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The Role of Opioid Prescription in Incident Opioid Abuse and Dependence Among Individuals with Chronic Non-Cancer Pain: The Role of Opioid Prescription

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Abstract

Objective—Increasing rates of opioid use disorders (abuse and dependence) among patients prescribed opioids are a significant public health concern. We investigated the association between exposure to prescription opioids and incident opioid use disorders (OUDs) among individuals with a new episode of a chronic non-cancer pain (CNCP) condition.

Methods—We utilized claims data from the HealthCore Database for 2000–2005. The dataset included all individuals aged 18 and over with a new CNCP episode (no diagnosis in the prior 6 months), and no opioid use or OUD in the prior 6 months (n=568,640). We constructed a single multinomial variable describing prescription opioid days supply (none, acute, and chronic) and average daily dose (none, low dose, medium dose, and high dose), and examined the association between this variable and an incident OUD diagnosis.

Results—Patients with CNCP prescribed opioids had significantly higher rates of OUDs compared to those not prescribed opioids. Effects varied by average daily dose and days supply: low dose, acute (odds ratio (OR)=3.03, 95% confidence interval (CI)= 2.32, 3.95); low dose, chronic (OR=14.92, 95% CI=10.38, 21.46); medium dose, acute (OR=2.80, 95% CI=2.12, 3.71); medium dose, chronic (OR=28.69, 95% CI=20.02, 41.13); high dose, acute (OR=3.10 95% CI=1.67, 5.77); and high dose, chronic (OR=122.45, 95% CI=72.79, 205.99).

Conclusion—Among individuals with a new CNCP episode, prescription opioid exposure was a strong risk factor for incident OUDs; magnitudes of effects were large. Duration of opioid therapy was more important than daily dose in determining OUD risk.

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Conflicts of Interest

There are no conflicts of interest for any author.

INTRODUCTION

Over the past three decades prescription opioids have been increasingly used long-term to manage chronic non-cancer pain (CNCP).¹⁻⁴ In the 1980's, efforts were made to liberalize use of opioids for CNCP, with much of the impetus for these liberalization efforts coming from prior successful opioid initiatives for patients with cancer pain.⁵ Treatment guidelines from numerous professional organizations have endorsed chronic opioid therapy.⁶⁻⁹

Increases in use of opioid therapy for CNCP have been paralleled by increased rates of opioid use disorders (OUDs), suggesting increases in use and abuse are linked. Prescription OUDs are the fastest growing form of drug abuse and overdose deaths involving opioids, either alone, or in combination with other drugs, rose from just over 4,000 to over 16,000 in 2010.¹⁰⁻¹³ About half of these opioid overdose deaths involved another drug, most commonly benzodiazepines.¹⁴ This has heightened concern regarding the risks opioids, and OUDs among individuals using prescription opioids for CNCP are now a significant public health concern. Thus, a key clinical issue facing clinicians is how to balance benefits of opioid therapy with risks of addiction in CNCP patients for whom they are contemplating initiating opioid therapy. The clinical importance of this issue is heightened by the fact that in some patients opioids are the only viable option for managing their pain.

Our objective was to investigate exposure to prescribed opioids as a risk factor for incident OUDs, among individuals with a new episode of CNCP who were not recently on opioids, while controlling for other possible confounders, such as mental health and substance abuse disorders. We were interested in addressing the risk of addiction associated with exposing patients to opioid treatment for CNCP, including: (i) the magnitude of OUD risk; (ii) the populations most vulnerable to OUDs; and (iii) the components of opioid exposure (e.g., daily dose, days used) most important in predicting OUDs. Previous studies, generally using small clinical samples from pain clinics, have investigated (i) and (ii). One review of 24 studies, with sample sizes ranging from 5 to 532, found that estimates of rates of OUDs following exposure to opioids varied widely, from 0 to 45%.¹⁵ Thus more precise estimates are needed, particularly in large populations representing both primary and specialty care, and different regions of the country. Studies suggest that individuals with a past history of substance use disorders have a higher likelihood of developing OUDs,¹⁶⁻¹⁹ although other risk factors remain to be identified. Information on how average daily dose and duration of opioid therapy (days supply) affect the likelihood of development of an incident OUD is limited, although such information is vital for clinicians as they contemplate starting or continuing opioid therapy for a patient with CNCP.

METHODS

Study Population

HealthCore—The HealthCore Integrated Research Database contains medical and pharmacy administrative claims and health plan eligibility data from five commercial health plans representing the West, Mid-West, and South-East regions. Data came from health plan members who were fully-insured via several commercial insurance products including health maintenance organizations, preferred provider organizations, and point-of-service

providers. Health plan members all had full medical and pharmacy coverage, with a range of co-pay and deductibles. Claims submitted with partial or complete subscriber liability (due to co-pay or deductible requirements) are captured.

Analytical Sample

The dataset included all individuals aged 18 years or older with a new episode of a CNCP condition. Data was from years 2000 to 2005. The following criteria were used to identify new episodes of a CNCP condition:

1. Two or more claims containing primary or secondary diagnoses of the same type of CNCP (back pain, neck pain, headache, arthritis, HIV) that occurred at least 1 month apart but were not separated by more than 1 year
2. No CNCP diagnoses of the same type in the 6 months prior to the first qualifying diagnosis

The day of the first diagnosis was defined as the index date. Individuals who already had a CNCP condition (e.g. back pain), were eligible for the analytical sample if they had a new episode of a different CNCP condition (e.g., headache). As we were interested in studying new onset (incidence) of OUDs among those newly prescribed opioids, individuals with OUD diagnoses and/or any prescription opioid use in the 6 months prior to the index date were excluded. Eligible individuals were required to have 12 months of continuous eligibility prior to and 18 months of continuous eligibility after the index date. Individuals with a cancer diagnosis at any time in the 12 months before or after 18 months after the index date (other than non-melanoma skin cancer) were excluded from our study, as were residents of nursing homes, and those receiving hospice benefits. There were 568,640 enrollees in the analytical sample. Additional details concerning the TROUP study have been reported elsewhere.^{3, 20}

Measures

Outcomes—The outcome of interest was any diagnosis of an OUD (opioid abuse or dependence) occurring in the 18-month period after the index date. The outcome was binary, and derived from ICD-9-CM codes (304.00, 305.50).

Independent Variables

Opioid Characteristics: Data on opioid characteristics was derived from the 12-month period following the index date. Because of collinearity between days supply and average daily dose (individuals with 0 days supply by definition also had 0 mg average daily dose), and to allow for interactions between days supply and average daily dose, we constructed a single 7-category multinomial variable describing both opioid days supply and average daily opioid dose for the 12 month period after the index date. Days supply could be none (0 days), acute (1–90 days), or chronic (91+ days). The 91-day threshold was chosen because it is unlikely that an individual would receive opioids for 91 days or more (usually four or more prescriptions) in a six-month period for acute conditions. Further, it appears that 91 days represents an important point in the treatment process where clinicians will want to know the clinical risk of continuing opioid therapy. Hence, we believe this is a reasonable

‘threshold’ for risk analyses. Other investigators have used similar definition for chronic use in their research.^{16, 21, 22} Average daily dose was measured in morphine equivalents and grouped as none (0 mg), low dose (1–36 mg), medium dose (36–120 mg), and high dose (120+mg). The 36 mg morphine equivalents threshold was chosen because it was the median opioid daily dose, among those with any use. The 120 mg threshold was chosen because it has been identified by the Washington State Opioid Dosing Guidelines as “high dose” opioid therapy which may need specialty consultation or more frequent and intense monitoring.²¹

The 7 levels were: (i) no opioid use (0 days supply, 0 mg average daily dose); (ii) low dose, acute; low dose, chronic; medium dose, acute; medium dose, chronic; high dose, acute; and high dose, chronic. Data included all opioid prescriptions (including date, dose, and type of opioid) regardless of indication for opioid use. Buprenorphine was excluded from dose and chronicity calculations, as the oral formulation is not FDA approved for pain treatment.

Total morphine equivalents for each prescription were calculated by multiplying the quantity of each prescription by the strength of the prescription (milligrams of opioid per unit dispensed). See Table 1. The quantity-strength product was then multiplied by conversion factors derived from published sources to estimate the milligrams of morphine equivalent to the opioids dispensed in the prescription.^{23–25} The total average dose in morphine equivalents per day supplied was calculated by summing the morphine equivalents for each prescription filled during the 12 months after the index date, and dividing by the number of days supplied. If the total days supply exceeded the number of days in the period (365 days), suggesting concurrent use of different opioid types, the daily dose was calculated by dividing the total dose dispensed by 365 days.

Sociodemographic factors: Data on sociodemographic and clinical characteristics were collected from claims records in the 12-month period prior to the index date.

Mental Health Disorders and Substance use Disorders: Using ICD-9-CM codes from the 12-month pre-index period we created variables for five types of mental health disorders using validated grouping software developed by the Agency for Healthcare Research and Quality:²⁶ adjustment disorders, anxiety disorders, mood disorders, personality disorders, and miscellaneous disorders (e.g., eating disorders, somatoform disorders). We summed the number of types of mental health disorders, and created three indicator variables: no mental health disorders, 1 mental health disorder, and 2+ mental health disorders. We included two indicator variables describing whether the patient had received (i) a pre-index alcohol abuse/dependence diagnosis, or (ii) a pre-index non-opioid drug abuse/dependence diagnosis.

Physical Health and Pain Diagnoses: The Charlson comorbidity index²⁷ calculated from the 12-month pre-index period was used as a measure of overall medical comorbidity. We also recorded ICD-9CM pain diagnoses received during the 12-month pre-index period. Arthritis/joint pain, back pain, neck pain, headache and HIV were selected as tracer pain diagnoses. The first four were the most commonly reported pain sites in the World Health Organization’s Collaborative Study of Psychological Problems in General Health Care,² a survey of primary care patients in 15 centers Asia, Africa, Europe, and the Americas. We

chose to investigate HIV as one of our tracer conditions, as there have been concerns regarding both under-treatment of pain and addiction in this group.²⁸ To further adjust for the overall burden of pain we also collected information on the presence of the following other (“non-tracer”) pain diagnoses: extremity pain, abdominal pain, chest pain, kidney stones/gallstones, pelvic pain, rheumatoid arthritis, fractures, neuropathic pain, fibromyalgia, and temporomandibular joint pain. The number of non-tracer conditions was summed and categorized as none, one, or two or more.

Analysis

We regressed our measure of an OUD on the independent variables in both unadjusted and adjusted logistic regression. All covariates used in the adjusted analyses are shown in Tables 2 and 3. Analyses were performed using SPSS V. 18.0.

RESULTS

There were 568,640 individuals in the analytical sample, i.e., individuals with a new episode of CNCP, not receiving opioids in the pre-index period, and no previous diagnosis of an OUD (Table 2). The majority (n=371,371, 65.3%) of the total sample had no prescribed opioid use in the 12 months following the index date. When opioids were prescribed, low dose/ acute use (15.9% of total sample) and medium dose/acute use (14.7% of total sample) were by far the most common types of opioid use, and high dose/chronic use was the least common (0.1% of the total sample). Among those prescribed opioids, 94.5% were acute users (either low, medium or high dose).

Among the total sample, 497 (0.1%) had a new diagnosis of an OUD in the post-index period. Among the 371,371 individuals with no prescribed opioids, 150 or 0.004% (150/371,371) had a post-index OUD diagnosis. The unadjusted rates of post-index OUD diagnoses for the various opioid dose/days categories were 0.12% (111/90,415) for low dose, acute; 0.72% (50/6902) for low dose, chronic; 0.12% (101/83,542) for medium dose, acute; 1.28% (47/3654) for medium dose, chronic; 0.12% (15/12,378) for high dose, acute; and 6.1% (23/378) for high dose, chronic.

Patterns of the associations between OUDs and the independent variables were generally similar in unadjusted and adjusted models (Table 3), and odds ratio described in the text are all from adjusted models. In a multiple logistic regression those prescribed opioids had significantly higher rates of OUDs compared to those not prescribed opioids, and the effect varied by average daily dose and days supply: low dose, acute (odds ratio (OR)=3.03, 95% confidence intervals (CI)= 2.32, 3.95, p<0.001); low dose, chronic (OR=14.92, 95% CI=10.38, 21.46, p<0.001); medium dose, acute (OR=2.80, 95% CI=2.12, 3.71, p<0.001); medium dose, chronic (OR=28.69, 95% CI=20.02, 41.13, p<0.001); high dose, acute (OR=3.10 95% CI=1.67, 5.77, p<0.001); and high dose, chronic (OR=122.45, 95% CI=72.79, 205.99, p<0.001).

Among sociodemographic factors, men had higher rates of OUDs (OR=2.27, 95% CI=1.85, 2.78, p<0.001), and younger individuals had higher rates than older individuals. For

example, the youngest group (ages 18 to 30) had an OR of 10.51 (95% CI=5.47, 20.20, $p<0.001$), compared to the reference group (age 65+).

Among the clinical variables, the Charlson index and the number of pre-index pain conditions were not significant predictors of an OUD. Individuals with four or more non-tracer pain conditions were more likely to receive a post-index OUD diagnosis than the reference group (OR=2.62, 95% CI=1.05, 6.55, $p<0.05$).

Individuals with pre-index mental health disorders had higher rates of OUDs (OR=3.12, 95% CI=2.41, 4.04, $p<0.001$ for those with 1 MH disorder type vs those with no MH disorder, and OR=5.71 (95% CI=3.83, 8.52, $p<0.001$) for those with 2 MH disorder types vs those with none. Individuals with a pre-index alcohol use disorder had a higher likelihood of a post-index OUD (adjusted OR=3.22, 95% CI=1.79, 5.80, $p<0.001$) compared to those with no pre-index alcohol use disorder. Similarly, those with pre-index non-opioid drug abuse disorders had higher rates of OUDs (OR=8.26, 95% CI=4.74, 14.39, $p<0.001$) than those without pre-index non-opioid drug abuse disorders.

DISCUSSION

This study provides detailed information on how exposure to differing levels of prescribed opioids, i.e., daily dose and days supplied, affects the likelihood of an incident OUD among individuals with a new episode of CNCP who were not previously on opioids. This type of epidemiological data is vital for clinicians to understand the risk of opioid addiction as they weigh the risks and benefits of initiating opioid treatment for CNCP and as they determine the most appropriate treatment regimen. The sample was large and sociodemographically diverse, and we utilized six years of “real world” data from health care plans covering multiple states and regions of the country.

The magnitudes of risk varied widely between the different average daily dose/chronicity categories. In un-adjusted results, 0.12% of individuals with low dose/acute opioid use had a post-index OUD diagnosis period, while 6.1% of individuals with high dose, chronic use had a post-index OUD. Our adjusted results highlight that the magnitude of the effects were especially large for those with chronic use (91 days or more). All adjusted OR's for acute use (low, medium, and high dose) were 3.10 or less, while all ORs for chronic use (low, medium, and high dose) were 14.92 or greater, and the OR for high dose/chronic use was 122.45. The 91 day cutoff used to differentiate acute from chronic use was defined prior to any analyses, and was primarily based on our clinical judgment and our knowledge of the frequency distribution of number of days of opioids supply from previous TROUP studies.²⁹ It is important to note that a recent meta-analysis of the efficacy of opioids for chronic back pain concluded that “our review, however, found that the evidence in favor of opioids is not always consistent, and when supportive, only supports this treatment for short periods (for example <4 months)”.³⁰ In fairness, in that meta-analysis the lack of support for the efficacy of chronic opioid treatment was primarily due to lack of studies rather than negative results. However, clinicians should be aware that as they proceed from acute to chronic opioid therapy the evidence of efficacy decreases while the OUD risk increases substantially.

In recent reports high opioid dose has been shown to be associated with adverse drug events, such as opioid drug overdose,^{31, 32} fractures,³³ and opioid misuse.³⁴ Our work adds to this growing literature demonstrating an association between high opioid dose with adverse outcomes. We found that among individuals with chronic opioid use, the likelihood of OUDs increased dramatically with increasing dose, with ORs of 12.64, 24.00, and 107.25 for low, medium and high dose respectively. We believe this finding adds to the validity of guidelines such as those from Washington State Agency Medical Directors' Group, which advise additional caution when using doses greater than 120 mg morphine equivalents.

While risks (as measured by ORs) were high, it could be argued that actual frequencies of OUDs were relatively low, i.e., under 1% for four of the six categories of opioid use. However, while "high" or "low" are ultimately subjective, we believe that an incident OUD rate of 6.1% among individuals with newly initiated high dose/chronic opioids is worrisome. This represents a number needed to harm (NNH)³⁵ of 16.7. Further, because our study relied on physician diagnoses of OUDs from administrative data with a limited follow-up period, our results should be viewed as lower bounds for the frequency of OUDs. While physician diagnoses are often viewed as the "gold standard," making an accurate diagnosis of addiction is extremely complex for all clinicians, including those with specialty training.

Our findings have important clinical implications, as they suggest that the risk of an incident OUD is relatively small for an acute trial of opioids. Our findings also suggest that if chronic opioid therapy is being used, low dose poses much less risk of OUDs than medium dose, and medium dose is much less risky than high dose. Our data suggest that it is almost meaningless to talk of a single "rate" of OUDs, as the rates of OUDs varied over 50-fold, depending on the average dose and chronicity (i.e., from 0.12% with acute, low dose, to 6.1% for chronic, high dose). Consistent with past studies, our multiple logistic regressions suggest that younger age, history of substance use disorders, and history of mental health disorders were all associated with OUDs.¹⁶⁻¹⁹ In this regard, it is interesting to note that the magnitude of the ORs for these well-established risk-factors were generally less than the ORs for the specific average dose/chronicity variables, suggesting the importance of specific features of the exposure to prescription opioids.

Some individuals may develop OUDs only after several years of opioid treatment, which again would not be measured in data with limited follow-up period. In particular, pathways to OUDs may involve several steps, moving from low dose/acute use to high dose/chronic use. Because we were studying incidence of OUDs we eliminated from our sample all individuals with an OUD diagnosis in the pre-index period; prevalence rates of OUDs would by definition be greater. Finally, studies have shown that aberrant use of prescription opioids that does not meet full criteria for DSM-IV abuse or dependence, but is nonetheless problematic, is even more common than OUDs.³⁴

Although our study was designed to study incidence of OUDs, it also provides descriptive data on incident opioid use for chronic pain. At 35%, incident opioid use was not uncommon among individuals with new onset of a CNCP episode. But among the 35% who received opioids, only 5% proceeded to chronic use (1.7% of total CNCP patients), and only 3% of these (0.1% of total CNCP patients) proceed to chronic use of high daily doses. This is a

steep selection process for patients achieving chronic high-dose therapy. Further, this selection process may be even steeper now than when our study was conducted, due to growing physician concerns regarding addiction. Evidence to date suggests that this is largely a self-selection process by the patients, where most patients started on opioid therapy choose not to continue on to chronic use.³⁶ An earlier study found that US veterans receiving high-dose opioid therapy were characterized by multiple pain problems and high levels of medical and psychiatric comorbidity.³⁷ We have shown in a separate sample that high daily dose and opioid misuse predict continued use of opioid therapy after 90 days of daily use.³⁸ Together, these past studies demonstrate that the patients selected for chronic high-dose opioid therapy have characteristics beyond the nature and intensity of their pain that may increase their risk of adverse outcomes.

Limitations

Our study should be viewed in the context of limitations common to analyses of administrative databases. Like many other studies investigating the relationship between opioid use and adverse outcomes,^{31, 39, 40} our study was observational, not experimental. Thus, our result should be viewed as associations, and not necessarily causal relationships. Unfortunately, it is unlikely that in the future there will be randomized controlled trials to address these important questions. It is difficult to envision a future study in which patients with CNCP are randomized to no opioid treatment, acute opioid treatment, or chronic opioid treatment, at low or high dose opioids. Further, the costs of such a study, adequately powered and with appropriate follow-up periods, i.e., one to two years, may be prohibitively expensive.

Second, our analyses included measures of painful diagnostic conditions, but no measure of pain severity or activity interference, as these were not available in our data. Third, current Diagnostic and Statistical Manual (DSM) IV diagnostic criteria are likely not optimal for prescription drug disorders. That is, individuals on chronic opioid therapy will likely develop tolerance, and withdrawal if they stop using opioids (2 of the 7 seven symptoms for opioid dependence), even if they are using opioids as prescribed by their physician. Fourth, physicians may have a higher index of suspicion for OUDs in patients on high dose, chronic opioid therapy, and thus be more likely to monitor and detect OUDs in this group. Fifth, we were able to assure that our subjects had not received a diagnosis of an OUD in the 6 months prior to being initiated on opioid therapy, but not to assure that they had never had a diagnosis or an undiagnosed problem. Sixth, although we excluded from our sample individuals who had been prescribed opioids during the 6-month period preceding the index date, some individuals could have been using opioids without a prescription. Seventh, our sample was extremely large, covered multiple states, and came from primary and specialty care settings, but was not necessarily nationally representative. Eighth, our study included only individuals with commercial insurance. Ninth, our data were from 2000 to 2005, and much may have changed in the opioid prescribing environment since then. However, a report recently published by the Centers for Disease Control and Prevention (CDC) in *Mortality and Morbidity Weekly Report (MMWR)* noted that “The epidemic of overdoses of opioid pain relievers has continued to worsen” and “These increases occurred despite numerous warnings and recommendations over the past decade for voluntary education of

providers about more cautious use of opioid pain relievers”.⁴¹ Tenth, our definition of high dose opioids, 120 mg, was based on the Washington State guidelines, but is nevertheless an arbitrary cut-off, as are all such cut-offs. Eleventh, we were not able to separate methadone used for pain from methadone used for methadone maintenance. However, methadone accounted for a relatively small percentage of total opioid use in our sample, and methadone maintenance is relatively uncommon. Finally, our original definition for OUD included an ICD-9-CM code for remission. However, post hoc analyses reveal that this diagnosis is very uncommon (less than 4 percent), and would likely be less common in our cohort, which consisted of individuals with new onset pain, newly initiated on opioids.

Conclusion

Among individuals with a new episode of a CNCP condition, the risk of incident OUDs varied widely according to duration and dose of prescribed opioid therapy. Characteristics of the opioid regimen may be as important in predicting OUDs as well-established risk factors such as past history of substance use disorders or younger age. Duration of opioid therapy appears more important than daily dose in determining risk for OUDs.

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Table 1Classification of opioid medications and morphine equivalent conversion factors per milligram of opioid.¹

Major Group	Type of Opioid	Morphine equivalent conversion factor per mg of opioid
Short-acting Non-Schedule II	Propoxyphene (with or without aspirin/acetaminophen/ibuprofen)	0.23
	Codeine + (acetaminophen, ibuprofen or aspirin)	0.15
	Hydrocodone + (acetaminophen, ibuprofen, or aspirin) Hydrocodone and homatropine	1.0
	Tramadol with or without aspirin	0.10
	Butalbital and codeine (with or without aspirin, ibuprofen, acetaminophen)	0.15
	Dihydrocodeine (with or without aspirin, ibuprofen, acetaminophen)	0.25
	Pentazocine (with or without aspirin, ibuprofen, acetaminophen)	0.37
Short-acting, Schedule II	Morphine sulfate	1.0
	Codeine sulfate	0.15
	Oxycodone (with or without aspirin, acetaminophen, ibuprofen)	1.5
	Hydromorphone	4.0
	Meperidine hydrochloride	0.1
	Fentanyl citrate transmucosal ²	0.125
	Oxymorphone	3.0
Long-acting (Schedule II)	Morphine sulfate sustained release	1.0
	Fentanyl transdermal ³	2.4
	Levorphanol tartrate	11.0
	Oxycodone HCL controlled release	1.5
	Methadone	3.0

¹Opioids delivered by pill, capsule, liquid, transdermal patch, and transmucosal administration were included. Opioids formulated for administration by injection or suppository were not included.

²Transmucosal fentanyl conversion to morphine equivalents assumes 50% bioavailability of transmucosal fentanyl and 100 micrograms transmucosal fentanyl is equivalent to 12.5 to 15 mg of oral morphine.

³Transdermal fentanyl conversion to morphine equivalents is based on the assumption that one patch delivers the dispensed micrograms per hour over a 24 hour day and remains in place for 3 days.

From: Von Korff M, Saunders K, Ray GT, Boudreau D, Campbell C, Merrill J, Sullivan MD, Rutter C, Silverberg M, Banta-Green C, Weisner C, De Facto Long-term Opioid Therapy for Non-Cancer Pain, *Clinical Journal of Pain*, 2008 Jul-Aug;24(6):521-7. doi: 10.1097/AJP.0b013e318169d03b, used with permission.

Table 2The Health Core Sample with new episodes of CNCP[#]

	Total Sample	Post-Index Opioid Abuse or Dependence Diagnosis	No Post-Index Opioid Abuse or Dependence Diagnosis
	N=568,640	N=497	N=568,143
	N (%)	N (%)	N (%)
Opioid Dose and Days Supply			
No opioid use	371,371 (65.3)	150 (30.2)	371,221 (65.30)
Low dose, acute	90,415 (15.9)	111 (22.3)	90,304 (15.9)
Low dose, chronic	6,902 (1.2)	50 (10.1)	6,852 (1.2)
Medium dose, acute	83,542 (14.7)	101 (20.3)	83,441 (14.7)
Medium dose, chronic	3,654 (0.6)	47 (9.5)	3,607 (0.6)
High dose, acute	12,378 (2.2)	15 (3.0)	12,363 (2.2)
High dose, chronic	378 (0.1)	23 (4.6)	355 (0.1)
Age in Years			
18–30	65,089 (11.4)	156 (31.4)	64,933 (11.4)
31–40	112,412 (19.8)	126 (25.4)	112,286 (19.8)
41–50	154,635 (27.2)	123 (24.7)	154,512 (27.2)
51–64	167,558 (29.5)	82 (16.5)	167,476 (29.5)
>=65	68,946 (12.1)	10 (2.0)	68,935 (12.1)
Gender			
Female	331,533 (58.3)	185 (37.2)	331,348 (58.3)
Male	237,107 (41.7)	312 (62.8)	236,795 (41.7)
# of types of tracer pains (of 5) in the PRE Index period			
None	504,208 (88.7)	448 (90.1)	503,760 (88.7)
One	58,348 (10.3)	42 (8.5)	58,306 (10.3)
Two or more	6,084 (1.1)	7 (1.4)	6,077 (1.1)
Number of Non-Tracer Pain Categories			
0	363,779 (64.0)	340 (68.4)	363,439 (64.0)
1	145,825 (25.6)	105 (21.1)	145,720 (25.6)
2–3	56,423 (9.9)	47 (9.5)	56,376 (9.9)
4+	2,316 (0.5)	5 (1.0)	2,608 (0.5)
Number of Non-Substance Mental Health Disorder Types			
0	525,555 (92.4)	346 (69.6)	525,209 (92.7)
1	36,659(6.4)	106 (21.3)	36,553 (6.4)
2+	5,426 (1.1)	45 (9.1)	6,381 (1.1)
Pre-index Substance Abuse/ Dependence Diagnoses			
Opioid	172 (0.0)	78 (15.7)	94 (0.0)
Non-Opioid	605 (0.1)	51 (10.3)	554 (0.1)
Alcohol	1,145 (0.2)	31 (6.2)	1,114 (0.2)
Charlson score - Mean (SD)	0.16 (0.50)	0.16 (0.50)	0.16 (0.50)

All independent variables, except the opioid variables (days supply, dose, category type) were measured in the 12 months prior to the index date. Opioid variables were measured in the 12-month period after the index date.

Table 3

Variables Associated with Incident OUDs

Variables [#]	UNADJUSTED OR (95% CI)	ADJUSTED OR (95% CI)
Opioid Dose and Days		
No opioid use (Reference)	1.00 (–)	1.00 (–)
Low dose, acute	3.31 (2.54 – 4.31)***	3.03 (2.32 – 3.95)***
Low dose, chronic	17.63 (12.33 – 25.20)***	14.92 (10.38 – 21.46)***
Med dose, acute	3.04 (2.30 – 4.01)***	2.80 (2.12 – 3.71)***
Med dose, chronic	35.19 (24.75 – 50.02)***	28.69 (20.02 – 41.13)***
High dose, acute	2.68 (1.45 – 4.98)**	3.10 (1.67 – 5.77)***
High dose, chronic	171.95 (105.97 – 279.00)***	122.45 (72.79 – 205.99)***
Age in Years – N (%)		
18–30	14.12 (7.43 – 26.86)***	10.51 (5.47 – 20.20)***
31–40	6.45 (3.37 – 12.33)***	4.62 (2.39 – 8.91)***
41–50	4.60 (2.40 – 8.80)***	3.27 (1.70 – 6.30)***
51–64	2.08 (1.44 – 5.44)**	2.18 (1.12 – 4.26)*
>=65 - Reference Group	1.00 (–)	1.00 (–)
Sex		
Female - Reference Group	1.00 (–)	1.00 (–)
Male	2.38 (1.96 – 2.91)***	2.27 (1.85 – 2.78)***
Charlson score (Pre)		
	1.01 (0.83 – 1.22)	1.11 (0.93 – 1.34)
# of types of tracer pains (of 5) in the PRE Index period		
None – Reference Group	1.00 (–)	1.00 (–)
One	0.73 (0.51 – 1.04)	0.76 (0.52 – 1.10)
Two or more	1.53 (0.72 – 3.23)	1.37 (0.63 – 3.01)
Number of Non-Tracer Pain Categories		
0 – Reference Group	1.00 (–)	1.00 (–)
1	0.68 (0.53 – 0.87)**	0.72 (0.56 – 0.93)**
2–3	0.88 (0.63 – 1.22)	0.95 (0.67 – 1.35)
4+	2.37 (0.98 – 5.74)	2.62 (1.05 – 6.55)*
Number of Non-Substance Mental Health Disorder Types		
0 – Reference Group		
1	3.85 (3.02 – 4.92)***	3.12 (2.41 – 4.04)***
2+	8.37 (5.78–12.12)***	5.71 (3.83 – 8.52)***
Pre-index Substance Abuse/Dependence Diagnoses		
Non-Opioid	60.95 (39.34 – 94.44)***	8.26 (4.74 – 14.39)***
Alcohol	23.35 (14.51 – 37.58)***	3.22 (1.79 – 5.80)***

[#] All independent variables, except the opioid variables (days supply, dose, category type) were measured in the 12 months prior to the index date. Opioid variables were measured in the 12-month period after the index date.

*
p<0.05

**
p<0.01

p<0.001