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Risks for opioid abuse and dependence among recipients of chronic opioid therapy: Results from the TROUP Study

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ABSTRACT

Objective: To estimate the prevalence of and risk factors for opioid abuse/dependence in long-term users of opioids for chronic pain, including risk factors for opioid abuse/dependence that can potentially be modified to decrease the likelihood of opioid abuse/dependence, and non-modifiable risk factors for opioid abuse/dependence that may be useful for risk stratification when considering prescribing opioids.
Methods: We used claims data from two disparate populations, one national, commercially insured population (HealthCore) and one state-based, publicly insured (Arkansas Medicaid). Among users of chronic opioid therapy, we regressed claims-based diagnoses of opioid abuse/dependence on patient characteristics, including physical health, mental health and substance abuse diagnoses, sociodemographic factors, and pharmacological risk factors.
Results: Among users of chronic opioid therapy, 3% of both the HealthCore and Arkansas Medicaid samples had a claims-based opioid abuse/dependence diagnosis. There was a strong inverse relationship between age and a diagnosis of opioid abuse/dependence. Mental health and substance use disorders were associated with an increased risk of opioid abuse/dependence. Effects of substance use disorders were especially strong, although mental health disorders were more common. Concerning opioid exposure; lower days supply, lower average doses, and use of Schedule III–IV opioids only, were all associated with lower likelihood of a diagnosis of opioid abuse/dependence.
Conclusion: Opioid abuse and dependence are diagnosed in a small minority of patients receiving chronic opioid therapy, but this may under-estimate actual misuse. Characteristics of the patients and of the opioid therapy itself are associated with the risk of abuse and dependence.

1. Introduction

Prescription opioids are increasingly used long-term to manage chronic non-cancer pain (CNCP) (Gilson et al., 2004; Gureje et al., 1998; Zacny et al., 2003). Initial enthusiasm for the use of opioids in CNCP was based on low rates of addiction reported in cancer pain patients, but the largest study focused on *inpatient* use of opioids (Porter and Jick, 1980). Low addiction rates were also initially reported for CNCP patients, but these were small, selected, and uncontrolled case series (Portenoy and Foley, 1986). Recent marked increased use of opioids for CNCP, often of 50–100% in the last decade (Boudreau et al., 2009; Caudill-Slosberg et al., 2004; Gilson et al., 2004; Sullivan et al., 2008), has been accompanied by a parallel increase in opioid abuse/dependence and accidental overdose (Chabal et al., 1997; Chelminski et al., 2005; Compton and Volkow, 2006; Cowan et al., 2003; Department of Health and Human Services, 2005; Gilson et al., 2004; Jonasson et al., 1998; Michna et al., 2004; Schieffer et al., 2005; Warner et al., 2009) in both clinical and population samples, making opioid abuse/dependence among individuals using opioids for CNCP a significant public health concern. Further, there is misuse of opioids that does not rise to the level of DSM-IV abuse or dependence. Estimates of rates of opioid abuse, dependence, and misuse vary, and risk factors for (i.e., the factors associated with) opioid abuse/dependence and misuse have varied according to the population studied (Chabal et al., 1997; Chelminski et al., 2005; Cowan et al., 2003; Jonasson et al., 1998; Michna et al., 2004; Reid et al., 2002; Schieffer et al., 2005). For example, a recent review of clinical

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Table 1
Morphine equivalent conversion table.

Major group	Type of opioid	Morphine equivalent conversion factor per mg of opioid
Schedule III and IV	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
	Oxymorphone	3.0
Long-acting (Schedule II)	Morphine sulfate sustained release	1.0
	Fentanyl transdermal	2.4
	Levorphanol tartrate	11.0
	Oxycodone HCL controlled release	1.5
	Methadone	3.0

surveys of patients on COT found widely varying (3–62%) estimates of the prevalence of opioid misuse (Turk et al., 2008).

A key issue in prescribing opioids for CNCP is balancing the possible benefits of pain relief and improved quality of life with the risks of addiction, overdose, reduced quality of life, and other negative outcomes. Reflecting the importance of balancing benefits and risks, the Food and Drug Administration recently indicated that manufacturers of some long-acting opioid formulations will be required to have a Risk Evaluation and Mitigation Strategy to "ensure that the benefits of the drugs continue to outweigh the risks" (Food and Drug Administration, 2009).

To achieve this balance, researchers, clinicians, and policy makers need better information on the prevalence of, and risk factors for, opioid abuse/dependence among those using chronic opioid therapy (COT) for CNCP. The existing literature on risk factors for opioid abuse/dependence among COT recipients must be interpreted with caution since studies have generally been conducted in small clinical samples from specialty pain clinics with unknown generalizability. We do know that treatment of acute or cancer pain is rarely associated with development of opioid abuse/dependence, but COT for CNCP may result in opioid abuse/dependence in 3–19% of patients (Compton and Volkow, 2006; Cowan et al., 2003; Fishbain et al., 1992; Porter and Jick, 1980).

The literature describing which classes of opioids have the greatest abuse potential is limited, generally not evidence-based, and sometimes conflicting. Most treatment guidelines for chronic pain recommend use of long-acting U.S. Drug Enforcement Administration (DEA) Schedule II opioids, based on the assumption that long-acting Schedule II opioids are best able to provide stable pain relief and are less prone to abuse (Kalso et al., 2003), but evidence that long-acting opioids limit abuse is limited. (For examples of types of opioids, their strength relative to morphine and their U.S. DEA schedule, see Table 1.) Further, Schedule III opioids, for example, hydrocodone with acetaminophen (Vicodin®), are defined in Chapter 21, Section 812, of the U.S. Code as having "a potential for abuse less than the drugs or other substances in Schedules I and II," but again this has not been demonstrated in chronic pain populations. Moreover, it is not known if co-administration of long and short-acting opioids for 'breakthrough pain' is protective or harmful (Vallerand, 2003).

The Trends and Risks of Opioid Use for Pain (TROUP) study was designed to assess trends in (years 2000–2005) and risks of opioid therapy for CNCP in two disparate populations, a national commercially insured population (HealthCore) and a state-based publicly insured population (Arkansas Medicaid) (Braden et al., 2008, in press; Edlund et al., 2010a,b; Sullivan et al., 2008; Thielke et al., 2010). Our primary objective in this report was to estimate the prevalence of and risk factors for opioid abuse/dependence in COT recipients, including both non-modifiable (e.g., age) risk factors that may be useful for risk stratification and risk factors that can potentially be modified (e.g., characteristics of the opioid regimen) to decrease the likelihood of opioid abuse/dependence. As possible risk factors we investigated patient characteristics, including physical health, mental health and substance abuse diagnoses, and sociodemographic factors, along with pharmacological risk factors. Our previous work suggests that individuals with mental health and substance abuse disorders are more likely to be prescribed opioids, at higher doses, and for longer periods of time, than individuals without such disorders (Braden et al., 2008, in press; Edlund et al., 2010a,b; Sullivan et al., 2008, 2006; Thielke et al., 2010). In the current paper, we hypothesized that individuals with a mental health or substance abuse disorder would also be more likely to abuse opioids. We also hypothesized that long-acting Schedule II opioids would have the weakest association with opioid abuse/dependence, that short-acting Schedule II opioids would have the strongest association, and that the association for Schedule III opioids would be intermediate.

A secondary objective was to estimate the prevalence of and risk factors for non-opioid substance abuse/dependence (e.g., alcohol abuse or dependence, or methamphetamine abuse or dependence) in COT recipients. Fatal overdoses involving opioid analgesics increased three fold between 1999 and 2006 (Warner et al., 2009). Risk of fatal overdose is increased when opioids are taken with other drugs or alcohol, and the majority of fatal opioid overdoses involve at least one other drug (Warner et al., 2009). Our previous research suggests that COT recipients have elevated rates of non-opioid substance abuse/dependence (Edlund et al., 2007b). Thus it is important that we understand risk factors for both opioid abuse/dependence, and for non-opioid substance abuse/dependence.

2. Methods

2.1. Study populations

2.1.1. Arkansas Medicaid. Arkansas Medicaid serves a disadvantaged and vulnerable population in the geographic region with the highest prescription opioid use in the country (Sullivan et al., 2006). Arkansas Medicaid covers all federally mandated services and nearly all optional services, including prescription drug services.

Most Arkansas Medicaid enrollees participate in the primary care physician program where recipients utilize a primary care provider to coordinate care. Arkansas Medicaid imposes some benefit limitations: 12 physician, clinic, and/or outpatient visits per year, three to six prescriptions per month, 24 inpatient days per year, and some co-insurance and co-payments for prescription drugs depending on eligibility type. Analyses indicate that Medicaid data are generally valid and suitable for epidemiologic uses (Hennessy et al., 2003).

2.1.2. 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.

2.2. Study sample

The sample consisted of adult enrollees (18 years and older) on COT. There is no standard definition of COT (Cicero et al., 2009; Edlund et al., 2007a, 2010b; Sullivan 2008), so we relied on our clinical judgment, and the frequency distribution of number of days of opioids supplied, to define COT as at least 90 days' continuous use of opioids within a 6-month period during the study period, 1/1/2001 and 12/31/2004. Continuous use was defined as multiple opioid prescription claims with no period greater than 32 days between opioid fill dates. This threshold was chosen because it is unlikely that an individual would receive opioids for greater than 90 days (usually four prescriptions) in a 6-month period for acute conditions. Further, it appears that greater than 90 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.

The first day of the opioid prescription fill date signaled the start of an opioid use episode and was defined as the index date. Eligible individuals were required to have 12 months of continuous enrollment before and after the index date. Thus, the post-index period was at least 12 months, and could be as long as 54 months; in HealthCore the mean of the post-index period was 818 days, and 1212 days in Arkansas Medicaid.

Research and guidelines on opioid use for chronic pain have generally differentiated between cancer pain and CNCP, primarily because of the markedly different natural histories, and resultant treatment goals, of these disorders. The goal of palliative cancer pain treatment is typically pain control, while the goal of COT for CNCP is typically conceptualized more broadly in terms of functioning. Thus, cancer pain treatment often employs higher opioid doses, and there is less concern regarding the possibility of addiction. Because of this, individuals with a cancer diagnosis at any time in the year before or 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 36,605 enrollees in HealthCore and 9651 enrollees in Arkansas Medicaid in the study samples. Additional details concerning the study have been reported elsewhere (Braden et al., 2008; Sullivan et al., 2008).

2.3. Measures

2.3.1. Outcomes. We studied two outcomes, both measured in the post-index date period: (i) any opioid abuse/dependence; and (ii) any non-opioid substance abuse/dependence. These outcomes were binary, and derived from ICD-9-CM codes. Non-opioid substance abuse/dependence was defined as any ICD-9-CM non-opioid drug abuse or dependence diagnosis, or any alcohol abuse or dependence diagnosis. Some examples of non-opioid substance abuse are: alcohol abuse and dependence, marijuana abuse and dependence, sedative/hypnotic abuse and dependence, cocaine abuse and dependence, and methamphetamine abuse and dependence.

2.3.2. Independent variables. Sociodemographic factors. Data on sociodemographic and clinical characteristics were collected from claims records in the 12-month period prior to the start of the opioid use episode, i.e., 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 (Agency for Health Care Research and Quality): 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 a (i) pre-index diagnosis of opioid abuse or dependence, or (ii) a pre-index non-opioid substance abuse or dependence diagnosis.

Physical health and pain diagnoses. The Charlson comorbidity index (Charlson et al., 1987) was used as a measure of overall medical comorbidity. We also recorded ICD-9-CM pain diagnoses made during the 12 months before the index date. Arthritis/joint pain, back pain, neck pain, and headache were selected as tracer pain diagnoses to be tracked individually because these were the most commonly reported pain sites in the World Health Organization's Collaborative Study of Psychological Problems in General Health Care (Gureje et al., 1998), a survey of primary care patients in 15 centers in Asia, Africa, Europe, and the Americas. 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 temperomandibular joint pain. The four tracer conditions were coded with four binary variables, while the number of non-tracer conditions was summed and used as a continuous variable.

Sedative/Hypnotics. From our administrative data we collected data on the days supply of prescribed sedative/hypnotics in the 12-month pre-index period. For the logistic regressions, the days supply of sedative/hypnotics variable was divided by 30, to give the number of months of sedative/hypnotic use.

Opioid characteristics. Variables describing opioid use were derived for the 6-month period after the index date. Data included all opioid prescriptions (including date, dose, and type of opioid) regardless of indication for opioid use. Buprenorphine was excluded, as the oral formulation is not FDA approved for pain treatment. Types of opioid received were determined based on opioid Schedule (as defined by the U.S. Drug Enforcement Administration) and duration of action (Table 1). Subjects were coded as receiving an opioid Schedule if they received at least 30 days supply within a 6-month period. Seven mutually exclusive opioid type categories were thus derived: Schedule III or IV only, Schedule II short-acting only, Schedule II long-acting only, Schedule III or IV plus Schedule II short-acting, Schedule II short-acting plus Schedule II long-acting, Schedule III or IV plus Schedule II long-acting, and all three opioid types.

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). 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 (American Pain Society, 2003; Fine and Portenoy, 2004; Vieweg et al., 2005). The total average dose in morphine equivalents per day supplied was calculated by summing the morphine equivalents (for all three major opioid groups) for each prescription filled during the 6 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 (183 days), suggesting concurrent use of different opioid types, the daily dose was calculated by dividing the total dose dispensed by 183 days. We divided the opioid mean daily dose into three categories: less than the median daily dose of opioids, measured in morphine equivalents; median daily dose to 120 mg morphine equivalents daily; and greater than 120 mg morphine equivalents daily. The median daily dose was 32 mg morphine equivalents and 35 mg morphine equivalents in HealthCore and Arkansas Medicaid, respectively. 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 (Washington State Agency Medical Directors' Group). We also utilized measures of opioid days supply; 91–160 days, 161–185 days, and 186+ days.

2.4. Analysis

We regressed our two outcomes on the independent variables, using logistic regression. This was done separately for the HealthCore and Arkansas Medicaid samples. Because the post-index period varied across subjects, as a sensitivity analysis, we also used discrete time survival analysis. Results were largely identical, and logistic results are reported here. All analyses were performed using SAS 9.1 (SAS Institute Inc., Cary, NC).

3. Results

The samples tended to be predominantly female, especially Arkansas Medicaid, whose adult enrollees are mainly female. The Arkansas sample tended to be sicker than the commercial sample, with higher rates of pain conditions, higher Charlson scores, and higher rates of mental health and substance use disorders (Table 2). In the pre-index period the claims-based diagnosis rates of opioid abuse/dependence were 0.7% and 0.6% for HealthCore and Arkansas Medicaid, respectively. In both samples the large majority of COT users were in the Schedule III or IV only opioid type category, 78.2% in HealthCore, 78.9% in Arkansas Medicaid.

3.1. Predictors of post-index opioid abuse/dependence

In the post-index period, 3.2% (1188 of 36,605) of the HealthCore sample and 2.9% (277 of 9651) of the Arkansas Medicaid

sample had a claims-based opioid abuse/dependence diagnosis; thus rates were more than four-fold higher in the post-index period than the pre-index period. The predictors of post-index opioid abuse/dependence were virtually identical in the two samples, although due to the smaller Medicaid sample, at times the results were significant only in the HealthCore sample. Younger individuals were much more likely to have abuse/dependence; the magnitude of the ORs was especially large for individuals 50 years and younger, with 18–30 year olds having OR's of 5.88 and 9.08 in HealthCore and Arkansas Medicaid, compared to the reference group of 65+ year olds (Table 3). Individuals with back pain and headache diagnoses were more likely to have post-index opioid abuse/dependence diagnoses, although these findings just missed being statistically significant at 0.05 level in the Arkansas Medicaid group. On the other hand, those with joint pain/arthritis were less likely to have post-index opioid abuse/dependence. Pre-index mental health and substance use disorders were strong predictors of opioid abuse/dependence, as was use of sedative/hypnotics.

In the HealthCore sample, higher average daily dose, and greater number of days supply were significantly associated with post-index opioid abuse/dependence. In Arkansas Medicaid, higher dose, but not greater days supply, was significantly associated with post-index abuse/dependence.

In HealthCore, all opioid type categories that included Schedule II long-acting opioids (i.e., Schedule II long-acting only, Schedule II long-acting and Schedule III or IV, and Schedule II long- and short-acting, and all three types) were associated with higher rates of post-index opioid abuse/dependence, compared to the reference group of Schedule III or IV only. In Arkansas Medicaid, all opioid type categories that included long- or short-acting Schedule II opioids had higher rates of opioid post-index abuse/dependence, compared to Schedule III or IV only, although the results were not always significant. Because of this, while the large majority of users of COT utilized only Schedule III or Schedule IV opioids (78.2% of COT users in HealthCore and 78.9% of COT users in Arkansas Medicaid), only 46.8% and 52.0% of HealthCore and Arkansas Medicaid COT users

Table 2
The sample of individuals receiving chronic opioid therapy.

Variables[a]	HealthCore		Arkansas Medicaid	
	Post-index opioid abuse or dependence diagnosis (n = 1188) n %	No post-index opioid abuse or dependence diagnosis (n = 35,417) n %	Post-index opioid abuse or dependence diagnosis (n = 277) n %	No post-index opioid abuse or dependence diagnosis (n = 9374) n %
Age				
18–30	132 (7.1%)	1725 (92.9%)	28 (4.2%)	632 (95.8%)
31–40	324 (5.2%)	5869 (94.8%)	96 (5.8%)	1573 (94.2%)
41–50	453 (3.9%)	11,278 (96.1%)	108 (4.4%)	2361 (95.6%)
51–64	242 (2.0%)	12,102 (98.0%)	40 (1.5%)	2548 (98.5%)
≥65	37 (0.8%)	4443 (99.2%)	5 (0.2%)	2260 (99.8%)
Gender				
Female	679 (3.1%).	20,924 (96.9%)	186 (2.7%)	6721 (97.3%)
Male	509 (3.4%)	14,493 (96.6%)	91 (3.3%)	2653 (96.7%)
CNCP				
Joint	162 (2.5%)	6236 (97.5%)	64 (1.8%)	3466 (98.2%)
Back	614 (4.6%)	12,800 (95.4%)	195 (4.0%)	4647 (96.0%)
Head	332 (5.7%)	5543 (94.3%)	107 (5.2%)	1950 (94.8%)
Neck	264 (4.8%)	5246 (95.2%)	74 (4.6%)	1546 (95.4%)
#Non-tracer pain conditions mean (SD)	1.5 (1)	1.0 (1)	2.1 (1)	1.6 (1)
Number of mental health disorder types				
0	702 (2.3%)	29,263 (97.7%)	124 (1.9%)	6495 (98.1%)
1	306 (6.1%)	4689 (93.9%)	74 (3.7%)	1916 (96.3%)
2+	180 (10.9%)	1465 (89.1%)	79 (7.6%)	963 (92.4%)
Pre-index substance abuse diagnosis				
Opioid	109 (42.2%)	149 (57.8%)	20 (33.9%)	39 (66.1%)
Non-opioid	165 (20.5%)	640 (79.5%)	63 (11.1%)	507 (88.9%)
Charlson score mean (SD)	0.4 (1)	0.4 (1)	1.0 (1)	1.1 (1)
Sedative/hypnotics days supply mean (SD)	117.3 (167)	70.2 (135)	116.2 (148)	77.4 (128)
Opioid daily dose				
0-Median mg/day	331 (1.8%)	17,973 (98.2%)	97 (2.0%)	4729 (98.0%)
Median-120 mg/day	608 (3.9%)	15,123 (96.1%)	126 (3.0%)	4108 (97.0%)
>120 mg/day	249 (9.7%)	2321 (90.3%)	54 (9.1%)	537 (90.9%)
Opioid days supply				
91–160 days	445 (2.0%)	21,478 (98.0%)	107 (2.0%)	5115 (98.0%)
161–185 days	175 (3.2%)	5323 (96.8%)	42 (2.4%)	1687 (97.6%)
>185 days	568 (6.2%)	8616 (93.8%)	128 (4.7%)	2572 (95.3%)
Opioid category type				
Schedule III or IV only	618 (2.2%)	28,003 (97.8%)	125 (1.6%)	7490 (98.4%)
Schedule II short only	27 (3.6%)	727 (96.4%)	9 (3.8%)	230 (96.2%)
Schedule II long only	164 (8.5%)	1775 (91.5%)	39 (7.8%)	463 (92.2%)
Schedule III or IV + Schedule II short	38 (3.6%)	1020 (96.4%)	20 (7.0%)	264 (93.0%)
Schedule III or IV + Schedule II long	191 (7.0%)	2557 (93.0%)	48 (7.7%)	574 (92.3%)
Schedule II short and long	89 (9.8%)	819 (90.2%)	20 (7.6%)	243 (92.4%)
Opioid all types	61 (10.6%)	516 (89.4%)	16 (12.7%)	110 (87.3%)

[a] 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 6-month period after the index date.

Table 3
Predictors of post-index opioid abuse/dependence diagnosis in patients receiving chronic opioid therapy.

Variables	HealthCore		Arkansas Medicaid	
	Odds ratio	95% CI	Odds ratio	95% CI
Age				
18–30	5.88	(3.99, 8.65)	9.08	(3.38, 24,41)
31–40	4.16	(2.92, 5.93)	11.39	(4.50, 28.82)
41–50	3.27	(2.32, 4.62)	9.55	(3.81, 23.95)
51–64	1.89	(1.33, 2.69)	4.25	(1.66, 10.91)
≥65	1.00	–	1.00	–
Female	0.85	(0.75, 0.96)	0.96	(0.72, 1.27)
CNCP				
Joint	0.75	(0.63, 0.90)	0.72	(0.53, 0.98)
Back	1.25	(1.10, 1.43)	1.31	(0.99, 1.74)
Head	1.26	(1.09, 1.47)	1.30	(0.98, 1.72)
Neck	0.93	(0.79, 1.09)	1.07	(0.79, 1.45)
#Non-tracer pain conditions	1.09	(1.04, 1.15)	1.07	(0.97, 1.18)
Number of mental health disorders				
0	1.00	–	1.00	–
1	1.73	(1.49, 2.01)	1.17	(0.85, 1.61)
2+	2.08	(1.69, 2.55)	1.70	(1.21, 2.39)
Pre-index substance abuse diagnosis				
Opioid	5.55	(4.06, 7.58)	5.50	(2.94, 10.30)
Non-opioid	2.87	(2.27, 3.61)	2.18	(1.55, 3.07)
Charlson score	0.93	(0.87, 1.00)	0.98	(0.89, 1.08)
Sedative/hypnotics, months of use	1.04	(1.03, 1.05)	1.03	(1.01, 1.06)
Opioid daily dose				
0-Median mg/day	1.00	–	1.00	–
Median-120 mg/day	1.48	(1.27, 1.72)	1.11	(0.82, 1.49)
>120 mg/day	2.19	(1.74, 2.74)	1.70	(1.07, 2.70)
Opioid days supply				
91–160 days	1.00	–	1.00	–
161–185 days	1.48	(1.23, 1.78)	1.01	(0.69, 1.47)
>185 days	1.79	(1.54, 2.09)	1.18	(0.86, 1.63)
Opioid category type				
Schedule III or IV only	1.00	–	1.00	–
Schedule II short only	1.14	(0.75, 1.73)	1.75	(0.86, 3.57)
Schedule II long only	1.83	(1.47, 2.27)	2.98	(1.92, 4.61)
Schedule III or IV + Schedule II short	1.09	(0.76, 1.54)	3.13	(1.88, 5.22)
Schedule III or IV + Schedule II long	1.70	(1.40, 2.08)	2.83	(1.88, 4.25)
Schedule II short and long	1.78	(1.35, 2.36)	2.16	(1.21, 3.87)
Opioid all types	1.85	(1.34, 2.57)	4.23	(2.28, 7.83)

with post-index opioid abuse/dependence utilized only Schedule III or Schedule IV opioids.

3.2. Predictors of non-opioid substance abuse

In the post-index period, 4.4% (1615 of 36,605) of the HealthCore sample and 13.8% (1335 of 9651) of the Arkansas Medicaid sample had a claims-based non-opioid substance abuse/dependence diagnosis. In both samples, older individuals were less likely to have post-index non-opioid abuse/dependence, as were females (Table 4). Diagnoses of head and back pain were significantly associated with post-index non-opioid substance abuse/dependence in HealthCore. In Arkansas Medicaid individuals with headache had a significantly higher likelihood of a post-index non-opioid abuse/dependence, while those with joint pain had lower rates. In both samples the number of non-tracer pain conditions was significantly associated with post-index non-opioid substance abuse/dependence. Both pre-index mental health disorders and substance use disorders were associated with post-index non-opioid substance abuse/dependence, and the strength of the association was particularly strong for substance use disorders.

In both samples the days supply of sedative/hypnotics, mean daily opioid dose greater than 120 mg morphine equivalents and opioid days supply greater than 185 days were associated with a higher likelihood of post-index non-opioid substance abuse/dependence.

4. Discussion

To our knowledge, this is the largest study to date of risk factors for opioid abuse/dependence and non-opioid substance abuse/dependence among COT users. The sample is sociodemographically diverse, and we utilized 5 years of "real world" data from health care plans covering multiple states and regions of the country. For these reasons we believe our results enjoy good generalizability.

In a sample with at least 90 days of continuous opioid use, we found that opioid abuse/dependence was diagnosed in 3.2% and 2.9% of HealthCore and Arkansas Medicaid enrollees, respectively. These rates are consistent with a study that used VA administrative data (Edlund et al., 2007a), but substantially higher than the 1.3% found in a study that used administrative data from Missouri (Cicero et al., 2009). However, the Missouri study only utilized 1 year of data, while the VA study and our current study utilized several years of data to increase sensitivity, as suggested by measurement experts (O'Malley et al., 2005). Our estimates of the

Table 4
Predictors of post-index non-opioid substance abuse/dependence diagnosis in patients receiving chronic opioid therapy.

Variables	HealthCore		Arkansas Medicaid	
	Odds ratio	95% CI	Odds ratio	95% CI
Age				
18–30	6.74	(4.86, 9.33)	3.67	(2.66, 5.07)
31–40	4.62	(3.43, 6.22)	3.59	(2.72, 4.73)
41–50	3.27	(2.45, 4.37)	3.36	(2.59, 4.38)
51–64	1.95	(1.45, 2.62)	2.07	(1.59, 2.71)
≥65	1.00	–	1.00	–
Female	0.82	(0.74, 0.92)	0.64	(0.55, 0.73)
CNCP				
Joint	0.91	(0.78, 1.06)	0.81	(0.70, 0.94)
Back	1.24	(1.11, 1.39)	1.03	(0.90, 1.18)
Head	1.18	(1.04, 1.34)	1.24	(1.06, 1.44)
Neck	0.94	(0.82, 1.08)	1.12	(0.96, 1.32)
#Non-tracer pain conditions	1.09	(1.04, 1.14)	1.12	(1.07, 1.18)
Number of mental health disorders				
0	1.00	–	1.00	–
1	1.80	(1.58, 2.05)	1.40	(1.19, 1.63)
2+	2.15	(1.79, 2.57)	1.67	(1.38, 2.02)
Pre-index substance abuse diagnosis				
Opioid	3.11	(2.28, 4.23)	2.29	(1.23, 4.27)
Non-Opioid	3.89	(3.19, 4.74)	7.26	(5.97, 8.83)
Charlson score	0.98	(0.92, 1.03)	0.96	(0.92, 1.01)
Sedative/hypnotics, months of use	1.05	(1.04, 1.06)	1.03	(1.01, 1.04)
Opioid daily dose				
0-Median mg/day	1.00	–	1.00	–
Median-120 mg/day	1.62	(1.43, 1.84)	1.06	(0.92, 1.22)
>120 mg/day	2.14	(1.75, 2.62)	1.51	(1.15, 1.99)
Opioid days supply/30 days				
91–160 days	1.00	–	1.00	–
161–185 days	1.36	(1.16, 1.60)	0.93	(0.77, 1.12)
>185 days	1.61	(1.42, 1.83)	1.30	(1.11, 1.52)
Opioid category type				
Schedule III or IV only	1.00	–	1.00	–
Schedule II short only	1.10	(0.77, 1.56)	1.53	(1.08, 2.17)
Schedule II long only	1.33	(1.08, 1.62)	1.32	(1.00, 1.73)
Schedule III or IV + Schedule II short	1.04	(0.78, 1.40)	1.64	(1.19, 2.24)
Schedule III or IV + Schedule II long	1.48	(1.24, 1.76)	1.34	(1.05, 1.71)
Schedule II short and long	1.49	(1.16, 1.93)	1.09	(0.76, 1.56)
Opioid all types	1.92	(1.45, 2.54)	1.19	(0.75, 1.88)

prevalence of opioid abuse/dependence are compatible with estimates of "problem opioid use," 3.5%, derived from interviews in the nationally representative Healthcare for Communities (HCC) household survey (Edlund et al., 2007b).

Both administrative and survey data may under-estimate actual rates of opioid abuse/dependence, and thus our estimates should be viewed as lower bounds. Regarding administrative data, under-detection of substance use disorders by clinicians, and indeed all kinds of disorders, is common (Borowsky et al., 2000; Cleary and McNeil, 1988; Lefevre et al., 1999; Spitzer et al., 1999; Wells et al., 1989); in household surveys, individuals may minimize their level of drug use, due to social-undesirability. Further, there is likely significant opioid misuse that does not rise to the level of DSM-IV abuse or dependence.

The rates of post-index non-opioid substance abuse/dependence, 4.4% in the HealthCore sample and 13.8% in the Arkansas Medicaid sample, were higher than rates of post-index opioid abuse/dependence. This suggests that clinicians must be vigilant for both opioid and non-opioid substance abuse disorders (e.g., alcohol abuse or dependence, or methamphetamine abuse or dependence) in COT patients. It is interesting that the predictors of post-index opioid abuse/dependence and post-index non-opioid substance abuse/dependence were similar, and several factors may be involved. The most worrisome possibility is that many individuals receiving COT may have a predisposition for substance abuse. On the other hand, it could be that clinicians are just more vigilant in detecting these disorders among individuals on COT.

The factors associated with a higher or lower likelihood of opioid abuse/dependence among those receiving COT were similar across our two disparate samples. Among non-modifiable risk factors, younger individuals had substantially higher rates of post-index opioid abuse/dependence. Age effects were strong; for example, the ORs for those ages 31–40 were 4.16 and 11.39 for HealthCore and Arkansas Medicaid, respectively, compared to the reference group of individuals 65 or older. These results are consistent with substance abuse patterns in general, which show higher rates in younger individuals (Compton et al., 2007; Grant et al., 2004a; Swendsen et al., 2009). The age results deserve emphasis, because COT patients are often young (23% of the HealthCore COT sample was age 40 or younger, and 23% of the Medicaid COT sample); age is highly protective from abuse of opioid abuse/dependence; and age can be assessed quickly and reliably. By way of comparison, the OR's for age were larger than the OR's for pre-index opioid abuse/dependence and pre-index non-opioid substance abuse/dependence, well recognized risk factors for opioid abuse/dependence. Given this, we believe that guidelines should emphasize that age, particularly younger age, is a risk

factor for opioid abuse and dependence, and standardized questionnaires developed for predicting aberrant opioid use in CNCP patients should include age.

The American Geriatrics Society recommends that opioids generally be used in geriatric populations before NSAIDs and Cox-II inhibitors (acetaminophen is recommended as first line agent) (American Geriatrics Society, 2009). While use of COT is a complex decision involving many factors, the protective effect of older age demonstrated in our data lends support to these recommendations. On the other hand, our results suggest that clinicians must be especially cautious in balancing the risks and benefits of COT in younger individuals.

Mental disorders can be difficult to successfully treat in patients with chronic pain (Bair et al., 2003; Thielke et al., 2007) and thus the extent to which mental health disorders are potentially modifiable in patients with CNCP is debatable. However, their importance as risk factors for opioid abuse/dependence is undeniable (Edlund et al., 2007a; Martins et al., 2009). In other studies (Cicero et al., 2009; Edlund et al., 2007a) and the present study mental health disorders are extremely common among patients receiving COT; 18% of the HealthCore sample had one or more mental health diagnosis, and 32% of the Arkansas Medicaid had one or more mental health diagnosis, and these estimates are likely conservative, due to well-documented under-diagnosis in primary care clinical practice. The magnitude of their effects were moderate, with OR's in HealthCore of 1.73 (1 mental health disorder vs no disorder) to 2.08 (2 mental health disorders vs no disorders). To the extent that mental health disorders can be successfully treated, such treatment might decrease the risk of development of opioid abuse/dependence in COT users. Thus, we believe our work highlights the importance of assessment and treatment of mental health disorders in patients receiving or being considered for COT.

Specific tracer chronic pain types were statistically associated with the likelihood of opioid abuse/dependence, although the effects were modest; statistically significant results with only modest size coefficients are not unusual with large samples. Because the magnitudes of the effects were relatively modest, we do not believe that clinicians should base decisions about COT solely on pain location.

The Washington State Opioid Dosing Guidelines has specified greater than 120 mg of morphine equivalents as "high dose" opioid therapy, which may require specialty consultation or closer monitoring. Our results generally supported this. Individuals on greater than 120 mg morphine equivalents did have significantly increased diagnoses of post-index opioid abuse/dependence. However, they also had significantly higher diagnoses of post-index non-opioid substance abuse/dependence. Thus there are multiple explanations for our findings, none of which are mutually exclusive: individuals with a predisposition for substance abuse may seek higher opioid doses from their clinicians; higher opioid doses may lead to both higher opioid abuse and non-opioid substance abuse; or clinicians may be more ready to diagnose substance use disorders with their patients treated with high doses of opioids. Likely all factors contribute to our results. In any event, those on opioid daily doses of greater than 120 mg do seem to comprise a high-risk group for substance abuse. The opioids days supply was also associated with the likelihood of post-index opioid abuse/dependence and post-index non-opioid abuse/dependence in HealthCore (but not in Arkansas Medicaid). This suggests that individuals with daily rather than intermittent use (e.g., 160–185 days group) and individuals using multiple opioid types (e.g., 185+ days group) may be at increased risk for abuse. The relationship between opioids day supply and post-index abuse/dependence is also likely complex and bi-directional. That is, daily use is likely a causal risk factor for opioid abuse/dependence, and patients with opioid abuse/dependence may be more likely to aggressively seek daily prescription opioids from their clinicians.

While we hypothesized that long-acting Schedule II opioids would have the weakest association with opioid abuse/dependence, in HealthCore all opioid type categories that included Schedule II long-acting opioids had a higher likelihood of post-index abuse/dependence. Some of the increased risk seen with long-acting opioids may be due to methadone prescribed for pain to high-risk individuals, although overall use of methadone was relatively infrequent in both HealthCore and Arkansas Medicaid. Individuals who used only Schedule III or IV opioids had lower rates of post-index opioid abuse/dependence than individuals in the opioid type categories that included Schedule II opioids, although these differences were not always significant. Schedule II long-acting opioids are the focus of the FDA's Risk Evaluation and Mitigation Strategy. However, in both samples of COT users the large majority of individuals had Schedule III or IV opioid use only, and about half of the individuals with post-index opioid abuse/dependence had Schedule III or IV use only. This suggests policy changes aimed at decreasing the incidence and prevalence of opioid abuse/dependence need to be directed at not only Schedule II opioids, but also Schedule III and Schedule IV opioids.

5. Limitations

Our work should be interpreted in light of several limitations. First, although we utilized pre-index variables to predict post-index opioid abuse/dependence so that the independent variables temporally preceded the outcomes, the study is observational, so we are describing associations, and not necessarily causal relationships. Further, to the extent that these relationships are causal, they may be bi-directional in many cases (Martins et al., 2009). Second, our sample was extremely large and covered multiple states, but not necessarily nationally representative. Third, we had information on type of pain conditions, but not pain severity. We thus cannot comment on the role of pain relief or lack thereof in the risk of an abuse diagnosis. Fourth, our finding that younger individuals had substantially higher rates of opioid abuse/dependence may be due to detection bias with younger individuals showing more visible aberrant drug behaviors than older individuals, or with providers having a higher degree of suspicion in younger individuals (Blazer and Wu, 2009; Wu et al., 2008). However, our age results are consistent with community epidemiological studies of substance abuse. These studies, which do not rely on physician diagnoses, find significantly higher rates of substance abuse in general in younger individuals (Compton et al., 2007; Grant et al., 2004b; Swendsen et al., 2009). Fifth, because the index date was defined as the date of the first prescription fill of the chronic opioid use episode, and not necessarily the first opioid prescription, the risk factors we report may not apply to all patients receiving opioids, but rather to patients who are on COT therapy. Sixth, our measure of abuse does not necessarily indicate an incident diagnosis as we allowed persons with pre-index opioid abuse/dependence diagnoses into the sample. It is unclear for those that had an abuse/dependence diagnosis in the pre-index period and in the post-index period if that represents relapsing abuse/dependence or one continuous disorder; however, given the much higher rates of abuse in the post-index period, most of abuse diagnoses may represent new cases. Seventh, our analyses and interpretation assumed a filled prescription was tantamount to use of the opioid prescription by the person for whom the prescription was written. That is, we used prescription fills as a proxy for opioid use by the person for whom the prescription was written. However, the opioids may not have always been used, or could have been diverted.

6. Conclusions

Opioid and non-opioid substance abuse and dependence are diagnosed in only a small minority of COT recipients. We found similar risk factors for receiving opioid and non-opioid abuse/dependence diagnoses among individuals receiving COT. We believe that the robustness of the results across dissimilar samples enhances the validity and generalizability of our findings. In terms of risk factors that cannot be modified, there was a strong inverse relationship between age and receiving a diagnosis of opioid and non-opioid abuse/dependence. This suggests that clinicians need to be particularly cautious when prescribing COT to younger patients. In terms of potentially modifiable risk factors, mental health and substance use disorders were associated with an increased risk of opioid abuse/dependence. The effects of substance use disorders were especially strong, although mental health disorders were more common. Recently released guidelines from the United States Veteran's Administration recommend that individuals meeting diagnostic criteria for current substance use disorders who are not in active substance abuse treatment should not be initiated on COT. Concerning opioid exposure, lower days supply, lower average doses, and use of non-Schedule II opioids only, were all associated with a lower likelihood of opioid abuse/dependence, although these results are likely complex and bi-directional.

Conflict of interest

There are no conflicts of interest for any authors.

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