(5.6%)	1005	(5.8%)	0.08	0.07
2008	2338	(5.0%)	989	(5.7%)	0.05	0.04
2009	2078	(4.4%)	1133	(6.6%)	0.01	0.04
2010	1995	(4.3%)	837	(4.9%)	0.05	0.08
2011	1997	(4.3%)	480	(2.8%)	0.01	0
2012	2395	(5.1%)	550	(3.2%)	0.07	0.1
2013	2065	(4.4%)	907	(5.3%)	0.01	0.05
2014	1662	(3.5%)	729	(4.2%)	0.03	0.02
Age[3]						
<30	2772	(5.9%)	1607	(9.3%)	0.08	0.03
30-<40	8286	(17.7%)	3484	(20.2%)	0.09	0.02
40-<50	12204	(26.0%)	4552	(26.4%)	0.04	0.02
50-<60	10475	(22.3%)	3711	(21.5%)	0.01	0.01
60-<70	6139	(13.1%)	2333	(13.5%)	0.03	0.04
70-<80	3280	(7.0%)	954	(5.5%)	0.07	0.01
≥ 80	3714	(7.9%)	580	(3.4%)	0.27	0.09

[1]Included in the propensity score calculation as a continuous variable

[2]Not included in the propensity score calculation as accounted for in the final analysis model using indicator variables

[3]Not included in the propensity score calculation as accounted for in final analysis model using cubic splines. Note: age groups are presented in the table for ease of interpretation.

Table 6.2. Crude and adjusted incidence rate ratios (IRR) for serious infections by immunosuppressive properties of the long-acting opioid among Tennessee Medicaid enrollees (1995-2014)

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)1	IPTW-Adjusted IRR (95% CI)2
Previously described immunosuppressive properties					
Immunosuppressive[3]	404	2.33	1.00 (reference)	1.00 (reference)	1.00 (reference)
Non-immunosuppressive[4]	92	1.48	0.64 (0.51, 0.80)	0.79 (0.62, 0.998)	0.78 (0.61, 0.99)

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

[2]Adjusted for cubic spline of the cumulative dose, cubic spline of age, calendar year and using inverse-probability of treatment weighting with the propensity score for treatment with non-immunosuppressive opioids

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

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

In the adjusted analysis accounting for the baseline propensity score for treatment, dose, and age and calendar year of the episode, the current use of non-immunosuppressive opioids was associated with a significantly lower rate of serious infections compared to immunosuppressive opioids [IRR: 0.79 (95% CI: 0.62, 0.998)]. Results were similar when using IPTW with the propensity score (Table 6.2). The model including interaction terms between dose and type of opioid received (immunosuppressive versus non-immunosuppressive) was not significantly different from the model without interaction terms (likelihood ratio test chi-square: 2.30; p = 0.13). The rate of infection was also highest in the first 30 days after long-acting opioid initiation [IRR: 2.06 (95% CI: 1.68, 2.53)] compared to prevalent use.

The crude incidence rate of serious infection was highest among fentanyl users and lowest among tramadol users (Table 6.3). In the adjusted analyses accounting for the baseline propensity score, dose, age, and calendar year of the episode, the rate during periods of current fentanyl and methadone (both immunosuppressive) use compared to current morphine was not significantly different [IRR: 0.90 (95% CI: 0.68, 1.21) and IRR: 1.02 (95% CI: 0.67, 1.53)] [Table 6.3]. Oxycodone (non-immunosuppressive) users had a significantly lower rate of infections compared to morphine (immunosuppressive) users [IRR: 0.69 (95% CI: 0.52, 0.92)] [Table 6.3]. However, a non-significant increased rate of infections was observed among oxymorphone users compared to morphine users (Table 6.3). The results were similar in the analysis using IPTW with the propensity score (Table 6.3).

In the sensitivity analysis excluding 24 patients that developed an infection within four days after long-acting opioid initiation, the results were similar for the primary comparison of non-immunosuppressive opioids versus immunosuppressive opioids [IRR: 0.78 (95% CI: 0.62,

1.00)]. The IRR when comparing new use to prevalent use when excluding these patients was 1.72 (95% CI: 1.38, 2.14).

CONCLUSIONS

Among patients initiating long-acting opioid analgesic use, we report a lower risk of infections associated with the use of prescribed opioids without previously reported immunosuppressive properties compared to the use of opioids with previously reported immunosuppressive properties. The association was independent of baseline covariates at the time of long-acting opioid initiation, age, and the dose of the prescribed opioid. Furthermore, no differences were observed among opioids previously described as immunosuppressive, while oxycodone users had a significantly lower risk of hospitalization for serious infection relative to morphine users.

Experimental evidence has shown that morphine, and other opioids with a similar chemical structure (i.e., fentanyl, methadone), have immunosuppressive properties.[14,37,49] In similar experimental studies, however, certain opioids have not exhibited the same immunosuppressive properties, including oxycodone, oxymorphone, and tramadol. Although some studies have reported an increased risk of infection associated with prescription opioid use among humans, few have been able to distinguish if the association differs based on different properties of the opioid.[18-20,28,29] In one such study among cancer patients, those with infections (confirmed through the diagnosis of infection, positive laboratory result and administration of an antibiotic) were more likely to have received morphine (immunosuppressive) relative to oxycodone (non-immunosuppressive) [OR: 3.60 (95% (CI: 1.40-9.26)].[150]

Table 6.3. Crude and adjusted incidence rate ratios (IRR) for serious infections by individual opioids among Tennessee Medicaid enrollees (1995-2014)

Opioid Type	Infections during current use (n)	Incidence per 100 person-years of current use	Crude IRR (95% CI)	Spline-Adjusted IRR[1] (95% CI)	IPTW-Adjusted IRR[2] (95% CI)
Opioids with previously recognized immunosuppressive properties					
Morphine	219	1.80	1.00 (reference)	1.00 (reference)	1.00 (reference)
Fentanyl	154	4.23	2.35 (1.91, 2.89)	0.90 (0.68, 1.21)	0.80 (0.59, 1.07)
Methadone	31	2.09	1.16 (0.80, 1.69)	1.02 (0.67, 1.53)	0.98 (0.65, 1.48)
Opioids without previously recognized immunosuppressive properties					
Oxycodone	78	1.68	0.94 (0.72, 1.21)	0.69 (0.52, 0.92)	0.69 (0.51, 0.92)
Oxymorphone	12	0.94	0.52 (0.29, 0.94)	1.85 (0.93, 3.69)	2.02 (0.80, 5.11)

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

[2]Adjusted for cubic spline of the cumulative dose, cubic spline of age, calendar year (two-year intervals) and using inverse-probability of treatment weighting with the propensity score for treatment with each opioid

However, in a recent retrospective study of 303 patients with advanced cancer using only a single opioid type, no difference in the risk of microbiologically and clinically-confirmed infections was reported between oxycodone (no evidence of immunosuppression) and morphine or fentanyl (opioids with known immunosuppressive properties).[20] Of note, these previous studies were limited to hospitalized patients or patients with cancer receiving very high opioid doses in the healthcare setting. Few studies have examined this association in the outpatient or community setting.

In one such study among community-dwelling older adults, a stronger association was observed between pneumonia and immunosuppressive opioid use compared to non-use [OR: 1.88 (95% CI: 1.26, 2.79)] relative to non-immunosuppressive opioid use compared to non-use [OR: 1.23 (95% CI: 0.89, 1.69)]. In a self-controlled case series among patients with rheumatoid arthritis, the association between opioid use and serious infections was stronger for periods of immunosuppressive opioid use [IRR: 1.72 (95% CI: 1.33, 2.23)] than non-immunosuppressive opioid use [IRR: 1.37 (95% CI: 1.15, 1.62)] relative to non-use. Our study finding that the risk of hospitalization for serious infection was 0.79 times lower (95% CI: 0.62, 0.998) among those initiating long-acting opioids without immunosuppressive properties compared to those with immunosuppressive properties is consistent with the findings of these previous studies. Furthermore, the rate of serious infections was lowest among oxycodone users relative to morphine users, providing further evidence that opioids with known immunosuppressive properties are associated with an increased risk of infection.

A strength of this study was the use of validated definitions for identifying hospitalizations for serious infection using administrative data in the TennCare population. In the previous chapter, these codes were shown to have a high positive predictive value (90.2%).

This reduces the impact of any non-differential disease misclassification on our estimates of the incidence rate ratios.[88,89] In addition, the new user design applied in this study helps ensure comparability of the study groups and allows the detection of events that occurred following the initiation of use.[151]

An important limitation of our study was that prescription opioid use was defined based on filled pharmacy prescription fills. Since actual use was not observed, it is possible patients did not complete their full prescription or did not take their medications exactly as prescribed. To account for this misclassification, we classified intervals covered by prescription days of supply as current use (representing the highest likelihood of prescription opioid exposure), while all other person-time was classified as non-use. Although we excluded patients with a substance or alcohol abuse disorder, a similar limitation was our inability to account for illicit opioid use (including heroin) and those that misuse/divert their opioid prescriptions. We were also unable to incorporate time-varying covariates into the analysis, including the use of short-acting opioid formulations (some of which are also known to have previously recognized immunosuppressive properties. This limitation meant that we might not have been appropriately accounting for changes among patients during follow-up that could impact their likelihood of opioid use or of developing a serious infection. The relatively short amount of follow-up in the study (median: 189 days of follow-up) and low number of infections identified during current use periods (n=496) reduced the power of the study to assess the association within important sub-groups, as well to assess any interaction between individual opioids and dose in the risk of developing a serious infection. Although the use of an active comparator group limits the possibility of confounding by indication, and the use of propensity scores helps to balance out any differences in baseline covariates between the two treatment groups, we also cannot rule out the possibility

of residual confounding. Additionally, the pre-planned sensitivity analysis excluding individuals with infections in 4 or less days after long-acting opioid initiation provided evidence that the observed association could not be explained by potential protopathic bias.

Our study findings indicate that the risk of serious infections is greater among those individuals initiating long-acting opioids with known immunosuppressive properties compared to those without immunosuppressive properties. These differences existed independent of dose or baseline differences in patients at the time of opioid initiation. Individually, oxycodone, an opioid without known immunosuppressive properties, was shown to have a significantly lower rate of infections relative to morphine (the most commonly used long-acting opioid during the study period).

As opioid analgesic use is likely to remain high in the future, its potential impact on the risk of serious infections is of great clinical importance, especially among older populations and those susceptible to an increased risk of infection. Therefore, understanding which specific opioid formulations are problematic is of particular interest to help clinicians and patients make well-informed pain management decisions.

In conclusion, patients using immunosuppressive opioids had a higher risk of serious infections compared with those using non-immunosuppressive opioids. In addition, patients using oxycodone had a significantly lower risk of serious infection compared with those using morphine. These findings are consistent with results from animal and *in-vitro* experimental studies showing immunosuppressive properties only in certain opioids, and provide further evidence of the role of opioid-induced immunosuppression in the development of serious infections among humans.

CHAPTER 7

SUMMARY AND FUTURE DIRECTIONS

Opioid analgesic use is associated with an increased risk for serious infection. The association was observed for both specific laboratory-confirmed IPD and hospitalizations for serious infection identified using validated discharge diagnosis codes. The association was strongest for the use of long-acting and high potency formulations, formulations previously described as immunosuppressive, and high dose opioids. Among those using long-acting opioids, opioids with previously recognized immunosuppressive properties were associated with a higher risk of hospitalization for serious infection compared to long-acting opioids without known immunosuppressive properties.

This observed association between opioid analgesic use and the risk of IPD and other serious infections complements the current experimental evidence from *in-vitro* and animal studies that certain opioids induce immunosuppression and increase vulnerability to infection.[14,34,49] Specifically, the immunosuppressive properties of morphine, fentanyl, and codeine are well recognized (immunosuppressive effects of methadone have been also suggested based on chemical structure and known affinity for immune cell receptors).[14,34,49] Yet other opioids examined in similar *in-vitro* and animal experimental studies have not been shown to induce the same immunosuppression (specifically oxycodone, oxymorphone, and tramadol).[14,34,37,49] The hypothesized reason for this difference is due to the presence of a carbon double bond in immunosuppressive opioids for which a single bond and carbonyl substitution are found in non-immunosuppressive opioids.[12] This difference in chemical structure is thought to impact how each type of opioid interacts with the immune system. Immunosuppressive opioids

increase susceptibility to infection by reducing the activity of lymphocytes, natural killer cells, and macrophages, as well as by impairing T-cell activity through a reduction in cytokine production.[14,56]

The results of our study provide further evidence for the association between opioid analgesic use and the risk of serious infections, but also support the findings in these prior studies that the association differs based on characteristics of the opioid. Specifically, we found that opioids with known immunosuppressive properties, long-acting and high potency opioids, and opioids at high doses had the strongest association with developing IPD. Further, using validated discharge diagnosis codes to identify serious infections, we found that among individuals initiating long-acting opioids, the rate of serious infection was higher for those using immunosuppressive opioids compared to non-immunosuppressive opioids, independent of dose and other baseline factors.

Our studies also complement the limited existing evidence provied by previous studies. Some previous studies only involved hospitalized patients or patients with cancer, for which risk factors for infection are numerous and for which etiology can be difficult to determine.[20,28,29,150] The few that have examined community-acquired infections were limited to community-dwelling older adults in a single healthcare system and patients with rheumatoid arthritis (known high-risk groups for developing infections and likely to have an increased level of opioid use compared to the general population).[18,19] Although our study was limited to patients enrolled in TennCare, we examined the association among all adults $\geq$18 years of age and among a large retrospective cohort of enrollees to ensure our findings could be generalizable to other populations (Chapter 6).

A major strength of each of these studies was that the analyses accounted for a substantial number of relevant covariates to reduce the possibility of confounding. In chapter 4, we accounted for all known risk factors for IPD in the regression model, as well as included an infection risk score to account for baseline differences in the risk of IPD among opioid users and non-opioid users (analogous to propensity score adjustment). We also conducted a sensitivity analysis to show that it was unlikely that an unmeasured confounder could explain the entirety of the observed association. In chapter 6, we used a propensity score strategy to balance the distribution of 124 covariates identified at baseline between the exposure groups of interest. We then used two different methods (i.e., including the propensity score as a cubic spline in the Poisson regression model and IPTW using the propensity score) to assess the robustness of our findings.

Another strength of our study was the use of highly specific infection definitions to limit misclassification of the outcome. In chapter 4, we identified laboratory-confirmed IPD cases by linking a retrospective cohort of TennCare enrollees to the existing ABCs system. This linkage likely minimized misclassification, as the specificity of laboratory-confirmed IPD identified in the ABCs system is very high. As IPD is a prototypical community-acquired infection, another benefit was that we reduced the likelihood that the etiology of infection was related to recent hospitalization or IV drug use, which could be associated with prescription opioid use. In addition, in chapters 5, we conducted an extensive validation process to determine that coding algorithms for identifying several different kinds of infections had a high PPV and that the PPV was consistent across different types of hospitals in Tennessee. These validated algorithms were then used to identify outcomes in chapter 6 to ensure that we limited any misclassification of the outcome.

There are also several limitations to consider in each of these studies. The first is that although we used specific selection criteria to identify our population, used laboratory-confirmed or validated definitions for infections, accounted for a large number of covariates in each study, and used sensitivity analyses to identify potential sources of bias or confounding, we are unable to rule out the possibility of residual confounding completely. However, evidence from randomized trials is very limited and as it is unlikely that new large randomized studies will be specifically designed to answer our specific research questions, the use of well-designed observational study designs is a viable strategy to address these important questions about the safety of commonly used opioid analgesics.

Another important limitation was the use of pharmacy prescriptions fills to identify exposures to prescription opioid analgesics. Although previous studies have shown high concordance between prescription fill data and use of other medications, actual use of the opioid prescriptions was not observed.[152,153] However, we did identify each person-day of current opioid use based on prescription fill date and days of supply and classified any period without an active prescription as recent or non-use. These classifications ensured that current use represented the period the patient had the highest likelihood of exposure to prescription opioid analgesics. Unfortunately, we were unable to account for potential diversion and illicit opioid use in our study. To address this limitation, we either accounted for a diagnosis of alcohol or substance abuse in our analysis (Aim 1) or excluded individuals with a substance abuse diagnosis from the analysis (Aim 3). These strategies minimized the possibility that diversion or illicit opioid use in the study population might bias our results, but cannot completely rule out exposure misclassification related to this issue.

Finally, we had limited statistical power to explore potentially important interactions and sub-group analyses in the association between opioid use and the risk of serious infections. In chapter 4, laboratory-confirmed IPD was a relatively rare disease and this limited our ability to make individual opioid comparisons. In chapter 6, the sample size was relatively small due to the low-level of long-acting opioid use, as well as the new user design and strict selection criteria. This precluded our ability to examine the association of interest in specific high-risk groups or stratified by infection type.

Future directions

Although the evidence suggests that prescription opioid use is a clinically important risk factor for serious infections, additional questions remain. Specifically, future studies will need to assess whether the risk of infection could be modified by the concomitant use of medications that may impact the metabolism of opioids. Additionally, it would be useful to study whether the observed association varies among patients with certain comorbidities that may lead to high levels of circulating opioids after ingestion (e.g., patients with declines in liver or renal function).

The results of each of these subsequent studies would help to inform prescribing and pain management practices among providers and patients by identifying opioid exposures or specific formulations that are associated with an increased risk of infection. Identifying potentially problematic opioid formulations would be of particular clinical importance and interest to individuals already at high-risk for serious infection.

Summary

Opioid analgesic use is associated with an increased risk of serious infections. The association was strongest among long-acting opioids, high potency opioids, opioid given at high doses, and among opioids with previously recognized immunosuppressive properties. The higher

risk of serious infections associated with immunosuppressive opioids (such as morphine) compared to non-immunosuppressive opioids (such as oxycodone) supports the existing experimental evidence derived from animal models and *in-vitro* studies. Opioid analgesic use, especially use of opioids with previously recognized immunosuppressive properties, represents a novel, independent and clinically important risk factor for serious infections.

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APPENDIX A - CHAPTER 4 APPENDIX

Appendix Table A1. Study Opioid Classifications[1]

	Potency	Duration of Action	Immunosuppressive	MME Dose[2]
Short-acting, Less Potent				
Propoxyphene[3]	Medium	Short-Acting	Unknown	0.23
Codeine[4]	Medium	Short-Acting	Yes	0.15
Hydrocodone[4]	Medium	Short-Acting	No	1.0
Tramado1 (immediate release)	Medium	Short-Acting	No	0.10
Butalbital/codeine[3]	Medium	Short-Acting	Yes	0.15
Dihydrocodeine	Medium	Short-Acting	Yes	0.25
Pentazocine[3]	Medium	Short-Acting	No	0.37
Tapentadol (immediate release)	Medium	Short-Acting	Unknown	0.40
Short-Acting, More Potent				
Morphine sulfate	High	Short-Acting	Yes	1.0
Codeine sulfate	High	Short-Acting	Yes	0.15
Oxycodone[3]	High	Short-Acting	No	1.5
Hydromorphone (immediate release)	High	Short-Acting	No	4.0
Meperidine hydrochloride[3]	High	Short-Acting	Unknown	0.1
Fentanyl (transmucosal)[5]	High	Short-Acting	Yes	125
Oxymorphone (immediate release)	High	Short-Acting	No	3.0
Long-acting				
Hydrocodone (extended release)	High	Long-Acting	No	1.0
Levorphanol	High	Long-Acting	Unknown	11.0
Tapentadol (extended release)	High	Long-Acting	No	0.40
Tramadol (extended release)	High	Long-Acting	No	0.1
Morphine sulfate (sustained release)	High	Long-Acting	Yes	1.0
Oxycodone controlled release	High	Long-Acting	No	1.5
Methadone	High	Long-Acting	Yes	3.0
Fentanyl (transdermal)[6]	High	Long-Acting	Yes	2.4
Oxymorphone (extended release)	High	Long-Acting	No	3.0
Hydromorphone (extended release)	High	Long-Acting	No	4.0

[1]Opioid characteristics were defined based on previous literature and classifications used in earlier studies[1-4]
[2]Morphine milligram equivalent (MME) conversion per mg of opioid, with conversion factors based on classifications used in earlier studies[1-4]
[3]Alone or in combination
[4]In combination
[5]The conversion factor to milligram morphine equivalents for transmucosal fentanyl assumes that the measurement of opioid strength is measured as milligrams per oral dose, and it assumes 50% bioavailability of transmucosal fentanyl (e.g., 0.100 grams transmucosal fentanyl is equivalent to 12.5 to 15 mg of oral morphine)[1]
[6]The conversion factor to milligram morphine equivalents for transdermal fentanyl assumes that the measurement of opioid strength is measured as micrograms per hours and assumes each patch remains in place for three days (e.g., 25 micrograms transdermal fentanyl/hour is equivalent to 60mg of oral daily morphine)[1]

Appendix Table A2. Covariates assessed in the 365-day period preceding the index date

Variable	Condition
Risk Factors for IPD	Alcohol and substance abuse/dependence, Cardiovascular disease (AMI, cardiac valve disease, heart failure, cardiomyopathy, cor pulmonale, congenital heart anomalies, obstructive coronary artery), Chronic lung disease (chronic obstructive pulmonary disease, asthma, pneumoconiosis, cystic fibrosis), Immune disorders or organ transplantation, Diabetes (including nephropathy, neuropathy, retinopathy, circulatory, ulcers, amputations other general complications not captured elsewhere), Smoking status (tobacco-related diagnosis), Serious hepatic disease, End-stage renal disease and/or hemodialysis, HIV, Malignancy (excluding non-melanoma skin cancer and carcinoma in situ), Sickle cell disease, Nursing home stay in 30 days prior to index date, Pneumococcal vaccination (polysaccharide) history in 365 days prior to index date, Number of emergency department visits in 365 days prior to index date, Number of outpatient office visits in 365 days prior to index date, Number of hospitalizations in 365 days prior to index date
Other conditions	Acute renal failure /chronic kidney disease (through Stage IV), Alterations of consciousness, Arrhythmias & conduction disorders, Atrial fibrillation/flutter, Autonomic neuropathy, Bipolar disorder, Cerebral palsy, Bronchiectasis, Dementia, Depression, Drug adverse events during therapeutic use, Drug poisoning (accidental), Drug poisoning/overdose (opioids, sedatives, psychotropic, stimulants), essential hypertension (includes hypertensive heart/renal disease and secondary hypertension), Lipid disorders, Mental retardation/intellect disability, Multiple sclerosis, Multiple system atrophy, Nephritis/acute nephritis/nephrotic syndrome, Nephritis/chronic nephritis, Obesity, Osteomyelitis, Osteoporosis, Other cerebrovascular disease/late effects of cerebrovascular diseases, Pacemaker/cardiac defibrillator, Parkinson's disease and related disorders, Peripheral artery disease and related factors, Peripheral neuropathy, Personality disorders, Pneumonia, Post-traumatic stress disorder, Pregnancy/delivery/puerperium-related events, Pulmonary embolism/infarction /phlebitis/thrombophlebitis (includes superficial), Respiratory failure/cardiorespiratory failure/pulmonary heart disease, Schizophrenia/delusional disorders, Seizures (includes febrile), Sepsis, Bacteremia, Viremia, Stroke/hemiplegia/other late effects, Thyroid disease, Transient ischemic attack, Urinary tract /kidney infection (includes acute cystitis)
Frailty Surrogates	Ambulation devices, Use of continuous positive airway pressure, Use of bi-level positive airway pressure, Debility, Cachexia/malnutrition/muscle-wasting/abnormal weight loss, Decubitus, pressure ulcers - related care equipment - including hospital beds, enteral & parenteral nutrition, Impaired mobility, Incontinence, Oxygen supplementation, Rehabilitation, Fitting & adjustment of prosthesis-devices, Physical therapy
Demographics	Sex (male or female), Race (White, Black and Other)
Acute and chronic pain conditions	Abdominal pain, Any infection associated with pain, Back pain, Dental Pain, External causes of Injury, Trauma, Headache, Musculoskeletal pain, Pain not otherwise specified (including psychogenic), Neuropathic pain
Medication Use	Influenza vaccine, Antiarrhythmics, Angiotensin-converting enzyme inhibitor (alone or in combination), Angiotensin receptor blocks (alone or in combination), Anticoagulants, Antibiotics, Antifungals, Aspirin, Non-aspirin antiplatelet agents, Beta-blockers alone or in combination, Digoxin and other inotropic agents, Statins, Other lipid-lowering agents, Loop diuretics, Thiazide and other diuretics alone or in combination, Nitrates, Other antihypertensives, Pentoxifylline or vasodilators, Hypoglycemic medications (non-insulin), Insulin, Thyroid hormones, Bronchodilators (beta-agonist), Bronchodilators (other), Proton pump inhibitors, Nonsteroidal anti-inflammatory drugs, Glucocorticoids, Antidepressants, Antipsychotics, Benzodiazepines, Sedatives, Lithium, Minor tranquilizers and barbiturates, Anticonvulsants, Dementia drugs, Attention-deficit/hyperactivity medication, Alcohol aversion agents, Disease-modifying anti-rheumatic drugs, Smoking cessation products

Calculation of IPD risk score

The IPD risk score, defined as the predicted probability of invasive pneumococcal disease (IPD) was calculated using a logistic regression model among cases and controls that were non-current opioid users (i.e., remote, past and recent opioid users). The model initially included 106 variables including demographic information, the presence of conditions in the 365 days preceding the index date (comorbidities and surrogates of frailty), and the use of certain medications in the 365 days preceding the index date (see Appendix Table A2). Well-recognized risk factors for IPD were not included in the infection risk score model, but those relevant factors were accounted for directly in the final model, which also included exposures and the IPD risk score deciles (see below).

Three variables were automatically dropped from the initial model as there were no IPD cases with those conditions identified (i.e. predicted the outcome perfectly). Overall, the number of subjects with those conditions was very small (multiple sclerosis, personality disorders, and multiple system atrophy). No multicollinearity issues were identified. The results from the final IPD risk score including 103 variables are outlined in Appendix Table A3.

Using the coefficients from the logistic regression model predicting IPD among all non-current opioid users we then calculated the predicted probability of IPD (i.e., the IPD risk score) for all subjects in the study population. We then created 10 mutually exclusive categories based on the decile distribution of the IPD risk score among the entire study population.

The results from a conditional logistic regression model with IPD as the outcome and including the main exposure variable, all well-recognized risk factors for IPD and the categorical infection risk score (deciles) as covariates are presented in Appendix Table A4.

Appendix Table A3. IPD risk score model. Adjusted Odds Ratios (aOR) for Laboratory-Confirmed Invasive pneumococcal disease (IPD) in a logistic regression model excluding all well-recognized risk factors for IPD, among non-current opioid users, Tennessee Medicaid (1995-2014) [n=21,800]

Covariate	aOR*	95% CI†
Comorbidities‡		
Acute renal failure / chronic kidney disease (through stage IV)	1.57	(1.12 to 2.19)
Alterations of consciousness	1.19	(0.46 to 3.10)
Arrhythmias & conduction disorders	1.03	(0.69 to 1.53)
Atrial fibrillation/flutter	1.29	(0.76 to 2.18)
Autonomic neuropathy	0.42	(0.05 to 3.42)
Bipolar disorder	0.65	(0.37 to 1.14)
Carotid revascularization	0.79	(0.10 to 6.58)
Cerebral palsy	0.78	(0.15 to 3.94)
Dementia	0.43	(0.23 to 0.82)
Depression	1.16	(0.87 to 1.54)
Drug adverse events during therapeutic use	1.23	(0.82 to 1.85)
Drug poisoning (accidental)	0.44	(0.09 to 2.08)
Drug poisoning (other drugs)	3.08	(1.18 to 8.09)
Drug poisoning/overdose (opioids, sedatives, psychotropic, stimulants)	0.63	(0.20 to 2.00)
Essential hypertension	1.18	(0.97 to 1.44)
Lipid disorders	0.73	(0.53 to 0.99)
Mental retardation/intellect disability	0.50	(0.18 to 1.41)
Nephritis, acute nephritis & nephrotic syndrome	0.92	(0.25 to 3.32)
Nephritis / chronic nephritis	1.05	(0.46 to 2.41)
Obesity	0.57	(0.38 to 0.86)
Bariatric surgery	4.74	(0.99 to 22.74)
Osteoporosis-related bone mass density testing	0.47	(0.22 to 1.04)
Osteomyelitis	0.28	(0.06 to 1.33)
Osteoporosis	0.49	(0.23 to 1.04)
Other cerebrovascular diseases, late effects of cerebrovascular diseases	1.05	(0.56 to 1.99)
Pacemaker / cardiac defibrillator	1.58	(0.97 to 2.58)
Parkinson's disease and related disorders	0.75	(0.49 to 1.15)
Peripheral artery disease and related factors	1.49	(1.23 to 1.82)
Peripheral neuropathy	1.23	(0.63 to 2.40)
Pneumonia	4.20	(3.23 to 5.46)
Infections	1.84	(1.49 to 2.26)
Amputations	0.81	(0.36 to 1.79)
Post-traumatic stress disorder	1.60	(0.53 to 4.81)
Pulmonary embolism, infarction, phlebitis, thrombophlebitis	0.79	(0.44 to 1.45)
Respiratory failure / cardiorespiratory failure / pulmonary heart disease	1.65	(1.18 to 2.29)
Schizophrenia/ delusional disorders	1.15	(0.71 to 1.87)
Seizures (includes febrile)	1.28	(0.89 to 1.85)
Sepsis/bacteremia/viremia	3.39	(2.43 to 4.72)
Stroke / hemiplegia & other late effects	0.81	(0.48 to 1.39)
Thyroid disease	1.09	(0.70 to 1.71)
Transient ischemic attack	0.64	(0.19 to 2.13)
Urinary tract / kidney infection (includes acute cystitis)	0.78	(0.58 to 1.05)
Pregnancy, delivery & puerperium related events	0.69	(0.43 to 1.10)
Frailty Surrogates‡		
Ambulation devices	1.16	(0.87 to 1.55)
Use of continuous positive or bi-level positive airway pressure,	0.65	(0.37 to 1.15)
Debility, cachexia/malnutrition, muscle wasting, abnormal weight loss	1.32	(0.94 to 1.87)
Decubitus/pressure ulcers / related care equipment	0.93	(0.63 to 1.38)
Enteral & Parenteral nutrition	0.76	(0.48 to 1.22)
Impaired mobility	0.11	(0.02 to 0.48)
Incontinence	1.21	(0.79 to 1.85)

Covariate	aOR*	95% CI†
Oxygen supplementation	1.46	(1.09 to 1.96)
Rehabilitation, fitting/adjustment of prosthesis, physical therapy	0.90	(0.63 to 1.28)
Hospice care	0.69	(0.13 to 3.55)
Pain Control Indications‡		
Abdominal pain§	0.97	(0.79 to 1.20)
Any infection that may be associated with pain	0.78	(0.61 to 1.00)
Back pain	1.10	(0.86 to 1.41)
Dental pain	1.83	(1.13 to 2.95)
External causes of injury‖	1.35	(0.91 to 2.00)
External causes of injury: self- inflicted, including suicide attempts	2.44	(0.79 to 7.58)
Trauma and other injuries¶	0.86	(0.62 to 1.18)
Headache	0.84	(0.57 to 1.24)
Musculoskeletal pain**	0.80	(0.65 to 0.97)
Pain, not specified, including psychogenic	0.98	(0.74 to 1.28)
Arthritis pain††	1.58	(1.08 to 2.31)
Neuropathic pain	1.02	(0.59 to 1.79)
Medication Use‡		
Influenza vaccine	1.16	(0.94 to 1.44)
Anti-arrhythmics	0.94	(0.63 to 1.42)
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocks	0.94	(0.78 to 1.14)
Anticoagulants	0.77	(0.56 to 1.07)
Antibiotics (focused on bacterial pathogens only)	1.25	(1.05 to 1.49)
Antifungals	1.26	(1.02 to 1.56)
Aspirin	1.11	(0.84 to 1.46)
Non-aspirin anti-platelet agents	1.11	(0.80 to 1.53)
Beta-blockers alone or in combination	0.93	(0.75 to 1.14)
Calcium-channel blockers alone or in combination	0.85	(0.70 to 1.04)
Digoxin and other inotropic agents	1.11	(0.79 to 1.56)
Statins	0.64	(0.51 to 0.82)
Other lipid-lowering agents	1.09	(0.78 to 1.54)
Loop diuretics	1.41	(1.14 to 1.73)
Thiazide and other diuretics, alone or in combination	0.78	(0.64 to 0.96)
Nitrates	1.01	(0.77 to 1.31)
Other antihypertensives	1.12	(0.88 to 1.43)
Pentoxifylline / vasodilators	1.71	(0.89 to 3.29)
Hypoglycemic medications, non-insulin	0.93	(0.74 to 1.17)
Insulin	0.94	(0.72 to 1.22)
Thyroid hormones	0.76	(0.53 to 1.09)
Bronchodilators, beta agonists	1.23	(1.02 to 1.49)
Bronchodilators, others	1.19	(0.94 to 1.50)
Proton Pump Inhibitors	0.93	(0.76 to 1.14)
Non-steroidal anti-inflammatory drugs	0.98	(0.84 to 1.14)
Glucocorticoids	1.11	(0.93 to 1.33)
Antidepressants	1.16	(0.98 to 1.38)
Anti-psychotics	1.10	(0.86 to 1.42)
Benzodiazepines	0.79	(0.64 to 0.98)
Sedatives	1.01	(0.70 to 1.46)
Lithium	1.07	(0.55 to 2.05)
Minor tranquilizers / barbiturates	1.01	(0.58 to 1.75)
Anticonvulsants	0.80	(0.63 to 1.02)
Dementia drugs	1.33	(0.83 to 2.15)
Attention-deficit hyperactivity disorder medications	1.21	(0.67 to 2.18)
Alcohol aversion agents	2.38	(0.53 to 10.74)
Smoking cessation products	0.76	(0.30 to 1.94)
Disease-modifying antirheumatic drugs	1.05	(0.48 to 2.31)

*Adjusted odds ratio (aOR) is the adjusted odds ratio of each estimate in a model including all covariates in the table
†95% confidence interval
‡Presence of comorbidity, procedure, frailty indicator, pain condition and medication use were assessed in 365-day window before index date for cases and controls
§Appendicitis, complicated hernia, intestinal obstruction, cholelithiasis, pancreatitis, urine stone, endometriosis
‖Accidents, including falls, injury inflicted by others
¶Dislocations, sprains, and strains, injuries intracranial, thorax, abdomen, pelvis, open wounds, contusions, burns
**Osteoarthrosis, other arthropathies and enthesopathies, and acquired deformities
††Arthritis/systemic lupus erythematosus and other inflammatory/connective tissue diseases
‡‡Well-recognized risk factors for IPD were excluded from the IPD risk score calculation, and instead were separately accounted with the IPD risk score in the final model

Appendix Table A4. Adjusted Odds Ratios (aOR) for Laboratory-Confirmed invasive pneumococcal disease (IPD) in logistic regression model with opioid exposure variable, known risk factors for IPD and IPD risk score, Tennessee Medicaid (1995-2014)

Exposure	Adjusted Odds Ratio* (95% CI)	
Opioid Exposure[†]		
Remote Use	1.00	(reference)
Past Use	0.84	(0.67 to 1.05)
Recent Use	1.00	(0.85 to 1.17)
Current Use	1.61	(1.35 to 1.91)
Female vs. Male		
Female	1.00	(reference)
Male	1.23	(1.08 to 1.40)
Race		
White	1.00	(reference)
Black	1.09	(0.93 to 1.27)
Other	1.00	(0.81 to 1.24)
Comorbidities[‡]		
Alcohol/Substance Abuse	1.32	(1.05 to 1.66)
Cardiovascular Disease	0.99	(0.82 to 1.19)
Serious hepatic disease	2.60	(1.86 to 3.63)
Chronic lung disease	1.35	(1.14 to 1.60)
End stage renal disease	1.59	(1.17 to 2.16)
HIV	6.60	(5.17 to 8.43)
Malignancy	2.01	(1.62 to 2.51)
Immune disorders	1.62	(0.94 to 2.80)
Diabetes	0.97	(0.82 to 1.15)
Sickle-cell disease	3.57	(1.76 to 7.27)
Smoking	1.29	(1.07 to 1.55)
Healthcare utilization patterns[‡]		
Pneumococcal vaccination - past year	0.85	(0.60 to 1.21)
Recent stay at nursing home (<30 days)	0.97	(0.71 to 1.32)
Outpatient visits - Past year		
0-4[§]	1.00	(reference)
5-9	0.88	(0.75 to 1.04)
10-19	0.92	(0.77 to 1.10)
$\geq$ 20	1.04	(0.80 to 1.35)
Emergency department visits - past year		
0	1.00	(reference)
1-2	1.24	(1.06 to 1.45)
3-4	1.36	(1.10 to 1.68)
$\geq$ 5	1.25	(0.98 to 1.61)
Hospitalizations - past year		
0	1.00	(reference)
1	1.32	(1.11 to 1.58)
2	1.34	(1.05 to 1.71)
$\geq$ 3	1.41	(1.07 to 1.85)
Infection Risk Score Category[‖]		
1	1.00	(reference)
2	1.41	(0.95 to 2.09)
3	1.46	(0.99 to 2.17)
4	1.50	(0.99 to 2.27)
5	1.85	(1.28 to 2.69)
6	2.05	(1.42 to 2.98)
7	2.00	(1.39 to 2.87)

Exposure	Adjusted Odds Ratio* (95% CI)
8	2.22 (1.56 to 3.17)
9	2.78 (1.97 to 3.92)
10	6.14 (4.43 to 8.50)

*Adjusted odds ratio are derived from the full model including all of the covariates listed in the table, taking into account the study design where controls were matched to cases on individual year of age, county of residence and eligibility on the index date (i.e. controls had to be eligible retrospective cohort members on the index date for the case)

†Opioid use (current, recent, past and remote) was assessed relative to the index date for cases and matched controls

‡Comorbidities and healthcare utilization patterns were assessed in the 365-day period preceding the index date for cases and controls (except "Recent Nursing Home Stay")

§As more than 75% of subjects had at least one outpatient visit, the reference category for this comparison was set at 0-4 outpatient visits in the past year

‖Infection risk score categorized into 10 categories based on decile-distribution of the risk score in full study population. 1 is lowest risk score category, 10 is highest risk score category

Expanded results of primary analysis

In the primary analysis, all well-recognized risk factors for invasive pneumococcal disease (IPD) were identified a priori and measured in the 365 days preceding the index date for cases and controls. Per the Advisory Committee on Immunization Practices (ACIP), these variables included diagnoses of certain conditions including: alcohol/substance abuse, cardiovascular disease, serious hepatic and chronic lung disease, end-stage renal disease, HIV, malignancy, immune disorders/transplant, diabetes, sickle cell disease, and smoking status, as well as healthcare encounter history, including pneumococcal vaccination history, recent nursing home stay in past 30 days and the number of hospitalizations, outpatient and emergency department visits in the past year.

All well-recognized risk factors for IPD were identified using study covariates according to the definitions in Appendix Table A2. The results from the full conditional logistic regression model including opioid exposure and all well-recognized risk factors for IPD (primary analysis) are presented in Appendix Table A5. The results from each of the full conditional logistic regression models stratifying current opioid use based on characteristics of the opioid are presented in Appendix Table A6.

Appendix Table A5. Adjusted Odds Ratios (aOR) for Laboratory-Confirmed Invasive Pneumococcal Disease in the Primary Analysis among Tennessee Medicaid Enrollees (1995-2014)

Exposure	Adjusted Odds Ratio* (95% CI)	
Opioid Exposure[†]		
Remote Use	1.00	(reference)
Past Use	0.87	(0.70 to 1.08)
Recent Use	1.03	(0.87 to 1.21)
Current Use	1.62	(1.36 to 1.92)
Male vs. Female		
Female	1.00	(reference)
Male	1.23	(1.08 to 1.41)
Race		
White	1.00	(reference)
Black	1.10	(0.94 to 1.28)
Other	1.03	(0.83 to 1.26)
Comorbidities[‡]		
Alcohol/substance abuse	1.31	(1.04 to 1.64)
Cardiovascular disease	1.04	(0.87 to 1.25)
Serious hepatic disease	2.94	(2.12 to 4.08)
Chronic lung disease	1.83	(1.55 to 2.15)
End stage renal disease	2.16	(1.60 to 2.91)
HIV	10.22	(8.08 to 12.92)
Malignancy	2.18	(1.76 to 2.70)
Immune disorders	1.91	(1.11 to 3.28)
Diabetes	0.94	(0.80 to 1.11)
Sickle cell disease	3.75	(1.86 to 7.58)
Smoking	1.33	(1.10 to 1.60)
Healthcare utilization patterns[‡]		
Pneumococcal vaccination - Past year	0.90	(0.64 to 1.28)
Recent stay at nursing home (<30 days)	1.05	(0.77 to 1.42)
Outpatient visits - Past year		
0-4[§]	1.00	(reference)
5-9	0.93	(0.79 to 1.09)
10-19	0.98	(0.82 to 1.17)
$\geq$ 20	1.14	(0.88 to 1.47)
Emergency department visits - Past year		
0	1.00	(reference)
1-2	1.36	(1.17 to 1.59)
3-4	1.52	(1.23 to 1.87)
$\geq$ 5	1.46	(1.14 to 1.87)
Hospitalizations - Past year		
0	1.00	(reference)
1	1.50	(1.26 to 1.78)
2	1.72	(1.36 to 2.17)
$\geq$ 3	1.90	(1.47 to 2.47)

*Adjusted odds ratio are derived from the full model including all of the covariates listed in the table, taking into account the study design where controls were matched to cases on individual year of age, county of residence and eligibility on the index date (i.e. controls had to be eligible retrospective cohort members on the index date for the case); [†]Opioid use (current, recent, past and remote) was assessed relative to the index date for cases and matched controls; [‡]Comorbidities and healthcare utilization patterns were assessed in the 365-day period preceding the index date for cases and controls (with the exception of "Recent Nursing Home Stay"); [§]As more than 75% of subjects had at least 1 outpatient visit, the reference category for this comparison was set at 0-4 outpatient visits in the past year

Appendix Table A6. Adjusted Odds Ratios (aOR)* for Laboratory-Confirmed Invasive Pneumococcal Disease by Characteristics of Opioid among Tennessee Medicaid Enrollees (1995-2014)

	Primary analysis - current opioid use	Current opioid use by duration of action	Current opioid use by potency	Current opioid use by previously described immunosuppressive properties	Current opioid use by MME daily dose
Opioid Exposure[†]					
Remote Use[‡]	1.00	1.00	1.00	1.00	1.00
Current Use	1.62				
Duration of Action					
Short-acting - SA		1.58			
Long-acting - LA		1.87			
Combo SA/LA		1.64			
Potency					
Medium Potency			1.52		
High Potency			1.72		
Combo Med/High			2.20		
Previously described immunosuppressive properties					
Unknown immunosuppressive				1.79	
Non-immunosuppressive				1.55	
Immunosuppressive				1.74	
Combo				1.72	
Dose					
<50mg					1.54
50-90mg					1.71
≥90mg					1.75
Male vs. Female					
Female[‡]	1.00	1.00	1.00	1.00	1.00
Male	1.23	1.23	1.23	1.23	1.23
Race					
White	1.00	1.00	1.00	1.00	1.00
Black	1.10	1.10	1.10	1.10	1.10
Other	1.03	1.03	1.03	1.03	1.03
Comorbidities[§]					
Alcohol/substance abuse	1.31	1.31	1.31	1.31	1.31
Cardiovascular disease	1.04	1.04	1.05	1.04	1.04
Serious hepatic disease	2.94	2.94	2.98	2.94	2.96
Chronic lung disease	1.83	1.83	1.83	1.83	1.83
End-stage renal disease	2.16	2.15	2.16	2.15	2.15
HIV	10.22	10.18	10.15	10.20	10.19
Malignancy	2.18	2.17	2.17	2.18	2.17
Immune disorders	1.91	1.91	1.92	1.91	1.92
Diabetes	0.94	0.94	0.94	0.94	0.94
Sickle Cell disease	3.75	3.77	3.75	3.77	3.73
Smoking	1.33	1.33	1.33	1.33	1.33
Healthcare Utilization[§]					
Pneumococcal vaccination[‖]	0.90	0.91	0.91	0.90	0.91
Nursing home stay[¶]	1.05	1.04	1.04	1.05	1.05
Outpatient visits					
0-4[‡,**]	1.00	1.00	1.00	1.00	1.00
5-9	0.93	0.93	0.93	0.93	0.93
10-19	0.98	0.98	0.97	0.98	0.98

	Primary analysis - current opioid use	Current opioid use by duration of action	Current opioid use by potency	Current opioid use by previously described immunosuppressive properties	Current opioid use by MME daily dose
≥ 20	1.14	1.13	1.12	1.13	1.13
ED visits					
0‡	1.00	1.00	1.00	1.00	1.00
1-2	1.36	1.36	1.36	1.36	1.36
3-4	1.52	1.52	1.52	1.52	1.52
≥ 5	1.46	1.46	1.46	1.46	1.46
Hospitalizations					
0‡	1.00	1.00	1.00	1.00	1.00
1	1.50	1.50	1.49	1.50	1.49
2	1.72	1.71	1.71	1.72	1.72
≥ 3	1.90	1.90	1.88	1.90	1.90

*Adjusted odds ratio are derived from full models including all of the covariates listed in the table, taking into account the study design where controls were matched to cases on individual year of age, county of residence and eligibility on the index date (i.e. controls had to be eligible retrospective cohort members on the index date for the case)

†Opioid use was assessed relative to the index date for cases and matched controls

‡Reference category for comparison

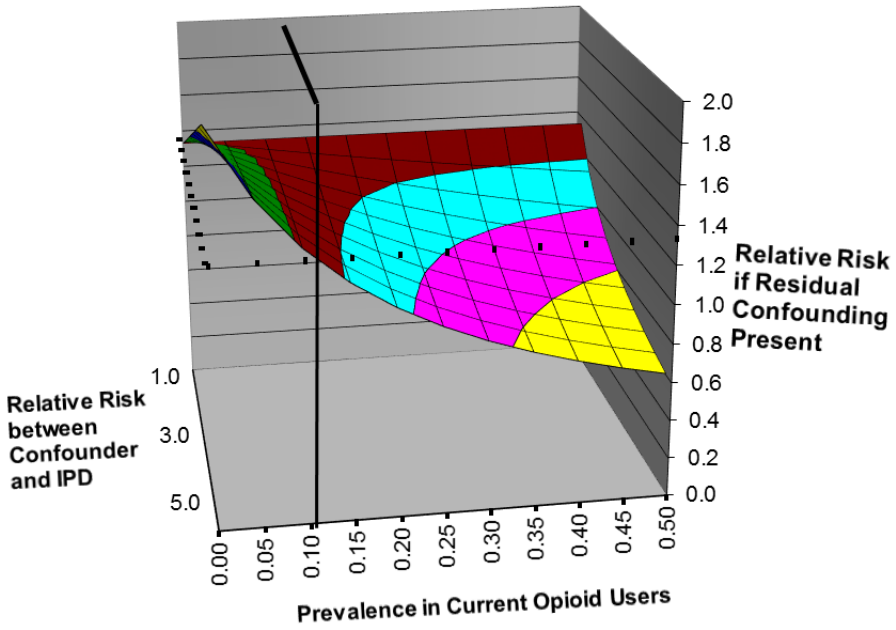
§Comorbidities and healthcare utilization patterns were assessed in the 365-day period preceding the index date for cases and controls (except "Recent Nursing Home Stay")

‖Pneumococcal polysaccharide vaccination

¶Recent nursing home stay assessed in 30-day period preceding index date for cases and controls

**As more than 75% of subjects had at least one outpatient visit, the reference category for this comparison was set at 0-4 outpatient visits in the past year

Appendix Figure A1. Residual confounding scenarios between opioid use and IPD with prevalence of confounder among remote opioid users at 10%



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APPENDIX B - CHAPTER 5 APPENDIX

Infection-Specific Definitions of Hospitalization for Serious Infection

We used a pre-specified adjudication process to determine whether each abstracted medical record corresponded to a true infection or not. Previous validation studies and expert clinical knowledge were used to define a priori definitions for each infection type.[1-3] Information abstracted from the medical record was compared to these a priori definitions for each infection type to make the final determination of whether a hospitalization represented a true infection or not.

I. Sepsis/Septicemia/Bacteremia/Septic Shock/Generalized Infection

Either of the following [1 or 2]:

1. **Positive culture of a non-contaminant pathogen**
    - i. Positive blood culture [any of the following (1-2)]
        1. Any gram-negative organism, except:
            - a. No predominant organism
        2. A gram-positive organism, except:
            - a. Coagulase-negative *Staphylococcus*
            - b. *Bacillus spp*. (other than *Bacillus anthracis*)
            - c. *Corynebacterium spp.*
            - d. *Propionibacterium spp.*
            - e. *Micrococcus*
            - f. Diptheroids
            - g. Viridians Group Streptococci
            - h. Enterococci
            - i. *Clostridium perfringens*
            - j. *Aerococcus*
            - k. *Alcaligenes faecalis*
            - l. *Citrobacter*
            - m. *Neisseria subflava*
            - n. *Stomatococcus*
            - o. *Streptococcus bovis*
            - p. *Veillonella candidemia*
            - q. *Mycobacterium tuberculosis*
            - r. *S. salivarius*
            - s. *"Gram-Positive"*

t. *"No predominant organism"*
u. *Streptococcus alpha*

2. **At least two of the following, documented at admission +/- 2 days [i-iii]**
    i. Hypotension
        1. Systolic BP ≤ 90 mmHg
        2. Reduction of systolic BP of 40mmHg from earliest measurement collected during the admission of interest
    ii. Two of the following [1-4]:
        1. Temperature ≥ 38^0C **or** ≤ 36^0C
        2. Heart rate ≥ 90 beats/minute
        3. Respiratory rate ≥ 20 breaths/min or $PaCO_2$ < 32 mmHg
        4. WBC ≥ 10,000 cells/mm^3 **or** ≤ 4,500 cells/mm^3 **or** WBC with > 10 % immature (band) forms
    iii. Initiation of antibiotic treatment specifically for sepsis/septicemia/bacteremia/septic shock/generalized infection

II. Pneumonia

1. Pneumonia identified through examination (**all three of the following [a-c]):**
    a. One of the following admission findings indicative of respiratory findings:
        1. New and/or increased cough
        2. Shortness of breath
        3. Pleuritic chest pain
        4. New purulent production
        5. Altered mental status ("agitation" and "lethargy" included)
        6. Crackles
            a. Physical evidence of consolidation such as egophony, whispered pectoriloquy, etc.
    b. One of the following examination findings indicative of systemic infection [1-4]:
        1. Temperature (T ≥ 100.4^0F (38^0C) or ≤ 96^0F) in first 48 hours of admission
        2. Systolic BP ≤ 90mmHg
        3. Shock
            a. Volume nonresponsive hypotension
        4. Blood peripheral WBC (≥ 10.0 x 10^9/L or ≤ 4.5 x 10^9/L)
    c. Treatment with antibiotics/antivirals indicated for suspected infection

OR

At least two of the following [1-3]:

1. Two of the following from #1 **([a and b], [a and c], or [b-c])**
2. Any of the following findings listed on chest imaging from radiologic report **documented at admission +/- 2 days**
    a. Pneumonia
    b. Lung abscess
    c. Opacity consistent with pneumonia/lung abscess
    d. Infiltrate consistent with pneumonia/lung abscess
    e. Consolidation consistent with pneumonia/lung abscess

f. Increased density consistent with pneumonia/lung abscess
g. Pleural effusion consistent with pneumonia/lung abscess
h. Interstitial edema consistent with pneumonia/lung abscess

3. Sterile Site Laboratory Findings
    i. Any one of the following [i through v]
        i. Sputum lab findings [any **one** of the following (1, 2)]:
            1. Sputum culture/PCR/serology/gram stain positive for an agent that is not considered a contaminant [see exclusion list below]:
                a. *Aspergillus* species, *Enterococcus* species, viridians group streptococci, and yeast
            2. Positive viral study (culture/PCR/antigen screen) for a viral pathogen
        ii. Blood lab findings [either of the following (1-3)]
            1. Blood culture/PCR/serology positive for an agent that is not considered a contaminant [see exclusion list below]:
                a. Exclusions
                    i. Coagulase-negative *Staphylococcus*
                    ii. *Bacillus spp.* (other than *Bacillus anthracis*)
                    iii. *Corynebacterium spp.*
                    iv. *Propionibacterium spp.*
                    v. *Micrococcus*
                    vi. Diptheroids
                    vii. Viridians Group Streptococci
                    viii. Enterococci
                    ix. *Clostridium perfringens*
                    x. *Aerococcus*
                    xi. *Alcaligenes faecalis*
                    xii. *Citrobacter*
                    xiii. *Neisseria subflava*
                    xiv. *Stomatococcus*
                    xv. *Streptococcus bovis*
                    xvi. *Veillonella candidemia*
                    xvii. *Mycobacterium tuberculosis*
                    xviii. *S. salivarius*
            2. Positive viral study (culture/PCR/antigen screen) for a viral pathogen
        iii. Pleural fluid lab findings [either of the following (1, 2)]
            1. Culture/PCR/serology positive for a bacterial pathogen
            2. Positive viral study (culture/PCR/antigen screen) for a viral pathogen
        iv. Bronchoscopic specimen or deep endotracheal tube aspiration lab findings [either of the following (1, 2)]
            1. Culture/PCR/serology positive for a bacterial pathogen
            2. Positive viral study (culture/PCR/antigen screen) for a viral pathogen
        v. Urine antigen detection testing [either of the following (1, 2)]
            1. *Legionella pneumophila*
            2. *Streptococcus pneumoniae*

III. Cellulitis/Soft-Tissue Infection

Both of the following:

1. Any mention of the following with recent onset (≤14 days) ***[any of the following]***
   a. Skin erythema
   b. Surgical site infection
   c. Superficial central line infection
   d. Ostomy site infection
   e. Skin infection with associated lymphangitis
2. Antibiotic treatment initiated for suspected infection

IV. Endocarditis

Any one of the following [1-3]:

1. Major Criteria [both of the following]:
   a. Suggestive microbiology [at least one of the following]:
      i. Positive blood culture of an ***endocarditis organism*** **[any of the following]:**
         1. *Streptococcus bovis*
         2. *Viridians streptococci*
         3. *Staphylococcus aureus*
         4. *Enterococcus spp.*
         5. HACEK organisms
         6. Coagulase negative staphylococci
   b. Evidence of endocardial involvement [at least one of the following]:
      i. New regurgitant murmur (a change in a preexisting murmur does not get scored)
      ii. Echocardiogram suspicious for any of the following:
         1. Intracardiac mass with no alternative explanation
         2. Endocardial abscess
         3. New partial prosthesis dehiscence
         4. Vegetation on valve
2. Minor Criteria [at least 4 of the following]:
   a. Predisposing valvular disease or IV drug use
   b. Temperature ≥ 100.4°F or 38°C
   c. Vascular phenomena
      i. Janeway lesions, conjunctival hemorrhages, arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial bleed
   d. Immunologic phenomena
      i. Osler nodes, Roth Spots, elevated Rheumatoid factor, hematuria in non-catheter urine, or other evidence of glomerulonephritis
   e. Positive blood cultures
      i. Excluding a single positive culture for coagulase negative staphylococci or a single positive culture for an organism that does not fall into the "reasonable

endocarditis organism" (i.e. coagulase-positive and coagulase-negative *S. aureus*, Enterococcus, viridians group Streptococci, *S. bovis*, HACEK organisms)

f. Positive serology for Brucella, Bartonella, Legionella, or Chlamydia
g. Antibiotic/antiviral/antifungal/antifungal treatment initiated/recommended for suspected infection

3. At least one Major Criteria **AND** 3 minor criteria.

V. Meningitis/Encephalitis

Any one of the following [1 or 2]:

1. Both of the following [a-b]
    a. Laboratory Findings [any one of the following (i-ix)]
        i. CSF demonstrates any bacterium
            1. Excluding Diptheroids, Propionibacteria, Bacillus, Coagulase Negative *Staphylococcus*
        ii. CSF demonstrates Diptheroids, Propionibacteria, Bacillus, Coagulase Negative *Staphylococcus* in the setting of past neurosurgical intervention **AND** physicians elected to treat with antibacterials
        iii. Blood cultures positive for any of the following:
            1. *S. pneumoniae*
            2. *H. influenza*
            3. *Neisseria meningitidis*
            4. Group B Streptococcus
        iv. Stool cultures positive for enterovirus
        v. Throat or sputum cultures positive for *Neisseria meningitidis* in the setting of a rapid onset, overwhelming infection syndrome, including petechiae
        vi. Serology positive for *Mycoplasma, Leptospira,* measles, mumps, lymphocytic choriomeningitis virus, arboviruses (e.g. St. Louis encephalitis virus), or HIV (if historically consistent with acute seroconversion).
        vii. Brain biopsy demonstrates encephalitis
        viii. Positive CSF culture or PCR detection for any of the following
        ix. Acute or convalescent serology demonstrates positive antibody pattern for any of the following:
            1. Encephalitis arbovirus (La Crosse, St. Louis, Eastern Equine, Western Equine, Powassan, Japanese, West Nile)
    b. Antibiotic/antiviral/antifungal/antifungal treatment initiated/recommended for suspected meningitis/encephalitis

2. At least two of the following [a-d]
    a. Clinical meningitis/encephalitis [at least two of the following]:
        i. Petechial rash
        ii. Nuchal rigidity (by history or exam)
        iii. Altered sensorium
        iv. Fever
        v. Altered level of consciousness, including "agitation" or "lethargy"
        vi. Behavioral change
        vii. Diminished level of consciousness (not easily roused)

viii. History of any of the following: headaches, altered mental status, or recent exposure to patient with known bacterial meningitis
ix. Reduction in fever within 72 hours of starting anti-bacterial

b. Inflammatory CSF [at least one of the following i-ii]
   i. Pleocytosis: $\geq$ 15 WBC/mm^3 (after subtracting one WBC for every 1,000 RBC)
   ii. Elevated protein (based on local lab-determined upper limits)
c. Suggestive Findings [at least one of the following (i-iv)
   i. Septic syndrome
   ii. Focal neurological deficits documented during examination (such as flaccid paralysis or speech alterations for West Nile Virus)
   iii. Abnormal imaging
      1. Computed tomography or magnetic resonance imaging (MRI) demonstrating focal edema or inflammation or hemorrhage
      2. Indicated as "meningitis/encephalitis" or "compatible with meningitis/encephalitis" or "cannot rule out meningitis/encephalitis"
   iv. Findings indicating an abnormal electroencephalography (such as focal periodic discharges)
d. Antibiotic/antiviral/antifungal/antifungal treatment initiated/recommended for presumed meningitis/encephalitis

VI. Pyelonephritis

At least two of the following [1-4]:

1. Suggestion of infection [at least one of the following]:
   a. Temperature $\geq$ 100.4°F (38°C)
   b. Peripheral blood WBC $\geq$ 10,000/mm^3
   c. Positive blood culture for any of the following:
      i. Gram Negative Rods
      ii. *Enterococcus spp.*
      iii. *Staphylococcus saprophyticus*
   d. Antibiotic/antiviral/antifungal/antifungal treatment initiated/recommended for suspected infection
2. Strong renal localization [at least one of the following]:
   a. CT, MRI, or Ultrasound Suggestive of Renal Inflammation
3. Minor Criteria [at least two of the following]:
   a. Flank pain
   b. Costovertebral angle tenderness
   c. Complaints of dysuria, frequency, or suprapubic pain
   d. Any pyuria
   e. Urine culture positive for a single organism
4. Antibiotic/antiviral/antifungal/antifungal treatment initiated/recommended for suspected pyelonephritis

VII. Septic Arthritis/Osteomyelitis

Any one of the following (1-5):

1. Synovial fluid gram stain or tissue gram stain or special stain demonstrating any organism
2. Joint culture/PCR/serology positive for any organism
3. At least two of the following (a-d):
    a. Positive blood culture/PCR/serology
    b. Joint with acute (≤ 7 days) worsening of inflammatory features (**at least two of the following):**
        i. Pain on history
        ii. ROM
        iii. Warmth
        iv. Effusion
        v. Swelling
        vi. Limited range of motion
    c. Antibiotic/antiviral/antifungal/antifungal treatment initiated/recommended for suspected infection
    d. Any one of the following (i-iv)
        i. Synovial fluid WBC ≥ 30,000/mm^3
        ii. Synovial fluid WBC ≥ 60,000/mm^3 with > 75% PMNs
        iii. Skin lesions, tenosynovitis, or urethral/cervical/rectal Gram stain or culture suggestive of *Neisseria gonorrhoeae*
        iv. Any indication of the following in the synovial fluid: needle-like crystals, CPPD crystals, uric acid.
4. Positive bone biopsy [at least one of the following (a-c)]:
    a. Positive culture for any organism
    b. Positive gram stain
5. Imaging and indirect features **[at least two of the following (a-c)]:**
    a. Consistent imaging [at least one of the following (i-iv)]:
        i. Plain X-ray read by a radiologist as suggestive of osteomyelitis
        ii. CT Scan read by a radiologist as suggestive of osteomyelitis
        iii. MRI read by a radiologist as suggestive of osteomyelitis
        iv. Bone scan or WBC scan read as suggestive of osteomyelitis
    b. Suggestive indirect features[at least one of the following (i-viii)]:
        i. Temperature > 100.4°F (38°C)
        ii. Bony pain or tenderness or erythema over bone suspected to be infected
        iii. Draining soft tissue sinus over bone suspected to be infected
        iv. Positive "probe to bone" (or visible bone in deep ulcer at suspected site)
        v. Blood culture positive for *S. aureus*
        vi. ESR ≥ 75 mm/hour
        vii. Intravenous drug use or indwelling catheter
        viii. Inflammation on imaging associated with an orthopedic prosthesis

c. Positive culture for any organism form wound sample over the bone suspected of infection
d. Antibiotic/antiviral/antifungal treatment for suspected infection

CHAPTER 5 REFERENCES

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APPENDIX C - CHAPTER 6 APPENDIX

Appendix Table C1. Coding algorithms for identification of exclusion criteria for retrospective cohort of new users of long-acting opioid analgesics (ICD9-CM)

Descriptive variable name	Drug Tree	ICD-9 Disease	ICD-9 Procedure	CPT / HCPCS
Acute renal failure / chronic kidney disease (through Stage IV)		403.*0, 404.*0, 404.*1, 584.*, 585.1-585.4	39.27, 39.95, 54.98	
Acute myocardial infarction		410.*		G8006-G8011
Carotid revascularization / endarterectomy / stent placement			00.61, 00.63, 00.64 38.11, 38.12, 39.28	35301, 0005T, 0006T, 0007T, 0075T, 0076T, 37215, 37216, 35501-35510, 35601-35606 S2211
Heart Failure/Cardiomyopathy (excluding post procedure-CHF)		402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.*, 428.*		G8027-G8032, G8183, G8184, G8450-G8452, G8468-G8470, G8472
Cor pulmonale - heart disease		416*		
Chronic liver disease		570.*-573.*		
Cystic fibrosis		277.0*		
Drug/alcohol abuse/dependence		292.0, 303.*, 304.*, 305.*	94.45, 94.54, 94.6*	99408, 99409 H0004-H0022, H0047, H0050, T1006-T1012
Drug poisoning/overdose[1]		965*, 967*, 969*, 970*		
End Stage Renal Disease (Stage V) / hemodialysis		403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 585.5, 585.6, V45.1*, V56.0, V56.1, 996.73	39.27, 39.42, 39.43, 39.95, 54.98	0505F, 0507F, 0514F, 4053F, 4054F, 4055F, 36145, 36825, 36830-36835, 36838, 36870, 90918-90925, 90930, 90935, 90937, 90939, 90940- 90947, 90951-90970, 90976-90979, 90982-90985, 90988-90999, 93990, 99512, 99559 G0257, G8714, G8715, M0916, M0920, M0923, M0928, M0931, M0932, M0936, M0937, M0944, M0945, M0948, M9052, M0986, M0987, M0992,

Descriptive variable name	Drug Tree	ICD-9 Disease	ICD-9 Procedure	CPT / HCPCS
				G0257, G0308-G0327, G0392-G0393, G8075-G8085, G8387, G8388
HIV	Level 3=297	042, 043, 044, 079.53, 795.71, V08		3495F, 3497F, 3498F
Immune disorders - non HIV		279.*		
Malignancy[2]	Level4 = 8, need to exclude level1= 1545 (methotrexate),1672 (Interferon Gamma 1-B)	140.*-208.* (exclude 173* - Other [non-melanoma] neoplasm of skin) 235*-237*, 238-238.1, 238.3, 238.5, 238.6, 238.8, 238.9, 239*, V581, V580, V66.1, V67.1, V66.2, V67.2, 285.22	92.21 - 92.29, 99.25, 99.85	3300F-3318F, 3321F, 3322F, 3370F-3390F 96400-96549 77401-77499, 77520, 77522, 77523, 77525, 77750-77799, Q0083-Q0085 J7150, J8999, J9000-J9999 S0353, S0354, G8875 G0256, G0261 G8371-G8384
Organ transplant		199.2, 238.77, 996.8*, E878.0, V42.0, V42.1, V42.6, V42.7, V42.8*, V42.9, V45.87, V58.44	00.91-00.93, 33.5*, 33.6, 37.5*, 41.0*, 41.94, 50.5*, 52.8*, 55.6*	32851, 32852, 32853, 32854, 33935, 33945, 38240, 38241, 38242, 44135, 44136, 44137, 47135, 47136, 48160, 48554, 48556, 50340, 50341, 50360, 50365, 50370, 50380 S2053, S2054, S2060, S2065, S2102, S2152 G0341, G0342, G0343
Other cerebrovascular disease/late effects of cerebrovascular diseases		437.*, 438.*		
Pulmonary embolism and infarction / Phlebitis and thrombophlebitis (includes superficial)		415.1*, 451.*, 452.*, 453.*, 459.1*, 671.3*, 671.4*, 671.5*, 671.9*, 673.2*, 673.8*		
Respiratory failure / cardiorespiratory failure / pulmonary heart disease		415.*, 416.*, 518.81, 518.83, 518.84, 799.1,	31.2*, 31.74, 96.55, 97.23	31600, 31601, 31603, 31605, 31610, 31611, 31612, 31613, 31614, 31615, 31820, 31825, 94002-94005, 99504, A4483, A4611, A4612, A4613, A4621, A4622, A4623, A4624, A4625, A4626, A4629, A7501-A7527, E0450, E0451, E0453, E0460, E0461, E0463, E0464, K0165, T3109,

Descriptive variable name	Drug Tree	ICD-9 Disease	ICD-9 Procedure	CPT / HCPCS
Stroke / hemiplegia & other late effects		342.*, 344.3*, 344.4*, 430.*-434.*, 436.*, 438.*		
Debility / cachexia / malnutrition / muscle wasting / abnormal weight loss		261, 262, 263.*, 728.2, 728.87, 783.2*, 783.3, 783.7, 799.3, 799.4		G8418
Hospice care				99377, 99378 (care plan oversight), G0065, G0182, Q5001-Q5010, S9126, T2042-T2046

[1]Opioids, sedatives, psychotropics, stimulants
[2]Does not include carcinoma in situ)

Table C2. Coding algorithms for chronic pain indications (ICD9-CM)

Descriptive variable name	ICD-9 Disease code	ICD-9 Procedure Code	CPT / HCPCS
Abdominal Pain[1]	540.*, 541.*-542.*, 550.0*, 550.1*, 551.*, 552.*, 555.*-558.*, 560.*, 562.*, 565.*-568.*, 569.4*, 569.8*, 574.*-577.*, 592.*, 594.*, 597.*, 601.*, 604.*, 608.2*, 614.*-617.*, 625.2, 625.3, 625.7*, 633.*, 787.3, 788.0, 788.1, 789.0*, 789.7	47, 47.0*, 47.2, 47.9, 55.01, 56.0, 56.2, 57.19, 58.0	44950, 44955, 44960, 44970, 44979, 47562, 47563, 47564, 47600, 47605, 47610, 47612, 47620,48000, 48105, 50961, 52310, 52315, 52325, 52336, 52352
Back pain	720.*-724.*, 737.*, 738.4, 739.1-739.4, 756.12	03.09, 81.0*, 81.3*, 81.6*	21920-21935, 22010-22899, 27096, 62263, 62264, 62274-62279, 62280, 62281, 62282, 62284, 62287, 62288, 62289, 62290, 62292, 62298, 62310, 62311, 62318, 62319, 62350, 62355, 62360, 62361, 62362, 62365, 62367, 62368, 64622, 64623, 64440-64443, 64470, 64472, 64475, 64476, 64479, 64480, 64483, 64484, 64490-64495, 64622, 64623, 64626, 64627, 72275, 72285
Dental pain	521.*-522.*, 528.0-528.3	23.*-24.*, 93.55, 96.54, 97.22,	41800, 41805, 41806, 41820, 41821, 41822, 41823, 41825, 41826, 41827, 41828, 41830, 41850, 41870, 41872, 41874, 41899, 42000, D2000-D2999, D3000-D3999, D4000-D4999, D6000-D6199, D7000-D7999
External causes of injury[2]	E800.*-E848.*, E880.*-E909.*, E916.*-E928.*, E960.*-E969.*, E980.*-E989.*		
Self-inflicted causes of injury	E950.*-E959.*		
Trauma[3]	338.21, 692.7*, 703.0*, 733.1*, 733.8*, 800.*- 904.*, 910.*-929.*, 940.*-959.* E800*-E848*, E880.*-E888.*, E890.*-E899.*, E916.*-E928.*	02.02, 03.53, 21.62, 21.71, 21.72, 76.7*, 76.93-76.97, 78.1*, 78.5*-78.69, 79.*, 81.93-81.96, 84.7*, 93.4*-93.59	01951, 01952, 01953, 16000-16036 21300-21495, 21800-21825, 22305-22328, 23395-23499, 23500-23700, 24300-24498, 24500-24685, 25259, 25260-25492, 25500-25695, 26340-26556, 26600-26785, 27097-27132, 27140-27275, 27380-27570, 27650-27860, 28200-28675, 29000-29799, 29847, 29851, 29855, 29856, E0276, E0920, E0930, E0946-E0948, L2100-L2160, L3917, L3980-L3999, L2180-L2192, L2840-L2999
Headache	307.81, 339.*, 346.*, 784.0		

Descriptive variable name	ICD-9 Disease code	ICD-9 Procedure Code	CPT / HCPCS
Musculoskeletal pain[4]	715.*-719.*, 725.*-732.*, 733.3*-733.9*, 735.*, 736.*, 738.*, 739.*	81.1*, 81.2*, 81.4*, 81.5*, 81.7*, 81.8*, , 81.91, 81.92, 81.97, 81.98, 82.9*, 83.96-83.98,	20526, 20550-20553, 20600-20610, 21116, 21501-21510, 21550-21632, 23000-23044, 23075-23350, 23800-24006, 24075-24220, 24800-25251, 25800-26320, 26560-26596, 26820-27036, 27047-27187, 27280-27310, 27325-27372, 27580-27612, 27615-27648, 27870-28193, 28705-28825, 29800-29999
Pain, not specified, including psychogenic	338.*, 379.91, 388.71, 388.72, 440.22, 780.96, 784.1, 784.92, 786.5*, V13.4		
Systemic lupus erythematosus and other inflammatory/connective tissue diseases	274.*, 710.*, 712.*-714.*		3470F, 3471F, 3472F, 3475F, 3476F
Neuropathic pain	053.*, 350.*-358.*, 723.1, 723.4		

[1]Appendicitis, complicated hernia, intestinal obstruction, cholelithiasis, pancreatitis, urinary stone, Endometriosis

[2]Accidents, including falls, injury inflicted by others

[3]Fractures, dislocations, sprains and strains, injuries intracranial, thorax, abdomen, pelvis, open wounds, contusions, burns

[4]Osteoarthrosis, arthropathies, enthesopathies and acquired deformities

Appendix Table C3. Discharge diagnosis code definitions for hospitalizations for serious infection (ICD9-CM)

Serious Infection	Primary (first listed) discharge diagnosis code
Pneumonia-primary definition	003.22, 480.*‡, 481, 482.*, 483.*, 484.*, 485.*, 486.*, 487.0
Pneumonia-secondary definition (pneumonia diagnosis (above) in any other diagnosis field)	510.*, 038.*, 790.7, 995.91, 995.92
Meningitis/ Encephalitis	003.21, 036.0, 0.47*, 049.*, 053.0, 054.72, 072.1, 091.81, 094.2, 098.82, 100.81, 320.*, 036.1, 054.3, 056.01, 058.21, 058.29, 062.*, 063.*, 064.*, 066.41, 072.2, 094.81, 130.0, 323.*
Bacteremia/ Sepsis†	038.*, 790.7, 995.91, 995.92
Cellulitis/ Soft-tissue infections	035, 040.0, 569.61, 681.*, 682.*, 728.86, 785.4
Endocarditis	036.42, 074.22, 093.2*, 098.84, 421.*, 422.92
Pyelonephritis	590.*
Septic Arthritis/ Osteomyelitis	003.23, 056.71, 098.5*, 711.0, 711.00-711.07, 711.09, 711.9*, 003.24, 376.03, 526.4, 730.0*, 730.1*, 730.2*

† Without a diagnosis of pneumonia in any other diagnosis field
‡ A * indicates all numeric values [0-9]

Appendix Table C4. Baseline characteristics and standardized mean differences for variables by treatment group before and after inverse-probability treatment weighting using the propensity score

	Immunosuppressive N=46,870		Non-immunosuppressive N=17,221		Absolute standardized mean differences	
					Before weighting	After weighting
Comorbidities						
Alcohol Abuse	108	(0.2%)	45	(0.3%)	0.01	0
Alterations of Consciousness	83	(0.2%)	18	(0.1%)	0.01	0
Arrhythmias	1058	(2.3%)	329	(1.9%)	0.04	0
Atrial Fibrillation	463	(1.0%)	151	(0.9%)	0.01	0
Autonomic neuropathy	70	(0.1%)	20	(0.1%)	0.02	0
Bipolar Disorder	747	(1.6%)	263	(1.5%)	0	0
Cardiac valve disease	252	(0.5%)	88	(0.5%)	0.03	0
Cerebral Palsy	97	(0.2%)	18	(0.1%)	0.06	0
Congenital heart anomalies	44	(0.1%)	17	(0.1%)	0.01	0
Chronic Bronchitis	6742	(14.4%)	2225	(12.9%)	0.02	0
Dementia	436	(0.9%)	50	(0.3%)	0.12	0
Depression	3722	(7.9%)	1174	(6.8%)	0.05	0
Diabetes	6639	(14.2%)	2227	(12.9%)	0.02	0.01
Drug adverse events	347	(0.7%)	89	(0.5%)	0.03	0
Drug poisoning (accidental)	20	(<1%)	10	(0.1%)	0.01	0
Drug poisoning (other drugs)	60	(0.1%)	20	(0.1%)	0	0
Essential hypertension	13439	(28.7%)	4495	(26.1%)	0.03	0.01
Lipid disorders	4626	(9.9%)	1514	(8.8%)	0.03	0
Mental retardation	35	(0.1%)	4	(<1%)	0.05	0
Multiple system atrophy	10	(<1%)	1	(<1%)	0.02	0
Acute Nephritis	9	(<1%)	9	(0.1%)	0.01	0
Chronic Nephritis	38	(0.1%)	16	(0.1%)	0	0
Obesity	1568	(3.3%)	565	(3.3%)	0	0
Bariatric surgery	83	(0.2%)	33	(0.2%)	0.01	0
Obstructive coronary artery disease	2735	(5.8%)	950	(5.5%)	0.01	0
Osteomyelitis	147	(0.3%)	54	(0.3%)	0	0
Osteoporosis	887	(1.9%)	252	(1.5%)	0.07	0
Osteoporosis-related BMD testing	1905	(4.1%)	531	(3.1%)	0.07	0.01
Pacemaker	401	(0.9%)	130	(0.8%)	0.02	0
Parkinson's Disease	2329	(5.0%)	708	(4.1%)	0.08	0
Peripheral artery disease	4993	(10.7%)	1647	(9.6%)	0.04	0
Peripheral neuropathy	2390	(5.1%)	783	(4.5%)	0.02	0
Personality disorders	96	(0.2%)	36	(0.2%)	0.01	0
Pneumonia	879	(1.9%)	245	(1.4%)	0.05	0
Infections	17658	(37.7%)	6313	(36.7%)	0.04	0

	Immunosuppressive N=46,870		Non-immunosuppressive N=17,221		Absolute standardized mean differences	
					Before weighting	After weighting
Diabetic neuropathy	88	(0.2%)	22	(0.1%)	0.03	0
Other neuropathy	764	(1.6%)	258	(1.5%)	0.03	0
Other diabetes complications	453	(1.0%)	145	(0.8%)	0.03	0
Retinopathy	136	(0.3%)	28	(0.2%)	0.04	0
Ulcers/amputations	90	(0.2%)	28	(0.2%)	0.01	0
Amputations	190	(0.4%)	49	(0.3%)	0	0
Post-traumatic stress disorder	138	(0.3%)	45	(0.3%)	0.02	0
Schizophrenia	202	(0.4%)	58	(0.3%)	0.02	0
Seizures	1173	(2.5%)	379	(2.2%)	0.05	0
Sepsis/Bacteremia	225	(0.5%)	54	(0.3%)	0.04	0
Hemolytic anemia	107	(0.2%)	25	(0.1%)	0.01	0
Sickle-cell diseases	98	(0.2%)	25	(0.1%)	0.01	0
Tobacco use	1261	(2.7%)	497	(2.9%)	0.05	0
Thyroid disease	1838	(3.9%)	581	(3.4%)	0.02	0
Pregnancy, Delivery & Puerperium	426	(0.9%)	246	(1.4%)	0.03	0.01
Pain indications						
Abdominal Pain	3270	(7.0%)	1214	(7.0%)	0	0
Back pain	21715	(46.3%)	7071	(41.1%)	0.02	0.01
Dental Pain	418	(0.9%)	230	(1.3%)	0.03	0
External causes of injury	1724	(3.7%)	735	(4.3%)	0	0
Self-inflicted	4	(<1%)	4	(<1%)	0.01	0
Trauma	5453	(11.6%)	2356	(13.7%)	0.04	0
Headache	2126	(4.5%)	771	(4.5%)	0.02	0
Musculoskeletal Pain	17512	(37.4%)	6044	(35.1%)	-0.02	0.01
Pain Not Specified	2529	(5.4%)	963	(5.6%)	0.03	0
Arthritis/SLE	1346	(2.9%)	505	(2.9%)	0.02	0.01
Neuropathic Pain	4695	(10.0%)	1491	(8.7%)	0.03	0
Multiple Sclerosis	188	(0.4%)	67	(0.4%)	-0.02	0
Medication use history						
Hydrocodone	17103	(36.5%)	5223	(30.3%)	0.16	0.01
Oxycodone	5845	(12.5%)	2918	(16.9%)	0.22	0
Other opioids	3552	(7.6%)	1327	(7.7%)	0.07	0
More than one SA opioid	20370	(43.5%)	7753	(45.0%)	0.03	0
Influenza vaccine	7657	(16.3%)	2378	(13.8%)	0.08	0
Pneumococcal vaccine	1228	(2.6%)	383	(2.2%)	0	0.01
Anti-arrhythmic	3486	(7.4%)	965	(5.6%)	0.09	0
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocks	16178	(34.5%)	5458	(31.7%)	0.04	0.01
Anticoagulants	2261	(4.8%)	675	(3.9%)	0.07	0

	Immunosuppressive N=46,870		Non-immunosuppressive N=17,221		Absolute standardized mean differences	
					Before weighting	After weighting
Antibiotics	35782	(76.3%)	12902	(74.9%)	0.02	0
Antifungals	6531	(13.9%)	2236	(13.0%)	0.03	0
Aspirin	3032	(6.5%)	941	(5.5%)	0	0.01
Non-aspirin anti-platelet agents	3054	(6.5%)	854	(5.0%)	0.07	0
Beta-blockers	10083	(21.5%)	3335	(19.4%)	0.07	0
Calcium-channel blockers	8749	(18.7%)	2937	(17.1%)	0.05	0
Digoxin	1193	(2.5%)	327	(1.9%)	0.02	0
Statins	11954	(25.5%)	3999	(23.2%)	0.03	0
Other lipid-lowering agents	4159	(8.9%)	1315	(7.6%)	0.03	0
Loop diuretics	9039	(19.3%)	2710	(15.7%)	0.1	0.01
Thiazide	8274	(17.7%)	2875	(16.7%)	0.02	0
Nitrates	4594	(9.8%)	1489	(8.6%)	0.01	0
Other anti-hypertensives	3424	(7.3%)	1100	(6.4%)	0.06	0.01
Pentoxifylline/vasodilators	431	(0.9%)	130	(0.8%)	0.02	0
Hypoglycemic medications	7121	(15.2%)	2363	(13.7%)	0.04	0
Insulin	3783	(8.1%)	1174	(6.8%)	0.09	0
Thyroid Hormones	5184	(11.1%)	1716	(10.0%)	0.04	0
Bronchodilators, beta agonists	12243	(26.1%)	4295	(24.9%)	0.01	0.01
Bronchodilators, other	7078	(15.1%)	2180	(12.7%)	0.06	0
Proton Pump Inhibitors	16861	(36.0%)	5239	(30.4%)	0.11	0
NSAIDs	29480	(62.9%)	10878	(63.2%)	0.01	0
Glucocorticoids	22953	(49.0%)	8033	(46.6%)	0.06	0.01
Antidepressants	30523	(65.1%)	10286	(59.7%)	0.13	0.01
Antipsychotics	7466	(15.9%)	1954	(11.3%)	0.18	0
Sedatives	7536	(16.1%)	2433	(14.1%)	0.05	0.01
Lithium	585	(1.2%)	207	(1.2%)	0.04	0
Minor tranquilizers/barbiturates	2048	(4.4%)	682	(4.0%)	0.02	0
Anticonvulsants	18705	(39.9%)	5694	(33.1%)	0.15	0.01
Dementia Drugs	1426	(3.0%)	200	(1.2%)	0.19	0
ADHD medications	1045	(2.2%)	403	(2.3%)	0	0
Alcohol aversion agents	31	(0.1%)	16	0.1%)	0.02	0
Smoking cessation products	540	(1.2%)	247	(1.4%)	0.02	0
Disease modifying anti-rheumatic drugs	983	(2.1%)	367	(2.1%)	0.02	0
Frailty						
TIA	116	(0.2%)	42	(0.2%)	0.02	0
Urinary Tract	2437	(5.2%)	722	(4.2%)	0.09	0
Ambulation devices	3564	(7.6%)	1085	(6.3%)	0.05	0
CPAP/BIPAP	1692	(3.6%)	504	(2.9%)	0	0
Decubitus/pressure ulcers	1533	(3.3%)	417	(2.4%)	0.07	0

	Immunosuppressive N=46,870		Non-immunosuppressive N=17,221		Absolute standardized mean differences	
					Before weighting	After weighting
Enteral & Parenteral nutrition	703	(1.5%)	166	(1.0%)	0.09	0
Impaired Mobility	628	(1.3%)	238	(1.4%)	0.01	0
Incontinence	1295	(2.8%)	357	(2.1%)	0.08	0
Oxygen supplementation	2958	(6.3%)	895	(5.2%)	0.03	0.01
Rehabilitation	1570	(3.3%)	713	(4.1%)	0.03	0
Healthcare utilization						
Nursing facility setting	522	(1.5%)	98	(0.8%)	0.23	0
Observation setting	1562	(4.6%)	553	(4.5%)	0	0
Emergency department setting	20463	(59.8%)	7322	(60.0%)	0.02	0.01
ED visits in prior year[1]						
0	13435	(39.2%)	4663	(38.2%)	0	0.01
1	8375	(24.5%)	2882	(23.6%)	0.02	0.02
2	4447	(13.0%)	1658	(13.6%)	0.04	0.03
$\geq$ 3	7982	(23.3%)	3003	(24.6%)	0.01	0.02
Outpatient visits in past year[1]						
0	8133	(23.8%)	3337	(27.3%)	0.01	0.03
1	7429	(21.7%)	2712	(22.2%)	0.04	0.01
2	8980	(26.2%)	2949	(24.2%)	0.03	0.06
$\geq$ 3	9697	(28.3%)	3208	(26.3%)	0.01	0.03
Hospitalizations in past year[1]						
0	26805	(78.3%)	9693	(79.4%)	0.07	0
1	6696	(19.6%)	2266	(18.6%)	0.07	0
$\geq$ 2	738	(2.2%)	247	(2.0%)	0.02	0.01
Demographics						
Sex						
Male	16947	(36.2%)	6757	(39.2%)	0.14	0
Female	29923	(63.8%)	10464	(60.8%)	0.14	0
Race						
White	37771	(80.6%)	13874	(80.6%)	0.02	0
Black/Other	9099	(19.4%)	3347	(19.4%)	0.02	0
Month of cohort entry						
January	4050	(8.6%)	1518	(8.8%)	0.02	0
February	3673	(7.8%)	1302	(7.6%)	0	0
March	3877	(8.3%)	1367	(7.9%)	0.07	0
April	3849	(8.2%)	1451	(8.4%)	0.02	0
May	3921	(8.4%)	1318	(7.7%)	0.03	0
June	3949	(8.4%)	1362	(7.9%)	0	0
July	3920	(8.4%)	1462	(8.5%)	0.04	0.01
August	4081	(8.7%)	1525	(8.9%)	0.01	0

	Immunosuppressive N=46,870		Non-immunosuppressive N=17,221		Absolute standardized mean differences	
					Before weighting	After weighting
September	3769	(8.0%)	1418	(8.2%)	0.02	0
October	4081	(8.7%)	1507	(8.8%)	0.02	0
November	3981	(8.5%)	1582	(9.2%)	0.03	0.01
December	3719	(7.9%)	1409	(8.2%)	0	0
Demographics (not included in the propensity score calculation)						
Year of cohort entry[2]						
1995	202	(0.4%)	0	(0.0%)	0.05	0.06
1996	271	(0.6%)	17	(0.1%)	0.07	0.08
1997	436	(0.9%)	39	(0.2%)	0.09	0.11
1998	791	(1.7%)	156	(0.9%)	0.1	0.12
1999	1333	(2.8%)	383	(2.2%)	-0.12	0.14
2000	2130	(4.5%)	1726	(10.0%)	0.01	0.01
2001	2869	(6.1%)	2380	(13.8%)	0.26	0.23
2002	3930	(8.4%)	1657	(9.6%)	0.2	0.19
2003	4839	(10.3%)	1592	(9.2%)	0.08	0.09
2004	5725	(12.2%)	815	(4.7%)	0.13	0.11
2005	4307	(9.2%)	817	(4.7%)	0.14	0.11
2006	2882	(6.1%)	1009	(5.9%)	0.09	0.07
2007	2625	(5.6%)	1005	(5.8%)	0.08	0.07
2008	2338	(5.0%)	989	(5.7%)	0.05	0.04
2009	2078	(4.4%)	1133	(6.6%)	0.01	0.04
2010	1995	(4.3%)	837	(4.9%)	0.05	0.08
2011	1997	(4.3%)	480	(2.8%)	0.01	0
2012	2395	(5.1%)	550	(3.2%)	0.07	0.1
2013	2065	(4.4%)	907	(5.3%)	0.01	0.05
2014	1662	(3.5%)	729	(4.2%)	0.03	0.02
Age[3]						
<30	2772	(5.9%)	1607	(9.3%)	0.08	0.03
30-<40	8286	(17.7%)	3484	(20.2%)	0.09	0.02
40-<50	12204	(26.0%)	4552	(26.4%)	0.04	0.02
50-<60	10475	(22.3%)	3711	(21.5%)	0.01	0.01
60-<70	6139	(13.1%)	2333	(13.5%)	0.03	0.04
70-<80	3280	(7.0%)	954	(5.5%)	0.07	0.01
≥ 80	3714	(7.9%)	580	(3.4%)	0.27	0.09

[1]Included in the propensity score calculation as a continuous variable

[2]Not included in the propensity score calculation as accounted for in the final analysis model using indicator variables

[3]Not included in the propensity score calculation as accounted for in final analysis model using cubic splines. Note age groups are presented in table for ease of interpretation.

Appendix Table C5. Baseline characteristics at first long-acting opioid prescription by opioid type

	Morphine N=30,745		Fentanyl N=12,037		Methadone N=4,088		Oxycodone N=12,520		Oxymorphone N=2,981		Tramadol N=1,720		Others N=105	
Comorbidities														
Alcohol Abuse	80	(0.3%)	27	(0.2%)	1	(<1%)	21	(0.2%)	22	(0.7%)	2	(0.1%)	2	(1.9%)
Alterations of Consciousness	39	(0.1%)	39	(0.3%)	5	(0.1%)	13	0.1%)	4	(0.1%)	1	(0.1%)	0	(0.0%)
Arrhythmias	560	(1.8%)	429	(3.6%)	69	(1.7%)	279	(2.2%)	31	(1.0%)	19	(1.1%)	2	(1.9%)
Atrial Fibrillation	208	(0.7%)	234	(1.9%)	21	(0.5%)	130	(1.0%)	11	(0.4%)	10	(0.6%)	0	(0.0%)
Autonomic neuropathy	51	(0.2%)	7	(0.1%)	12	(0.3%)	13	(0.1%)	5	(0.2%)	2	(0.1%)	0	(0.0%)
Bipolar Disorder	524	(1.7%)	157	(1.3%)	66	(1.6%)	165	(1.3%)	69	(2.3%)	29	(1.7%)	1	(1.0%)
Cardiac valve disease	149	(0.5%)	80	(0.7%)	23	(0.6%)	72	(0.6%)	7	(0.2%)	9	(0.5%)	0	(0.0%)
Cerebral Palsy	59	(0.2%)	35	(0.3%)	3	(0.1%)	15	(0.1%)	1	(<1%)	2	(0.1%)	2	(1.9%)
Cong anom of heart	31	(0.1%)	11	(0.1%)	2	(<1%)	12	(0.1%)	3	(0.1%)	2	(0.1%)	0	(0.0%)
Chronic Bronchitis	4420	(14.4%)	1793	(14.9%)	529	(12.9%)	1678	(13.4%)	378	(12.7%)	169	(9.8%)	10	(9.5%)
Dementia	104	4 (0.3%)	327	(2.7%)	5	(0.1%)	41	(0.3%)	5	(0.2%)	4	(0.2%)	0	(0.0%)
Depression	2531	(8.2%)	907	(7.5%)	284	(6.9%)	870	(6.9%)	219	(7.3%)	85	(4.9%)	5	(4.8%)
Diabetes	4346	(14.1%)	1751	(14.5%)	542	(13.3%)	1721	(13.7%)	315	(10.6%)	191	(11.1%)	10	(9.5%)
Drug adverse events	205	(0.7%)	108	(0.9%)	34	(0.8%)	75	(0.6%)	8	(0.3%)	6	(0.3%)	2	(1.9%)
Drug poisoning (accidental)	10	(<1%)	8	(0.1%)	2	(<1%)	9	(0.1%)	0	(0.0%)	1	(0.1%)	0	(0.0%)
Drug poisoning (other drugs)	36	(0.1%)	18	(0.1%)	6	(0.1%)	17	(0.1%)	2	(0.1%)	1	(0.1%)	0	(0.0%)
Drug poisoning/overdose	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Essential hypertension	8958	(29.1%)	3374	(28.0%)	1107	(27.1%)	3461	(27.6%)	667	(22.4%)	367	(21.3%)	28	(26.7%)
Lipid disorders	3052	(9.9%)	1171	1 (9.7%)	403	(9.9%)	1190	(9.5%)	219	(7.3%)	105	5 (6.1%)	9	(8.6%)
Mental retardation	14	(<1%)	21	(0.2%)	0	(0.0%)	2	(<1%)	0	(0.0%)	2	(0.1%)	0	(0.0%)
Multiple system atrophy	2	(<1%)	7	(0.1%)	1	(<1%)	1	(<1%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Acute Nephritis	3	(<1%)	6	(<1%)	0	(0.0%)	8	(0.1%)	1	(<1%)	0	(0.0%)	0	(0.0%)
Chronic Nephritis	27	(0.1%)	7	(0.1%)	4	(0.1%)	15	(0.1%)	1	(<1%)	0	(0.0%)	0	(0.0%)
Obesity	1147	(3.7%)	318	(2.6%)	103	(2.5%)	388	(3.1%)	115	(3.9%)	62	(3.6%)	6	(5.7%)
Bariatric surgery	50	(0.2%)	28	(0.2%)	5	(0.1%)	15	(0.1%)	12	(0.4%)	6	(0.3%)	0	(0.0%)
Obstructive coronary artery disease	1639	(5.3%)	906	(7.5%)	190	(4.6%)	808	(6.5%)	91	(3.1%)	51	(3.0%)	2	(1.9%)
Osteomyelitis	90	(0.3%)	45	(0.4%)	12	(0.3%)	50	(0.4%)	3	(0.1%)	1	(0.1%)	0	(0.0%)
Osteoporosis	460	(1.5%)	379	(3.1%)	48	(1.2%)	228	(1.8%)	17	(0.6%)	7	(0.4%)	2	(1.9%)
Osteoporosis-related BMD testing	1154	(3.8%)	590	(4.9%)	161	(3.9%)	497	(4.0%)	2	(0.1%)	32	(1.9%)	1	(1.0%)
Pacemaker	223	(0.7%)	153	(1.3%)	25	(0.6%)	92	(0.7%)	28	(0.9%)	10	(0.6%)	0	(0.0%)
Parkinson's Disease	1357	(4.4%)	803	(6.7%)	169	(4.1%)	469	(3.7%)	158	(5.3%)	81	(4.7%)	5	(4.8%)
Peripheral artery disease	3463	(11.3%)	1097	7 (9.1%)	433	(10.6%)	1073	(8.6%)	372	(12.5%)	202	(11.7%)	7	(6.7%)
Peripheral neuropathy	1642	(5.3%)	465	(3.9%)	283	(6.9%)	580	(4.6%)	133	(4.5%)	70	(4.1%)	2	(1.9%)
Personality disorders	68	(0.2%)	21	(0.2%)	7	(0.2%)	30	(0.2%)	2	(0.1%)	4	(0.2%)	0	(0.0%)
Pneumonia	497	(1.6%)	314	(2.6%)	68	(1.7%)	209	(1.7%)	23	(0.8%)	13	(0.8%)	0	(0.0%)
Infections	11729	(38.1%)	4367	(36.3%)	1562	(38.2%)	4547	(36.3%)	1070	(35.9%)	696	(40.5%)	43	(41.0%)
Diabetes: neuropathy	55	(0.2%)	28	(0.2%)	5	(0.1%)	17	(0.1%)	5	(0.2%)	0	(0.0%)	0	(0.0%)
Potential: neuropathy	510	(1.7%)	173	(1.4%)	81	(2.0%)	190	(1.5%)	39	(1.3%)	29	(1.7%)	1	(1.0%)
Other Diabetes Complications	286	(0.9%)	128	(1.1%)	39	(1.0%)	117	(0.9%)	17	(0.6%)	11	(0.6%)	0	(0.0%)
Retinopathy	95	(0.3%)	33	(0.3%)	8	(0.2%)	24	(0.2%)	2	(0.1%)	2	(0.1%)	0	(0.0%)
Ulcers/amputations	57	(0.2%)	26	(0.2%)	7	(0.2%)	28	(0.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Amputations	116	(0.4%)	60	(0.5%)	14	(0.3%)	40	(0.3%)	8	(0.3%)	1	(0.1%)	0	(0.0%)
Post-traumatic stress disorder	96	(0.3%)	31	(0.3%)	11	(0.3%)	28	(0.2%)	11	(0.4%)	6	(0.3%)	0	(0.0%)
Schizophrenia	123	(0.4%)	62	(0.5%)	17	(0.4%)	43	(0.3%)	10	(0.3%)	5	(0.3%)	0	(0.0%)
Seizures	755	(2.5%)	301	(2.5%)	117	(2.9%)	298	(2.4%)	58	(1.9%)	23	(1.3%)	3	(2.9%)

	Morphine N=30,745		Fentanyl N=12,037		Methadone N=4,088		Oxycodone N=12,520		Oxymorphone N=2,981		Tramadol N=1,720		Others N=105	
Sepsis/Bacteremia	112	(0.4%)	103	(0.9%)	10	(0.2%)	45	(0.4%)	6	(0.2%)	3	(0.2%)	0	(0.0%)
Serious Hepatic Disease	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Hemolytic anemia	93	(0.3%)	9	(0.1%)	5	(0.1%)	23	(0.2%)	2	(0.1%)	0	(0.0%)	0	(0.0%)
Sickle-cell diseases	87	(0.3%)	8	(0.1%)	3	(0.1%)	23	(0.2%)	2	(0.1%)	0	(0.0%)	0	(0.0%)
Tobacco use	1007	(3.3%)	186	(1.5%)	68	(1.7%)	205	(1.6%)	243	(8.2%)	49	(2.8%)	9	(8.6%)
Thyroid disease	1116	(3.6%)	585	(4.9%)	137	(3.4%)	423	(3.4%)	113	(3.8%)	45	(2.6%)	5	(4.8%)
Pregnancy, Delivery & Puerperium	327	(1.1%)	44	(0.4%)	55	(1.3%)	133	(1.1%)	59	(2.0%)	54	(3.1%)	1	(1.0%)
Pain indications														
Abdominal Pain	2136	(6.9%)	819	(6.8%)	315	(7.7%)	987	(7.9%)	125	(4.2%)	102	(5.9%)	8	(7.6%)
Back pain	15910	(51.7%)	3811	(31.7%)	1994	(48.8%)	4764	(38.1%)	1734	(58.2%)	573	(33.3%)	64	(61.0%)
Dental Pain	300	(1.0%)	87	0.7%)	31	0.8%)	185	(1.5%)	22	(0.7%)	23	(1.3%)	0	(0.0%)
External causes of injury	1087	(3.5%)	465	5 (3.9%)	172	2 (4.2%)	620	(5.0%)	50	(1.7%)	65	(3.8%)	4	(3.8%)
Self-inflicted	2	(<1%)	2	(<1%)	0	(0.0%)	3	(<1%)	0	(0.0%)	1	.1%)	0	(0.0%)
Trauma	3662	(11.9%)	1270	(10.6%)	521	(12.7%)	1876	(15.0%)	254	(8.5%)	226	(13.1%)	9	(8.6%)
Headache	1492	(4.9%)	413	(3.4%)	221	(5.4%)	581	(4.6%)	116	(3.9%)	74	4.3%)	2	(1.9%)
Musculoskeletal Pain	12370	(40.2%)	3677	(30.5%)	1465	(35.8%)	4363	(34.8%)	1149	(38.5%)	532	(30.9%)	41	(39.0%)
Pain Not Specified	1866	(6.1%)	483	(4.0%)	180	(4.4%)	576	(4.6%)	321	(10.8%)	66	3.8%)	13	(12.4%)
Arthritis/SLE	880	(2.9%)	373	(3.1%)	93	2.3%)	420	(3.4%)	61	2.0%)	24	1.4%)	2	(1.9%)
Neuropathic Pain	3365	(10.9%)	872	(7.2%)	458	(11.2%)	1046	(8.4%)	337	(11.3%)	108	8 (6.3%)	15	(14.3%)
Multiple Sclerosis	107	(0.3%)	52	(0.4%)	29	(0.7%)	55	(0.4%)	7	(0.2%)	5	(0.3%)	1	(1.0%)
Medication use history														
Hydrocodone	10950	(35.6%)	4704	(39.1%)	1449	(35.4%)	4052	(32.4%)	713	(23.9%)	458	(26.6%)	28	(26.7%)
Oxycodone	4431	(14.4%)	946	7.9%)	468	(11.4%)	1616	(12.9%)	1217	(40.8%)	85	4.9%)	20	(19.0%)
Other opioids	1771	5.8%)	1468	(12.2%)	313	(7.7%)	830	(6.6%)	67	2.2%)	430	(25.0%)	10	(9.5%)
More than one SA opioid	13593	(44.2%)	4919	(40.9%)	1858	(45.5%)	6022	(48.1%)	984	(33.0%)	747	(43.4%)	47	(44.8%)
Influenza vaccine	5189	(16.9%)	1919	(15.9%)	549	(13.4%)	1531	(12.2%)	541	(18.1%)	306	(17.8%)	15	(14.3%)
Pneumococcal vaccine	782	(2.5%)	353	(2.9%)	93	(2.3%)	284	(2.3%)	65	(2.2%)	34	(2.0%)	1	(1.0%)
Anti-arrhythmics	2044	(6.6%)	1183	(9.8%)	259	(6.3%)	793	(6.3%)	105	5 (3.5%)	67	(3.9%)	6	(5.7%)
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocks	10501	(34.2%)	4394	(36.5%)	1283	(31.4%)	3978	(31.8%)	944	(31.7%)	536	(31.2%)	30	(28.6%)
Anticoagulants	1122	2 (3.6%)	1010	(8.4%)	129	9 (3.2%)	547	(4.4%)	86	(2.9%)	42	(2.4%)	4	(3.8%)
Antibiotics	23062	(75.0%)	9562	(79.4%)	3158	(77.3%)	9598	(76.7%)	1988	(66.7%)	1316	(76.5%)	76	(72.4%)
Antifungals	4020	(13.1%)	1972	(16.4%)	539	(13.2%)	1628	(13.0%)	319	(10.7%)	289	(16.8%)	21	(20.0%)
Aspirin	1842	(6.0%)	881	(7.3%)	309	(7.6%)	900	(7.2%)	8	(0.3%)	33	(1.9%)	0	(0.0%)
Non-aspirin anti-platelet agents	1650	(5.4%)	1188	(9.9%)	216	(5.3%)	646	(5.2%)	125	5 (4.2%)	83	(4.8%)	6	(5.7%)
Beta-blockers	6289	(20.5%)	3013	(25.0%)	781	(19.1%)	2480	(19.8%)	548	(18.4%)	307	(17.8%)	22	(21.0%)
Calcium-channel blockers	5299	(17.2%)	2789	(23.2%)	661	(16.2%)	2400	(19.2%)	321	(10.8%)	216	(12.6%)	10	(9.5%)
Digoxin	528	(1.7%)	620	(5.2%)	45	(1.1%)	288	(2.3%)	21	(0.7%)	18	(1.0%)	0	(0.0%)
Statins	7807	(25.4%)	3232	(26.9%)	915	(22.4%)	2908	(23.2%)	680	(22.8%)	411	(23.9%)	33	(31.4%)
Other lipid-lowering agents	2726	(8.9%)	1056	(8.8%)	377	(9.2%)	989	(7.9%)	193	(6.5%)	133	(7.7%)	9	(8.6%)
Loop diuretics	5000	(16.3%)	3413	(28.4%)	626	(15.3%)	2224	(17.8%)	287	(9.6%)	199	(11.6%)	16	(15.2%)
Thiazide	5179	(16.8%)	2345	(19.5%)	750	(18.3%)	2262	(18.1%)	355	(11.9%)	258	(15.0%)	15	(14.3%)
Nitrates	2555	(8.3%)	1710	(14.2%)	329	(8.0%)	1296	(10.4%)	114	4 (3.8%)	79	(4.6%)	11	(10.5%)
Other anti-hypertensives	2080	(6.8%)	1065	(8.8%)	279	(6.8%)	887	(7.1%)	132	(4.4%)	81	(4.7%)	5	(4.8%)
Pentoxifylline/vasodilators	230	(0.7%)	168	(1.4%)	33	(0.8%)	123	(1.0%)	5	(0.2%)	2	(0.1%)	0	(0.0%)
Hypoglycemic medications	4524	(14.7%)	2044	(17.0%)	553	(13.5%)	1767	(14.1%)	351	(11.8%)	245	(14.2%)	12	(11.4%)
Insulin	2198	(7.1%)	1301	(10.8%)	284	(6.9%)	904	(7.2%)	166	(5.6%)	104	4 (6.0%)	4	(3.8%)

	Morphine N=30,745		Fentanyl N=12,037		Methadone N=4,088		Oxycodone N=12,520		Oxymorphone N=2,981		Tramadol N=1,720		Others N=105	
Thyroid Hormones	2884	(9.4%)	1917	(15.9%)	383	(9.4%)	1230	(9.8%)	314	(10.5%)	172	(10.0%)	19	(18.1%)
Bronchodilators, beta agonists	8106	(26.4%)	3095	(25.7%)	1042	(25.5%)	3083	(24.6%)	819	(27.5%)	393	(22.8%)	36	(34.3%)
Bronchodilators, other	4492	(14.6%)	2004	(16.6%)	582	(14.2%)	1743	(13.9%)	286	(9.6%)	151	1 (8.8%)	9	(8.6%)
Proton Pump Inhibitors	10269	(33.4%)	5147	(42.8%)	1445	(35.3%)	3954	(31.6%)	770	(25.8%)	515	(29.9%)	48	(45.7%)
NSAIDs	20144	(65.5%)	6642	(55.2%)	2694	(65.9%)	8027	(64.1%)	1700	(57.0%)	1151	(66.9%)	65	(61.9%)
Glucocorticoids	15940	(51.8%)	5196	(43.2%)	1817	(44.4%)	5636	(45.0%)	1509	(50.6%)	888	(51.6%)	58	(55.2%)
Antidepressants	19641	(63.9%)	8109	(67.4%)	2773	(67.8%)	7789	(62.2%)	1584	(53.1%)	913	(53.1%)	58	(55.2%)
Antipsychotics	4359	(14.2%)	2481	(20.6%)	626	(15.3%)	1427	(11.4%)	324	(10.9%)	203	(11.8%)	12	(11.4%)
Sedatives	4968	(16.2%)	1957	(16.3%)	611	(14.9%)	1685	(13.5%)	466	(15.6%)	282	(16.4%)	18	(17.1%)
Lithium	431	(1.4%)	101	(0.8%)	53	(1.3%)	151	(1.2%)	40	(1.3%)	16	(0.9%)	1	(1.0%)
Minor tranquilizers/barbiturates	1365	(4.4%)	492	(4.1%)	191	(4.7%)	449	(3.6%)	140	(4.7%)	93	(5.4%)	5	(4.8%)
Anticonvulsants	12653	(41.2%)	4423	(36.7%)	1629	(39.8%)	3597	(28.7%)	1468	(49.2%)	629	(36.6%)	50	(47.6%)
Dementia Drugs	393	(1.3%)	980	(8.1%)	53	(1.3%)	161	(1.3%)	19	(0.6%)	20	(1.2%)	1	(1.0%)
ADHD medications	752	(2.4%)	167	(1.4%)	126	(3.1%)	214	(1.7%)	139	(4.7%)	50	(2.9%)	2	(1.9%)
Alcohol aversion agents	17	(0.1%)	7	(0.1%)	7	(0.2%)	13	(0.1%)	2	(0.1%)	1	(0.1%)	0	(0.0%)
Smoking cessation products	387	(1.3%)	105	5 (0.9%)	48	(1.2%)	136	(1.1%)	73	(2.4%)	38	(2.2%)	1	(1.0%)
DMARDs	613	(2.0%)	303	(2.5%)	67	(1.6%)	301	(2.4%)	48	(1.6%)	18	(1.0%)	4	(3.8%)
Frailty														
TIA	69	(0.2%)	38	(0.3%)	9	(0.2%)	37	(0.3%)	3	(0.1%)	2	(0.1%)	0	(0.0%)
Urinary Tract	1403	(4.6%)	864	(7.2%)	170	(4.2%)	591	(4.7%)	73	(2.4%)	58	(3.4%)	3	(2.9%)
Ambulation devices	2125	(6.9%)	1186	(9.9%)	253	(6.2%)	864	(6.9%)	138	(4.6%)	83	(4.8%)	7	(6.7%)
CPAP/BIPAP	1224	(4.0%)	329	(2.7%)	139	(3.4%)	314	(2.5%)	121	(4.1%)	69	(4.0%)	4	(3.8%)
Decubitus/pressure ulcers	806	(2.6%)	632	(5.3%)	95	(2.3%)	365	(2.9%)	36	(1.2%)	16	(0.9%)	0	(0.0%)
Enteral & Parenteral nutrition	317	(1.0%)	332	(2.8%)	54	(1.3%)	117	(0.9%)	28	(0.9%)	21	(1.2%)	2	(1.9%)
Impaired Mobility	370	(1.2%)	185	(1.5%)	73	(1.8%)	199	(1.6%)	29	(1.0%)	10	(0.6%)	2	(1.9%)
Incontinence	727	(2.4%)	489	(4.1%)	79	(1.9%)	262	(2.1%)	67	(2.2%)	28	(1.6%)	5	(4.8%)
Oxygen supplementation	1977	(6.4%)	799	(6.6%)	182	(4.5%)	608	(4.9%)	204	(6.8%)	83	(4.8%)	4	(3.8%)
Rehabilitation	1051	(3.4%)	381	(3.2%)	138	(3.4%)	578	(4.6%)	70	(2.3%)	65	(3.8%)	3	(2.9%)
Healthcare utilization														
Nursing facility in past year	152	(0.6%)	352	(5.0%)	18	(0.6%)	78	(0.9%)	8	(0.4%)	12	(1.1%)	1	(1.2%)
Observation setting in past year	1043	(4.3%)	394	(5.6%)	125	(4.1%)	416	(4.7%)	83	(3.7%)	54	(4.8%)	2	(2.4%)
Outpatient/ED visit in past year	14379	(59.5%)	4199	(60.1%)	1885	(61.1%)	5329	(60.5%)	1284	(56.7%)	709	(62.5%)	42	(51.2%)
ED visits in past year														
0	9533	(39.5%)	2791	(39.9%)	1111	(36.0%)	3274	(37.2%)	978	(43.2%)	411	(36.2%)	42	(51.2%)
1	5950	(24.6%)	1746	(25.0%)	679	(22.0%)	1984	(22.5%)	629	(27.8%)	269	(23.7%)	13	(15.9%)
2	3136	(13.0%)	898	(12.8%)	413	(13.4%)	1180	(13.4%)	313	(13.8%)	165	(14.5%)	16	(19.5%)
$\geq$ 3	5543	(22.9%)	1557	(22.3%)	882	(28.6%)	2367	(26.9%)	346	(15.3%)	290	(25.6%)	11	(13.4%)
Outpatient visits in past year														
0	5405	(22.4%)	2012	(28.8%)	716	(23.2%)	2541	(28.9%)	432	(19.1%)	364	(32.1%)	11	(13.4%)
1	5292	(21.9%)	1444	(20.7%)	693	(22.5%)	1986	(22.6%)	454	(20.0%)	272	(24.0%)	18	(22.0%)
2	6554	(27.1%)	1655	(23.7%)	771	(25.0%)	2003	(22.7%)	681	(30.1%)	265	(23.3%)	20	(24.4%)
$\geq$ 3	6911	(28.6%)	1881	(26.9%)	905	(29.3%)	2275	(25.8%)	699	(30.8%)	234	(20.6%)	33	(40.2%)
Hospitalizations in past year														
0	19453	(80.5%)	4932	(70.5%)	2420	(78.4%)	6712	(76.2%)	2016	(89.0%)	965	(85.0%)	73	(89.0%)
1	4258	(17.6%)	1837	(26.3%)	601	(19.5%)	1870	(21.2%)	241	(10.6%)	155	(13.7%)	9	(11.0%)
$\geq$ 2	451	(1.9%)	223	(3.2%)	64	(2.1%)	223	(2.5%)	9	(0.4%)	15	(1.3%)	0	(0.0%)
Demographics														

	Morphine N=30,745		Fentanyl N=12,037		Methadone N=4,088		Oxycodone N=12,520		Oxymorphone N=2,981		Tramadol N=1,720		Others N=105	
Age														
<30	2101	(6.8%)	366	(3.0%)	305	(7.5%)	1005	(8.0%)	289	(9.7%)	313	(18.2%)	16	(15.2%)
30-<40	6227	(20.3%)	1182	(9.8%)	877	(21.5%)	2291	(18.3%)	772	(25.9%)	421	(24.5%)	17	(16.2%)
40-<50	8793	(28.6%)	2080	(17.3%)	1331	(32.6%)	3295	(26.3%)	875	(29.4%)	382	(22.2%)	24	(22.9%)
50-<60	7444	(24.2%)	2056	(17.1%)	975	(23.9%)	2764	(22.1%)	674	(22.6%)	273	(15.9%)	23	(21.9%)
60-<70	3896	(12.7%)	1841	(15.3%)	402	(9.8%)	1883	(15.0%)	273	(9.2%)	177	(10.3%)	18	(17.1%)
70-<80	1484	(4.8%)	1663	(13.8%)	133	(3.3%)	784	(6.3%)	76	2.5%)	94	5.5%)	5	(4.8%)
≥ 80	800	(2.6%)	2849	(23.7%)	65	1.6%)	498	(4.0%)	22	0.7%)	60	3.5%)	2	(1.9%)
Race														
White	24511	(79.7%)	9970	(82.8%)	3290	(80.5%)	10178	(81.3%)	2441	(81.9%)	1255	(73.0%)	83	(79.0%)
Black/Other/Unknown	6234	(20.3%)	2067	(17.2%)	798	(19.5%)	2342	(18.7%)	540	(18.1%)	465	(27.0%)	22	(21.0%)
Year of cohort entry	152	0.5%)	38	0.3%)	12	0.3%)	0	.0%)	0	(0.0%)	0	(0.0%)	1	(1.0%)
1995	216	0.7%)	46	0.4%)	9	.2%)	17	0.1%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
1996	343	1.1%)	65	0.5%)	28	0.7%)	39	0.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
1997	588	1.9%)	111	(0.9%)	92	2.3%)	156	(1.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
1998	1029	(3.3%)	140	(1.2%)	164	(4.0%)	383	(3.1%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
1999	1631	(5.3%)	284	(2.4%)	215	(5.3%)	1726	(13.8%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
2000	1684	(5.5%)	928	(7.7%)	257	(6.3%)	2380	(19.0%)	0	(0.0%)	0	(0.0%)	1	(1.0%)
2001	1768	(5.8%)	1613	(13.4%)	549	(13.4%)	1657	(13.2%)	0	(0.0%)	0	(0.0%)	1	(1.0%)
2002	2410	(7.8%)	1926	(16.0%)	503	(12.3%)	1592	(12.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
2003	3684	(12.0%)	1544	(12.8%)	497	(12.2%)	815	(6.5%)	0	(0.0%)	0	(0.0%)	1	(1.0%)
2004	2738	(8.9%)	1042	(8.7%)	527	(12.9%)	817	(6.5%)	0	(0.0%)	0	(0.0%)	16	(15.2%)
2005	1801	(5.9%)	773	(6.4%)	308	(7.5%)	550	(4.4%)	9	(0.3%)	450	(26.2%)	0	(0.0%)
2006	1649	(5.4%)	718	(6.0%)	258	(6.3%)	531	(4.2%)	35	(1.2%)	439	(25.5%)	0	(0.0%)
2007	1579	(5.1%)	574	(4.8%)	185	(4.5%)	484	(3.9%)	223	(7.5%)	282	(16.4%)	0	(0.0%)
2008	1481	(4.8%)	464	(3.9%)	133	(3.3%)	356	(2.8%)	610	(20.5%)	167	(9.7%)	1	(1.0%)
2009	1597	(5.2%)	341	(2.8%)	57	1.4%)	187	(1.5%)	588	(19.7%)	62	3.6%)	0	(0.0%)
2010	1629	(5.3%)	329	(2.7%)	39	1.0%)	148	(1.2%)	285	(9.6%)	47	2.7%)	3	(2.9%)
2011	1994	(6.5%)	352	(2.9%)	49	1.2%)	191	(1.5%)	299	(10.0%)	60	3.5%)	27	(25.7%)
2012	1543	(5.0%)	370	(3.1%)	152	(3.7%)	271	(2.2%)	539	(18.1%)	97	5.6%)	25	(23.8%)
2013	1229	(4.0%)	379	(3.1%)	54	1.3%)	220	(1.8%)	393	(13.2%)	116	(6.7%)	29	(27.6%)
2014														
Month of cohort entry	2707	(8.8%)	1005	(8.3%)	338	(8.3%)	1145	(9.1%)	246	(8.3%)	127	(7.4%)	9	(8.6%)
January	2437	(7.9%)	924	(7.7%)	312	(7.6%)	982	(7.8%)	201	(6.7%)	119	(6.9%)	6	(5.7%)
February	2529	(8.2%)	991	(8.2%)	357	(8.7%)	968	(7.7%)	223	(7.5%)	176	(10.2%)	18	(17.1%)
March	2523	(8.2%)	987	(8.2%)	339	(8.3%)	1024	(8.2%)	237	(8.0%)	190	(11.0%)	7	(6.7%)
April	2554	(8.3%)	1020	(8.5%)	347	(8.5%)	993	(7.9%)	190	(6.4%)	135	(7.8%)	13	(12.4%)
May	2569	(8.4%)	972	(8.1%)	408	(10.0%)	929	(7.4%)	305	(10.2%)	128	(7.4%)	14	(13.3%)
June	2520	(8.2%)	995	(8.3%)	405	(9.9%)	1107	(8.8%)	213	(7.1%)	142	(8.3%)	8	(7.6%)
July	2661	(8.7%)	1068	(8.9%)	352	(8.6%)	1087	(8.7%)	300	(10.1%)	138	(8.0%)	5	(4.8%)
August	2418	(7.9%)	1048	(8.7%)	303	(7.4%)	1026	(8.2%)	250	(8.4%)	142	(8.3%)	9	(8.6%)
September	2676	(8.7%)	1057	(8.8%)	348	(8.5%)	1066	(8.5%)	286	(9.6%)	155	(9.0%)	7	(6.7%)
October	2650	(8.6%)	1029	(8.5%)	302	(7.4%)	1141	(9.1%)	300	(10.1%)	141	(8.2%)	2	(1.9%)
November	2501	(8.1%)	941	(7.8%)	277	(6.8%)	1052	(8.4%)	230	(7.7%)	127	(7.4%)	7	(6.7%)
December	2101	(6.8%)	366	(3.0%)	305	(7.5%)	1005	(8.0%)	289	(9.7%)	313	(18.2%)	16	(15.2%)
Sex	11873	(38.6%)	3417	(28.4%)	1657	(40.5%)	5161	(41.2%)	1143	(38.3%)	453	(26.3%)	35	(33.3%)
Male	18872	(61.4%)	8620	(71.6%)	2431	(59.5%)	7359	(58.8%)	1838	(61.7%)	1267	(73.7%)	70	(66.7%)
Female	11873	(38.6%)	3417	(28.4%)	1657	(40.5%)	5161	(41.2%)	1143	(38.3%)	453	(26.3%)	35	(33.3%)

Appendix Table C6. Description of follow-up among prescribed study drugs

Opioid Type	Total initiating at baseline (t_0)	Median duration of current use follow-up in days (mean)	Total person-years of follow-up [total = 40,497 person-years (py)]							
			Inactive (713 py)		New Use (4,165 py)		Current Use (19,371 py)		Unexposed (16,248 py)	
Morphine	30,475	62 (132)	331	2%	2118	11%	10074	50%	7578	38%
Fentanyl	12,037	49 (112)	154	2%	686	10%	2958	45%	2771	42%
Methadone	4,088	65 (130)	44	2%	272	10%	1212	46%	1132	43%
Oxycodone	12,520	66 (132)	166	2%	736	9%	3902	47%	3556	43%
Oxymorphone	2,981	65 (129)	9	0%	227	12%	1049	56%	588	31%
Tramadol	1,720	58 (99)	9	1%	118	13%	165	19%	597	67%
Other Opioids	105	31.5 (87)	1	2%	7	16%	12	27%	25	56%

Appendix Table C7. Reasons for end of follow-up according to type of long-acting opioid prescribed

	Morphine N=30,745		Fentanyl N=12,037		Methadone N=4,088		Oxycodone N=12,520		Oxymorphone N=2,981		Tramadol N=1,720		Others N=1,05	
Endpoint														
End of study	667	(2.2%)	97	(0.8%)	42	(1.0%)	64	(0.5%)	216	(7.2%)	51	(3.0%)	6	(5.7%)
Death	481	(1.6%)	1246	(10.4%)	51	(1.2%)	152	(1.2%)	23	(0.8%)	5	(0.3%)	0	(0.0%)
Developed serious condition	9056	(29.5%)	3336	(27.7%)	1137	(27.8%)	3531	(28.2%)	940	(31.5%)	361	(21.0%)	14	(13.3%)
Loss of eligibility	2385	(7.8%)	723	(6.0%)	311	(7.6%)	873	(7.0%)	307	(10.3%)	153	(8.9%)	8	(7.6%)
Switched long-acting opioid	5653	(18.4%)	2138	(17.8%)	920	(22.5%)	2501	(20.0%)	552	(18.5%)	91	(5.3%)	36	(34.3%)
Use of non-study opioid	2477	(8.1%)	866	(7.2%)	267	(6.5%)	643	(5.1%)	248	(8.3%)	137	(8.0%)	4	(3.8%)
No use in 180 days	9672	(31.5%)	3399	(28.2%)	1317	(32.2%)	4614	(36.9%)	678	(22.7%)	916	(53.3%)	37	(35.2%)
Serious infection	354	(1.2%)	232	(1.9%)	43	(1.1%)	142	(1.1%)	17	(0.6%)	6	(0.3%)	0	(0.0%)

Appendix Table C8. Standardized mean difference of covariates before and after weighting with the inverse-probability of treatment for each pairwise comparison

	Standardized differences before and after inverse-probability of treatment weighting									
	Morphine vs. Fentanyl		Morphine vs. Oxycodone		Morphine vs. Methadone		Morphine vs. Oxymorphone		Morphine vs. Tramadol	
Comorbidities	Before	After	Before	After	Before	After	Before	After	Before	After
Alcohol Abuse	0.03	0.01	0.05	0.00	0.08	0.00	0.06	0.02	0.06	0.00
Alternation of Consciousness	0.02	0.00	0.01	0.00	0.04	0.01	0.02	0.01	0.01	0.01
Arrhythmias	0.12	0.00	0.02	0.00	0.01	0.01	0.08	0.01	0.06	0.01
Atrial Fibrillation	0.11	0.00	0.03	0.00	0.08	0.00	0.03	0.00	0.02	0.02
Autonomic neuropathy	0.05	0.00	0.03	0.00	0.02	0.01	0.01	0.00	0.03	0.01
Bipolar Disorder	0.01	0.01	0.02	0.01	0.01	0.00	0.07	0.00	0.01	0.01
Cardiac valve disease	0.03	0.00	0.01	0.00	0.03	0.00	0.07	0.00	0.05	0.01
Cerebral Palsy	0.01	0.00	0.06	0.00	0.08	0.00	0.08	0.00	0.07	0.00
Cong heart anomalies	0.03	0.00	0.00	0.00	0.03	0.00	0.01	0.00	0.00	0.01
Chronic Bronchitis	0.02	0.03	0.03	0.01	0.05	0.01	0.05	0.00	0.09	0.01
Dementia	0.24	0.02	0.03	0.00	0.05	0.00	0.06	0.01	0.05	0.04
Depression	0.02	0.01	0.06	0.00	0.01	0.01	0.02	0.01	0.12	0.01
Comorbidity. Diabetes	0.04	0.02	0.02	0.01	0.01	0.00	0.08	0.02	0.00	0.01
Drug adverse events	0.04	0.00	0.01	0.00	0.02	0.00	0.05	0.01	0.06	0.02
Drug poisoning (accidental)	0.03	0.00	0.00	0.00	0.01	0.00	0.02	0.00	0.01	0.00
Drug poisoning (other drugs)	0.03	0.00	0.00	0.00	0.03	0.00	0.04	0.01	0.01	0.00
Drug poisoning/overdose	.	.	.	.	.	.	.	.	.	.
Essential hypertension	0.04	0.02	0.03	0.01	0.03	0.00	0.10	0.00	0.14	0.01
Lipid disorders	0.02	0.01	0.01	0.00	0.01	0.00	0.07	0.01	0.10	0.00
Mental retardation	0.06	0.01	0.04	0.00	0.04	0.00	0.04	0.00	0.02	0.00
Multiple system atrophy	0.00	0.00	0.01	0.00	0.01	0.00	0.02	0.00	0.02	0.00
Acute Nephritis	0.02	0.01	0.02	0.00	0.03	0.00	0.02	0.00	0.03	0.00
Chronic Nephritis	0.02	0.00	0.00	0.00	0.01	0.00	0.01	0.01	0.03	0.00
Obesity	0.07	0.00	0.04	0.00	0.07	0.00	0.04	0.01	0.00	0.01
Bariatric surgery	0.02	0.00	0.00	0.00	0.02	0.00	0.05	0.03	0.04	0.01
Obstructive coronary artery disease	0.09	0.01	0.05	0.00	0.01	0.01	0.10	0.01	0.13	0.00
Osteomyelitis	0.01	0.00	0.01	0.00	0.01	0.00	0.07	0.00	0.08	0.00
Osteoporosis	0.15	0.01	0.01	0.01	0.02	0.01	0.14	0.00	0.08	0.02
Osteoporosis-related BMD testing	0.04	0.02	0.02	0.01	0.04	0.00	0.27	0.00	0.09	0.01
Pacemaker	0.05	0.01	0.00	0.00	0.01	0.01	0.01	0.01	0.02	0.02
Parkinson's Disease	0.15	0.00	0.06	0.00	0.03	0.00	0.02	0.00	0.00	0.00
Peripheral artery disease	0.09	0.01	0.11	0.00	0.02	0.01	0.08	0.02	0.02	0.02
Peripheral neuropathy	0.08	0.01	0.03	0.00	0.03	0.01	0.03	0.00	0.01	0.01
Personality disorders	0.02	0.01	0.01	0.00	0.03	0.00	0.06	0.00	0.02	0.01
Pneumonia	0.06	0.00	0.02	0.00	0.04	0.01	0.10	0.00	0.09	0.01
Infections	0.04	0.01	0.02	0.01	0.00	0.00	0.08	0.02	0.01	0.01
Diabetic neuropathy	0.01	0.02	0.04	0.00	0.03	0.01	0.07	0.00	0.02	0.01
Neuropathy	0.02	0.00	0.03	0.00	0.03	0.00	0.01	0.03	0.05	0.00
Diabetes related	0.01	0.01	0.03	0.00	0.03	0.01	0.06	0.00	0.07	0.00
Retinopathy	0.01	0.00	0.02	0.00	0.02	0.00	0.04	0.01	0.01	0.00
Ulcers/amputations	0.02	0.00	0.05	0.00	0.03	0.00	0.05	0.00	0.05	0.00

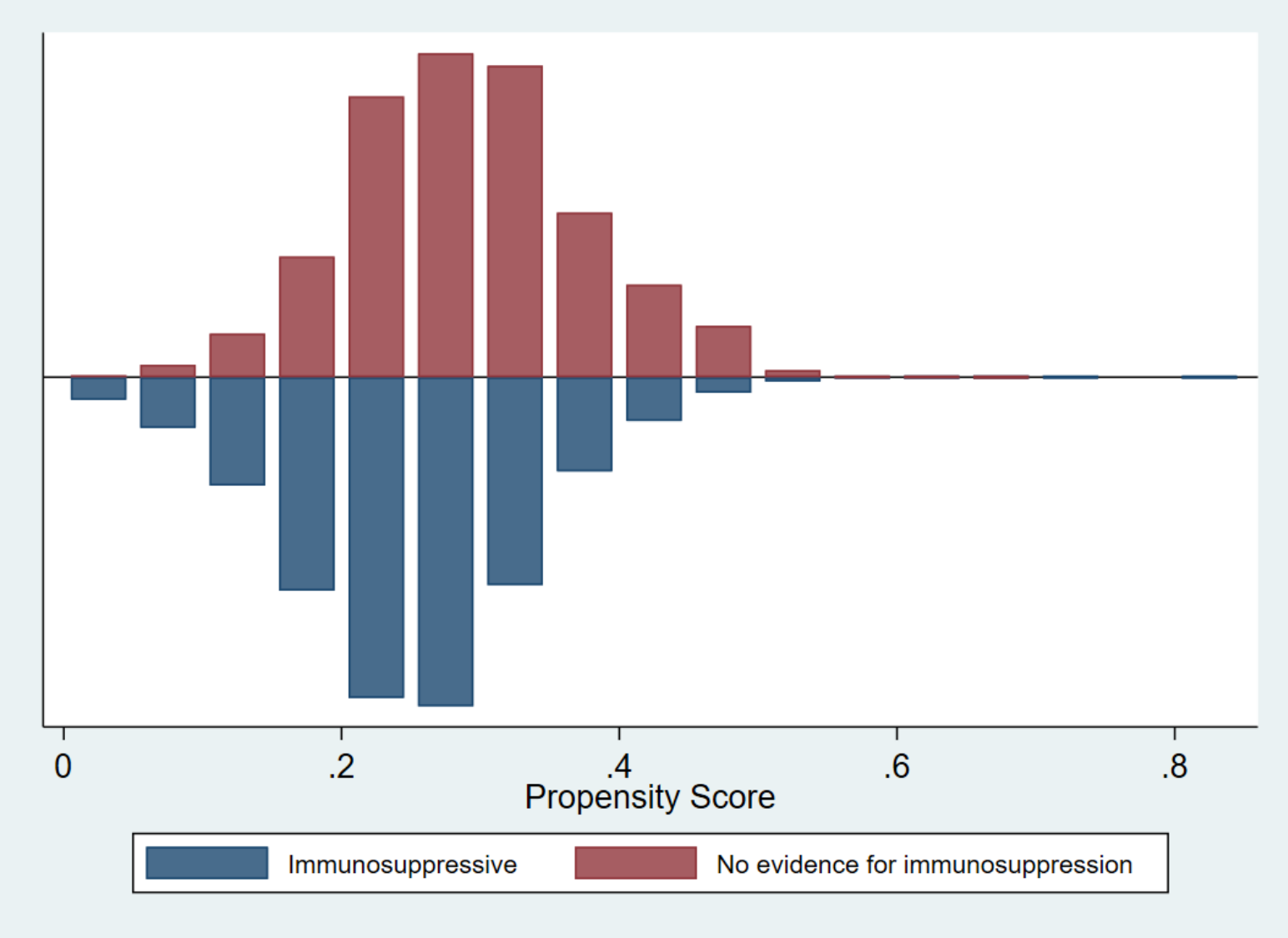
	Standardized differences before and after inverse-probability of treatment weighting									
	Morphine vs. Fentanyl		Morphine vs. Oxycodone		Morphine vs. Methadone		Morphine vs. Oxymorphone		Morphine vs. Tramadol	
Comorbidities	Before	After	Before	After	Before	After	Before	After	Before	After
Amputations	0.02	0.01	0.00	0.00	0.02	0.00	0.05	0.00	0.05	0.00
Post-traumatic stress disorder	0.01	0.01	0.01	0.00	0.03	0.00	0.01	0.02	0.07	0.00
Schizophrenia	0.02	0.00	0.03	0.00	0.03	0.00	0.01	0.01	0.00	0.00
Seizures	0.04	0.00	0.02	0.00	0.04	0.01	0.01	0.01	0.05	0.01
Sepsis/Bacteremia	0.04	0.01	0.03	0.00	0.07	0.01	0.02	0.01	0.10	0.01
Serious Hepatic Disease	0.07	0.00	0.01	0.00	0.02	0.01	0.07	0.00	0.02	0.00
Hemolytic anemia	.	.	.	.	.	.	.	.	.	.
Sickle-cell diseases	0.01	0.01	0.01	0.00	0.05	0.00	0.03	0.00	0.06	0.00
Tobacco use	0.01	0.01	0.01	0.00	0.05	0.00	0.03	0.00	0.05	0.00
Thyroid disease	0.07	0.00	0.05	0.00	0.08	0.01	0.22	0.02	0.08	0.03
Pregnancy	0.11	0.01	0.02	0.00	0.02	0.01	0.02	0.00	0.06	0.01
Alcohol Abuse	0.08	0.00	0.01	0.01	0.04	0.00	0.10	0.01	0.07	0.01
Abdominal Pain	0.00	0.02	0.01	0.00	0.00	0.00	0.04	0.00	0.07	0.01
Back pain	0.59	0.03	0.23	0.01	0.09	0.01	0.13	0.01	0.37	0.03
Dental Pain	0.05	0.00	0.02	0.01	0.02	0.00	0.01	0.00	0.02	0.00
External causes of injury	0.04	0.00	0.04	0.00	0.01	0.00	0.12	0.00	0.05	0.00
Self-inflicted	0.00	0.00	0.01	0.00	0.01	0.00	0.01	0.00	0.01	0.01
Trauma	0.04	0.00	0.05	0.00	0.07	0.00	0.08	0.02	0.11	0.02
Headache	0.11	0.01	0.01	0.00	0.05	0.01	0.03	0.00	0.04	0.01
Musculoskeletal Pain	0.29	0.03	0.11	0.01	0.10	0.00	0.00	0.01	0.23	0.02
Pain Not Specified	0.12	0.01	0.06	0.00	0.11	0.00	0.19	0.01	0.11	0.01
Arthritis/SLE	0.01	0.01	0.03	0.01	0.06	0.00	0.05	0.01	0.14	0.00
Neuropathic Pain	0.15	0.01	0.07	0.00	0.01	0.01	0.02	0.00	0.18	0.01
Multiple Sclerosis	0.02	0.00	0.01	0.01	0.04	0.01	0.06	0.00	0.05	0.01
Hydrocodone	0.17	0.01	0.06	0.01	0.02	0.00	0.31	0.00	0.35	0.04
Oxycodone	0.20	0.00	0.03	0.01	0.10	0.00	0.70	0.01	0.31	0.02
Other opioids	0.19	0.02	0.03	0.00	0.11	0.00	0.19	0.00	0.67	0.06
More than one SA opioid	0.15	0.02	0.05	0.01	0.01	0.01	0.26	0.00	0.01	0.00
Influenza vaccine	0.03	0.02	0.12	0.00	0.09	0.00	0.01	0.01	0.11	0.02
Pneumococcal vaccine	0.04	0.01	0.03	0.01	0.01	0.00	0.02	0.01	0.02	0.01
Anti-arrhythmics	0.14	0.01	0.04	0.00	0.01	0.00	0.12	0.01	0.07	0.02
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocks	0.05	0.01	0.05	0.00	0.09	0.00	0.00	0.01	0.03	0.04
Anticoagulants	0.26	0.01	0.03	0.01	0.01	0.00	0.05	0.00	0.12	0.01
Antibiotics	0.07	0.01	0.03	0.01	0.01	0.00	0.15	0.03	0.02	0.03
Antifungals	0.14	0.01	0.00	0.00	0.01	0.01	0.00	0.01	0.21	0.02
Aspirin	0.00	0.01	0.07	0.01	0.06	0.01	0.33	0.00	0.24	0.02
Non-aspirin anti-platelet agents	0.20	0.01	0.00	0.01	0.03	0.00	0.06	0.00	0.03	0.01
Beta-blockers	0.09	0.02	0.05	0.01	0.03	0.01	0.05	0.00	0.07	0.00
Calcium-channel blockers	0.17	0.00	0.04	0.00	0.04	0.00	0.17	0.01	0.11	0.01
Digoxin	0.18	0.01	0.06	0.00	0.06	0.00	0.09	0.00	0.07	0.01
Statins	0.02	0.02	0.03	0.00	0.07	0.01	0.02	0.02	0.02	0.00
Other lipid-lowering agents	0.01	0.01	0.02	0.00	0.03	0.00	0.05	0.03	0.03	0.02
Loop diuretics	0.34	0.00	0.04	0.01	0.03	0.00	0.21	0.01	0.07	0.00
Thiazide	0.03	0.02	0.02	0.00	0.05	0.01	0.13	0.01	0.02	0.01

	Standardized differences before and after inverse-probability of treatment weighting									
	Morphine vs. Fentanyl		Morphine vs. Oxycodone		Morphine vs. Methadone		Morphine vs. Oxymorphone		Morphine vs. Tramadol	
Comorbidities	Before	After	Before	After	Before	After	Before	After	Before	After
Nitrates	0.19	0.01	0.12	0.00	0.04	0.01	0.13	0.01	0.14	0.03
Other anti-hypertensives	0.15	0.00	0.01	0.01	0.03	0.00	0.14	0.00	0.05	0.01
Pentoxifylline/vasodilators	0.06	0.00	0.02	0.00	0.01	0.00	0.09	0.00	0.09	0.01
Hypoglycemic medications	0.03	0.01	0.03	0.00	0.03	0.00	0.06	0.02	0.06	0.01
Insulin	0.15	0.00	0.05	0.01	0.03	0.01	0.06	0.01	0.04	0.01
Thyroid Hormones	0.24	0.01	0.02	0.00	0.02	0.01	0.05	0.00	0.14	0.05
Bronchodilators, beta ag	0.02	0.01	0.03	0.01	0.04	0.00	0.04	0.00	0.06	0.02
Bronchodilators, other	0.02	0.03	0.03	0.01	0.05	0.00	0.16	0.01	0.17	0.00
Proton Pump Inhibitors	0.25	0.03	0.03	0.01	0.01	0.01	0.11	0.01	0.06	0.05
NSAIDs	0.23	0.01	0.04	0.00	0.04	0.00	0.22	0.01	0.03	0.03
Glucocorticoids	0.23	0.02	0.16	0.00	0.14	0.00	0.00	0.02	0.01	0.00
Antidepressants	0.15	0.01	0.04	0.01	0.03	0.00	0.27	0.01	0.14	0.01
Antipsychotics	0.29	0.01	0.10	0.01	0.02	0.00	0.09	0.00	0.03	0.02
Sedatives	0.02	0.01	0.07	0.01	0.10	0.00	0.00	0.02	0.02	0.02
Lithium	0.05	0.00	0.02	0.00	0.00	0.00	0.05	0.01	0.05	0.01
Tranquilizers/barbiturates	0.01	0.00	0.03	0.01	0.01	0.00	0.04	0.01	0.02	0.01
Anticonvulsants	0.01	0.00	0.23	0.01	0.04	0.01	0.14	0.03	0.04	0.01
Dementia Drugs	0.46	0.01	0.00	0.01	0.05	0.00	0.08	0.00	0.07	0.04
ADHD medications	0.07	0.01	0.06	0.00	0.01	0.00	0.10	0.01	0.02	0.00
Alcohol aversion agents	0.02	0.00	0.03	0.01	0.03	0.01	0.01	0.00	0.02	0.00
Smoking cessation products	0.03	0.01	0.00	0.01	0.02	0.00	0.05	0.01	0.08	0.02
DMARDs	0.02	0.01	0.04	0.00	0.04	0.00	0.02	0.00	0.10	0.01
TIA	0.03	0.01	0.01	0.00	0.02	0.00	0.03	0.01	0.06	0.01
Urinary Tract	0.16	0.01	0.03	0.00	0.03	0.00	0.12	0.01	0.00	0.01
Ambulation devices	0.08	0.01	0.01	0.00	0.07	0.01	0.15	0.01	0.10	0.02
CPAP/BIPAP	0.07	0.01	0.06	0.00	0.05	0.00	0.09	0.00	0.05	0.00
Decubitus/pressure ulcers	0.14	0.00	0.00	0.00	0.00	0.00	0.12	0.01	0.14	0.00
Enteral & Parenteral nutrition	0.19	0.01	0.04	0.00	0.00	0.01	0.04	0.01	0.08	0.00
Impaired Mobility	0.02	0.00	0.02	0.00	0.04	0.01	0.10	0.00	0.05	0.01
Incontinence	0.11	0.01	0.05	0.00	0.01	0.01	0.02	0.00	0.01	0.03
Oxygen supplementation	0.07	0.01	0.07	0.01	0.07	0.00	0.02	0.02	0.05	0.02
Rehabilitation	0.01	0.01	0.05	0.01	0.01	0.00	0.09	0.00	0.10	0.02
Transient ischemic attack	0.65	0.00	0.04	0.00	0.03	0.00	0.07	0.00	0.17	0.03
Urinary Tract	0.01	0.00	0.01	0.00	0.02	0.01	0.01	0.00	0.02	0.01
Ambulation devices	0.11	0.01	0.05	0.00	0.01	0.00	0.03	0.02	0.06	0.04
Race: White	0.08	0.02	0.05	0.01	0.04	0.00	0.06	0.02	0.15	0.02
Race: Black/Other	0.08	0.02	0.05	0.01	0.04	0.00	0.06	0.02	0.15	0.02
January	0.01	0.00	0.02	0.00	0.10	0.00	0.06	0.01	0.04	0.01
February	0.03	0.00	0.02	0.00	0.04	0.00	0.04	0.02	0.03	0.02
March	0.03	0.01	0.08	0.01	0.02	0.00	0.08	0.00	0.07	0.02
April	0.01	0.00	0.02	0.00	0.00	0.00	0.02	0.00	0.12	0.03
May	0.03	0.01	0.01	0.00	0.11	0.01	0.02	0.01	0.02	0.01
June	0.02	0.00	0.02	0.00	0.06	0.00	0.09	0.00	0.06	0.01
July	0.01	0.01	0.08	0.01	0.10	0.00	0.05	0.00	0.02	0.02
August	0.01	0.01	0.01	0.00	0.00	0.00	0.04	0.01	0.03	0.04
September	0.04	0.00	0.02	0.01	0.05	0.00	0.09	0.00	0.04	0.00
October	0.01	0.02	0.00	0.00	0.03	0.00	0.10	0.01	0.10	0.01

	Standardized differences before and after inverse-probability of treatment weighting									
	Morphine vs. Fentanyl		Morphine vs. Oxycodone		Morphine vs. Methadone		Morphine vs. Oxymorphone		Morphine vs. Tramadol	
Comorbidities	Before	After	Before	After	Before	After	Before	After	Before	After
November	0.04	0.01	0.03	0.00	0.05	0.00	0.03	0.01	0.05	0.01
December	0.02	0.01	0.00	0.00	0.05	0.00	0.05	0.01	0.03	0.03
Age: <30[1]	0.16	0.06	0.01	0.03	0.07	0.04	0.16	0.11	0.31	0.23
Age: 30-<40[1]	0.33	0.14	0.04	0.04	0.01	0.02	0.19	0.09	0.16	0.12
Age: 40-<50[1]	0.40	0.18	0.05	0.04	0.08	0.07	0.03	0.02	0.19	0.13
Age: 50-<60[1]	0.27	0.17	0.03	0.01	0.01	0.03	0.09	0.05	0.27	0.23
Age: 60-<70[1]	0.02	0.03	0.05	0.06	0.12	0.10	0.10	0.06	0.07	0.10
Age: 70-<80[1]	0.41	0.23	0.09	0.07	0.12	0.09	0.11	0.03	0.14	0.18
Age: >=80[1]	0.82	0.41	0.09	0.03	0.01	0.03	0.17	0.06	0.18	0.16
1995[1]	0.01	0.02	0.06	0.08	0.03	0.04	0.06	0.03	0.06	0.06
1996[1]	0.06	0.06	0.08	0.10	0.06	0.07	0.08	0.04	0.08	0.06
1997[1]	0.07	0.07	0.10	0.14	0.06	0.08	0.12	0.06	0.12	0.10
1998[1]	0.09	0.07	0.11	0.15	0.02	0.04	0.16	0.08	0.16	0.15
1999[1]	0.15	0.13	0.13	0.16	0.02	0.03	0.23	0.12	0.23	0.21
2000[1]	0.17	0.16	0.04	0.00	0.03	0.03	0.31	0.17	0.31	0.30
2001[1]	0.06	0.03	0.36	0.32	0.08	0.04	0.34	0.18	0.34	0.31
2002[1]	0.12	0.19	0.35	0.33	0.21	0.20	0.36	0.18	0.36	0.33
2003[1]	10.21	0.31	0.26	0.26	0.21	0.20	0.40	0.21	0.40	0.33
2004[1]	0.08	0.10	0.02	0.03	0.12	0.10	0.48	0.26	0.48	0.43
2005[1]	0.06	0.04	0.05	0.04	0.08	0.07	0.47	0.27	0.47	0.43
2006[1]	0.01	0.04	0.07	0.07	0.01	0.00	0.37	0.26	0.29	0.27
2007[1]	0.01	0.05	0.10	0.07	0.02	0.00	0.32	0.28	0.51	0.45
2008[1]	0.02	0.06	0.08	0.05	0.05	0.03	0.12	0.15	0.32	0.24
2009[1]	0.02	0.06	0.10	0.07	0.08	0.06	0.25	0.23	0.15	0.13
2010[1]	0.04	0.07	0.14	0.11	0.17	0.14	0.46	0.42	0.02	0.04
2011[1]	0.07	0.09	0.21	0.18	0.21	0.17	0.38	0.27	0.01	0.04
2012[1]	0.08	0.10	0.23	0.21	0.26	0.22	0.21	0.02	0.02	0.02
2013[1]	0.06	0.08	0.20	0.19	0.15	0.11	0.35	0.15	0.09	0.09
2014[1]	0.01	0.01	0.16	0.14	0.13	0.09	0.42	0.16	0.21	0.17
ED visits: 0	0.15	0.00	0.03	0.01	0.04	0.00	0.05	0.03	0.04	0.06
ED visits: 1	0.02	0.01	0.05	0.01	0.06	0.00	0.03	0.05	0.03	0.08
ED visits: 2	0.05	0.02	0.02	0.04	0.02	0.02	0.05	0.04	0.07	0.05
ED visits: 3	0.14	0.03	0.00	0.02	0.09	0.02	0.16	0.01	0.08	0.02
Outpatient visits: 0	0.58	0.10	0.19	0.04	0.07	0.02	0.08	0.04	0.28	0.01
Outpatient visits: 1	0.21	0.09	0.01	0.01	0.04	0.06	0.04	0.02	0.03	0.04
Outpatient visits: 2	0.30	0.06	0.15	0.09	0.11	0.06	0.05	0.02	0.15	0.01
Outpatient visits: 3	0.22	0.02	0.07	0.06	0.01	0.03	0.06	0.00	0.24	0.04
Hospitalizations: 0	0.20	0.01	0.04	0.00	0.03	0.00	0.25	0.00	0.14	0.01
Hospitalizations: 1	0.19	0.02	0.04	0.01	0.02	0.00	0.23	0.01	0.11	0.02
Hospitalizations: 2	0.05	0.03	0.01	0.03	0.03	0.01	0.08	0.01	0.10	0.05
Sex: Male	0.41	0.04	0.10	0.00	0.03	0.01	0.07	0.01	0.40	0.05
Sex: Female	0.41	0.04	0.10	0.00	0.03	0.01	0.07	0.01	0.40	0.05

[1]Age and calendar year were not included in the propensity score model, but were included as covariates in the final Poisson regression model

Appendix Figure C1. Distribution of the propensity score for the comparison of non-immunosuppressive and immunosuppressive opioid use among new long-acting opioid users, Tennessee Medicaid (1995-2014)



Appendix Figure C2. Distribution of the propensity score for the comparison of different opioid types relative to morphine among new long-acting opioid users, Tennessee Medicaid (1995-2014)