Long-Term Chronic Opioid Therapy Discontinuation Rates from the TROUP Study

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OBJECTIVE: To report chronic opioid therapy discontinuation rates after five years and identify factors associated with discontinuation.

METHODS: Medical and pharmacy claims records from January 2000 through December 2005 from a national private health network (HealthCore), and Arkansas (AR) Medicaid were used to identify ambulatory adult enrollees who had 90 days of opioids supplied. Recipients were followed until they discontinued opioid prescription fills or disenrolled. Kaplan Meier survival models and Cox proportional hazards models were estimated to identify factors associated with time until opioid discontinuation.

RESULTS: There were 23,419 and 6,848 chronic opioid recipients followed for a mean of 1.9 and 2.3 years in the HealthCore and AR Medicaid samples. Over a maximum follow up of 4.8 years, 67.0% of HealthCore and 64.9% AR Medicaid recipients remained on opioids. Recipients on high daily opioid dose (greater than 120 milligrams morphine equivalent (MED)) were less likely to discontinue than recipients taking lower doses: HealthCore hazard ratio (HR) = 0.66 (95%CI: 0.57–0.76), AR Medicaid HR=0.66 (95%CI: 0.50–0.82). Recipients with possible opioid misuse were also less likely to discontinue: HealthCore HR=0.83 (95%CI: 0.78–0.89), AR Medicaid HR=0.78 (95%CI: 0.67–0.90).

CONCLUSIONS: Over half of persons receiving 90 days of continuous opioid therapy remain on opioids years later. Factors most strongly associated with continuation were intermittent prior opioid exposure, daily opioid dose$\geq$120 mg MED, and possible opioid misuse. Since high dose and opioid misuse have been shown to increase the risk of adverse outcomes special caution is warranted when prescribing more than 90 days of opioid therapy in these patients.

KEY WORDS: opioids; opioid misuse; persistence; discontinuation.
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INTRODUCTION

The long-term efficacy and safety of chronic opioid therapy (COT) for chronic non-cancer pain (CNCP) is not well established. In randomized controlled trials, oral opioids offer improved pain relief for musculoskeletal and neuropathic pain versus placebo over weeks to months.[1] Efficacy data on longer term opioid use is limited to open label extensions of short term trials. These show that discontinuation of opioids is common, generally due to side effects or lack of efficacy.[2–4] Professional pain guidelines note limitations in the evidence supporting COT and potential serious harms, but state that COT can "be effective therapy for carefully selected and monitored patients".[2,5]

Use of COT for CNCP has dramatically increased over the past three decades.[6–8] There has been a parallel increase in abuse of prescribed opioids[7,9] with prescription opioid abuse the fastest growing form of drug abuse[9] and prescription opioids most frequently associated with accidental fatal drug overdose.[10] Evidence linking prescribed opioid dose with risk of adverse outcomes is emerging.[11,12]

It is not known how long COT recipients generally continue opioid therapy or who is likely to continue COT long term. Electronic health care data offers a unique opportunity to investigate duration of COT within large clinical populations over long time periods. In this study, we report opioid discontinuation rates of COT users over a follow-up period of up to five years and investigate factors associated with discontinuation in a geographically diverse national sample of COT recipients with commercial insurance and a state-based Medicaid sample.

METHODS

Data Source

Data were obtained from claims records from January 2000 through December 2005 from HealthCore, the country's largest private health network, and Arkansas Medicaid. HealthCore data included plans from 14 states in the Western, Mid-Western, and South-Eastern United States. These two populations were chosen to assess the range of opioid use and its consequences in disparate populations. A waiver of the requirements for informed consent was granted from the Human Subjects Review Committees at participating institutions.

Study Sample

The analytical sample consisted of adult enrollees with continuous chronic opioid use. *Inclusion Criteria:* 1) At least one chronic opioid use episode with>90 days of opioid supplied in any 6 month period between 3/6/2001 and 12/31/2004. Continuous chronic opioid use was defined as opioid use without a 32 day gap occurring between fill dates. The first day of the chronic opioid use episode was defined as the index date. 2) Continuous enrollment for 24 months, 12 months before and after the index date. *Exclusion Criteria:* 1) Any claim for long-term or hospice care, 2) Cancer diagnosis in the year prior to the index date (other than non-melanoma skin cancer). 23,419 enrollees in HealthCore and 6,848 in Arkansas Medicaid met these criteria. Details of the HealthCore and Arkansas Medicaid populations and their opioid use have been described elsewhere.[8,13]

Opioid Discontinuation

Subjects were followed from their first chronic opioid use episode until disenrollment, death, opioid discontinuation, or until the study period ended. Opioid discontinuation was defined as a period of at least 182 days of enrollment without any opioid prescription claims from the run out date (prescription fill date+days supplied) of the last prescription.

Sociodemographic and Clinical Variables

Data on sociodemographic variables came from the recipient enrollment files. For the HealthCore sample, census tracts and state level codes were used to describe minority, education, and income characteristics of the recipient's area of residence. In each case, we coded whether a recipient came from a tract above or below the median value for the country. Clinical characteristics of the recipients based on ICD-9-CM codes were collected from claims records in the 12 months preceding the index date. The Charlson comorbidity index[14] a common measure which weights 22 comorbidities that has been adapted for use with administrative data was used as a measure of overall medical comorbidity. Arthritis/joint pain, back pain, neck pain, and headache—the most common diagnoses for long-term opioid use in a general medical population[8]—were selected as tracer pain diagnoses, and tracked individually. The count of 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 was used as a measure of non-CNCP pain. Mental health and substance use disorders were grouped based on ICD-9-CM diagnoses using validated grouping software developed by the Agency for Healthcare Research and Quality[15]: adjustment disorders, anxiety disorders, mood disorders, personality disorders, and substance use disorders. Mood disorders were further classified as unipolar depression or bipolar disorder, and substance use disorders were further classified as alcohol use disorder, non-opioid drug use disorder, or opioid use disorder. Adjustment, anxiety, mood and personality disorders were summed to create a variable identifying the number of mental health disorder types.

Medication Variables

Data for medication use were collected for the 12-month pre-index and the 6-month post-index period. Morphine equivalent dose (MED) in the initial 6 month COT episode was calculated by multiplying the quantity of each prescription by the opioid strength, and multiplying this by a morphine equivalent conversion factor.[8] Average opioid dose per day supplied was calculated by adding the total morphine equivalents for the three major opioid groups and dividing by the sum of the total days supply. If the total days supply exceeded the number of days in the period (180 days), suggesting concurrent use of different opioid types, daily dose was calculated by dividing total dose dispensed by 180 days. Mean daily dose was trichotomized: daily dose<median MED dose in each sample (33 mg MED HealthCore; 36 mg MED AR Medicaid), median MED≤daily dose<120 mg, daily dose≥120 mg MED. 120 mg MED was chosen because Washington State and Centers for Disease Control guidelines urge special precautions for doses greater than 120 mg MED. Types of opioid received were determined based on opioid class (defined by DEA schedule and duration of action). Subjects were coded as receiving a particular opioid class if they received at least 30 days supply of that class within the six-month period. Seven mutually exclusive opioid categories were derived: (1) Non-Schedule II short-acting (eg: hydrocodone/acetaminophen), (2) Schedule II short-acting (eg: morphine), (3) Schedule II long-acting (eg: oxycodone controlled release), (4) Non-schedule II plus Schedule II short acting, (5) Schedule II short-acting plus Schedule II long-acting, (6) Non-Schedule II short-acting plus Schedule II long-acting, and (7) all three opioid types. Intermittent prior exposure to opioids was defined as having 30 or more days of opioid supplied in the 6-month period immediately prior to the COT episode. We used data on days supply and measures of any exposure for the following non-opioid medications, often used in the treatment of patients with CNCP: sedative/hypnotics (mainly benzodiazepines, but also other hypnotic drugs), muscle relaxants, stimulants, Cox-II inhibitors, anticonvulsants, tricyclic antidepressants, serotonin or serotonin-norepinephrine re-uptake inhibitors (SSRI/SNRI), and other analgesic medications. An opioid misuse score based on excess days supplied of short- and long-acting opioids, the number of unique opioid pharmacies and opioid prescribers was calculated in the six-month post-index period.[16] The misuse score was trichotomized with misuse scores of 0 to 1 representing the lowest probability of opioid misuse, 2–3 representing possible misuse, and scores of 4 or greater representing the highest probability of misuse.

Statistical Analysis

Descriptive statistics were calculated for demographic and clinical variables. We used Kaplan Meier survival models to estimate unadjusted time to discontinuation. Stepwise Cox proportional hazards models were estimated to identify factors associated with time until opioid discontinuation. Variables were classified into 6 groups, and the groups were ordered as follows: (1) demographic variables, (2) misuse variables, (3) pain diagnoses and Charlson index, (4) pharmacological variables, and (5) mental health/substance abuse diagnoses. Within each group, we performed a model selection process to choose the "final model" using the STEPWISE option in SAS

Table 1. Demographic, Comorbidity, Drug and Medical Use Variables HealthCore and Arkansas Medicaid 2000 – 2005

Variables	Categories	HealthCore	AR Medicaid	P-value
		N=23,419	N=6,848	
Age	18–30	1282 (5.5%)	518 (7.6%)	<0.001
	31–40	4001 (17.1%)	1186 (17.3%)	
	41–50	7305 (31.2%)	1730 (25.3%)	
	51–64	7927 (33.8%)	1822 (26.6%)	
	>=65	2904 (12.4%)	1592 (23.2%)	
Female		13739 (58.7%)	4969 (72.6%)	<0.001
Index year	2001	5678 (24.2%)	1718 (25.1%)	<0.001
	2002	6462 (27.6%)	1662 (24.3%)	
	2003	6308 (26.9%)	1609 (23.5%)	
	2004	4971 (21.2%)	1859 (27.1%)	
Race – black*		—	1421 (20.8%)	—
From census tract with:				
Predominantly some college†		12448 (56.8%)	—	—
Predominantly Minority†		8624 (39.3%)	—	
Median Income or Higher†		10749 (49.0%)	—	
Pre-index opioid days supplied>30		12595 (53.8%)	4165 (60.8%)	<0.001
CNCP type	None	10501 (44.8%)	1865 (27.2%)	<0.001
	back pain only	3949 (16.9%)	1200 (17.5%)	
	neck pain only	629 (2.7%)	105 (1.5%)	
	joint pain only	1648 (7.0%)	929 (13.6%)	
	headache only	1305 (5.6%)	312 (4.6%)	
	2 or more CNCP	5387 (23.0%)	2437 (35.6%)	
Charlson score	Mean(SD)	0.4 (1)	1.1 (1)	<0.001
Non-tracer pain	0	9666 (41.3%)	1746 (25.5%)	<0.001
	1	6634 (28.3%)	1863 (27.2%)	
	2-3	6066 (25.9%)	2587 (37.8%)	
	>=4	1053 (4.5%)	652 (9.5%)	
Opioid type	non-class II only	18639 (79.6%)	5576 (81.4%)	<0.001
	class II short only	500 (2.1%)	179 (2.6%)	
	class II long only	1042 (4.4%)	284 (4.1%)	
	non-class II+class II short	761 (3.2%)	237 (3.5%)	
	non-class II+class II long	1578 (6.7%)	370 (5.4%)	
	class II short+long	538 (2.3%)	127 (1.9%)	
	All 3 types	361 (1.5%)	75 (1.1%)	
Opioid daily dose	< median	12835 (54.8%)	3844 (56.1%)	<0.001
	median-120	9595 (41.0%)	2788 (40.7%)	
	>120	989 (4.2%)	216 (3.2%)	
Misuse Score	No misuse (0–1)	19474 (83.2%)	6003 (87.7%)	<0.001
	Possible misuse (2–3)	3399 (14.5%)	747 (10.9%)	
	Probable Misuse (4+)	523 (2.2%)	98 (1.4%)	
Pre-Index Pharmacological Variables				
NSAIDS/COXII		3481 (14.9%)	975 (14.2%)	0.198
Muscle relaxants		7550 (32.2%)	2367 (34.6%)	<0.001
Sedative/hypnotics		9024 (38.5%)	2693 (39.3%)	0.236
SSRI/SNRI		8550 (36.5%)	2352 (34.3%)	<0.001
Stimulants		496 (2.1%)	63 (0.9%)	<0.001
Antimigraine		1979 (8.5%)	164 (2.4%)	<0.001
Anticonvulsants		3106 (13.3%)	1007 (14.7%)	<0.001
Any of above RX use pre-index		17419 (74.4%)	5252 (76.7%)	<0.001
Post-Index Pharmacological Variables				
NSAIDS/COXII		3157 (13.5%)	613 (9.0%)	<0.001
Muscle relaxants		8111 (34.6%)	2362 (34.5%)	0.827
Sedative/hypnotics		9768 (41.7%)	2782 (40.6%)	0.109
SSRI/SNRI		8723 (37.2%)	2285 (33.4%)	<0.001
Stimulants		522 (2.2%)	71 (1.0%)	<0.001
Antimigraine		1703 (7.3%)	130 (1.9%)	<0.001
Anticonvulsants		3814 (16.3%)	999 (14.6%)	0.001
Any of Above RX use post-index		18602 (79.4%)	5399 (78.8%)	0.289
Adjustment disorder		439 (1.9%)	134 (2.0%)	0.661
Anxiety disorder		1777 (7.6%)	1203 (17.6%)	<0.001
Mood disorder		2758 (11.8%)	1544 (22.5%)	<0.001
Personality disorder		46 (0.2%)	135 (2.0%)	<0.001
Substance disorder		547 (2.3%)	427 (6.2%)	<0.001
Miscellaneous Psychiatric disorder		611 (2.6%)	125 (1.8%)	<0.001
Alcohol use disorder		309 (1.3%)	225 (3.3%)	<0.001
Opioid use disorder		130 (0.6%)	36 (0.5%)	0.772
Non-opioid drug use disorder		242 (1.0%)	235 (3.4%)	<0.001

**Race was only available for AR Medicaid*
†Based on Geographic Area of Residence
CNCP – Chronic Non-Cancer Pain

9.1 with a criteria of p<=0.05 to select and retain variables in the model.[17] For each group, the models always retained the variables in the final model from the previous group(s). For example, if age was included in the final model of group (1), then it was retained in subsequent models evaluating variables in groups (2), (3), (4), and (5).

RESULTS

Of the 23,419 continuous chronic opioid recipients in HealthCore, 58.7% were female, 12.4% were 65 years of age or older and 55.2% had one or more tracer pain diagnoses (Table 1). The AR Medicaid sample of 6,848 chronic opioid recipients were comprised of more elderly (23.2%) and females (72.6%) (p <0.001). The maximum follow-up time was 4.82 years in both samples and the median and mean follow-up times were 1.69 and 1.93 years in the HealthCore sample and 1.99 and 2.25 years in the AR Medicaid sample. The AR Medicaid sample had more tracer pain diagnoses, mental health diagnoses, and medical comorbidities (Charlson score) than the HealthCore sample (p<0.05). Use of sedatives and non-opioid drugs with potential analgesic properties were similar in the two samples. In both samples, approximately 80% of chronic opioid users used schedule III and IV opioids (non-class II) as their primary opioid in the first six months; 3–4% of the samples used more than 120 mg MED per day. The mean days supplied of opioids in the six-month post-index period were 148 and 143 days in the HealthCore and AR Medicaid samples reflecting near daily consumption. Over half the persons in each sample received 30 or more days supply of opioids in the prior six months. Possible or probable misuse in the first six months (misuse scores≥2) occurred in 16.7% and 12.3% of the HealthCore and AR Medicaid samples.

Sixty seven percent and 64.9% of HealthCore and AR Medicaid chronic opioid patients remained on opioids before they became censored (Fig. 1). In both samples, the most significant and consistent predictors of opioid discontinuation were mean daily opioid dose and prior intermittent opioid use [Table 2]. Persons on average daily doses greater than 120 MED were 34% less likely to discontinue than persons taking doses at or below the median daily dose in the both samples (Fig. 2). Persons with a misuse score of≥2 were about 20% less likely to discontinue than persons with a misuse score of<2 in the HealthCore sample (Fig. 3). Persons with opioid exposure prior to beginning their COT were 24–45% less likely to discontinue as those without 30 days or more of exposure. For AR Medicaid, the types of opioid used were not associated with discontinuation. However, in HealthCore persons prescribed only short acting Schedule II opioids were significantly more likely to continue than persons prescribed only schedule III and IV opioids.

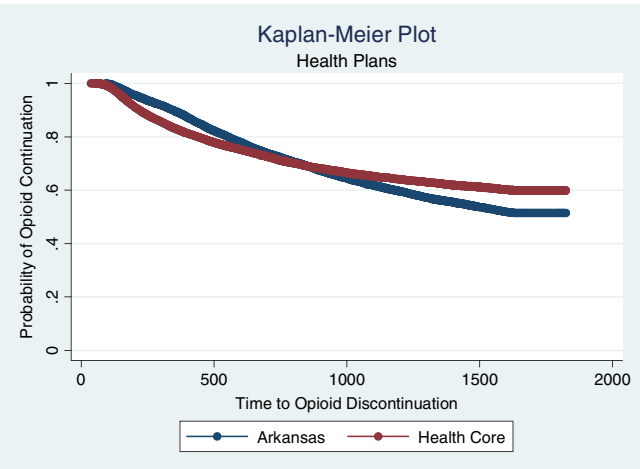

Figure 1. Days until opioid discontinuation by health plan type, 2001–2005.

Demographic factors were not strongly associated with discontinuation, though persons between the ages of 41 and 64 were approximately 10% less likely to discontinue than elderly counterparts. Persons with multiple tracer pain conditions were 18% less likely to discontinue than persons without any tracer conditions in AR Medicaid. Discontinuation was not associated with the number of non-tracer painful conditions in either sample. Persons with a personality disorder were 76% more likely to discontinue in HealthCore than those without any personality disorders. An alcohol abuse diagnosis in AR Medicaid and HealthCore was associated with a greater likelihood of discontinuation,; however, an opioid abuse diagnosis was not associated with discontinuation in either sample (variable not entered in stepwise selection process). Use of sedative hypnotics, muscle relaxants, antidepressants, and anti-migraine medications was associated with a lower likelihood of discontinuation in HealthCore, but not in AR Medicaid.

DISCUSSION

Among this large and diverse sample of continuous chronic opioid users, approximately two thirds of persons remained on opioid therapy years later. This suggests that continuous opioid therapy for at least three months often leads to a course of opioid therapy that persists over years.

Previous evidence on COT duration is limited to withdrawal rates from extensions of open label clinical trials, where it has been reported that 32% discontinue due to adverse events and 12% due to inadequate pain relief over a 6- to 18-month time period.[1] However, professional COT guidelines address discontinuation largely as a consequence of aberrant drug behaviors.[2] There are no randomized trials or controlled observational studies comparing outcomes with continuation vs. discontinuation of COT over extended periods. In our current study, we are unable to distinguish between patients who discontinue because of improved pain and function vs. those who discontinue because of side effects, analgesic failure, or aberrant drug behaviors. What can be learned from our data is that once a person has transitioned to COT, more than half will likely continue to use opioids a half a decade later under existing practice patterns. This is an important point for clinicians to consider and discuss with patients prior to deciding on a regimen of COT.

Prior intermittent opioid use had the strongest association with opioid discontinuation, even though we required at least a 32-day gap between any prior intermittent use and the beginning of their COT therapy, so that the start point of their COT could be clearly defined. Over half of persons who go on to receive COT, have intermittent use beforehand, implying that

Table 2. Cox Proportional Hazard Model Results of Time until Opioid Discontinuation HealthCore and Arkansas Medicaid, 2000–2005

Variables	HEALTHCORE		ARKANSAS MEDICAID	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Age: 18–30	1.11	[0.99, 1.25]	1.04	[0.87, 1.23]
Age: 31–40	1.03	[0.95, 1.13]	0.88	[0.77, 1.01]
Age: 41–50	0.90	[0.83, 0.97]	0.77	[0.69, 0.87]
Age: 51–64	0.89	[0.82, 0.96]	0.80	[0.72, 0.90]
Referent: Age: 65+				
Female	0.85	[0.81, 0.89]	—	—
Referent: Male				
Index year: 2002	—	—	0.93	[0.84, 1.02]
Index year: 2003	—	—	0.77	[0.69, 0.87]
Index year: 2004	—	—	0.50	[0.43, 0.58]
Referent: Index year 2001				
Some college or above	1.11	[1.06, 1.16]	—	—
Referent: high school or less				
Ethnic minority	1.04	[0.99, 1.10]	—	—
Referent: non-minority				
Misuse score 2-3	0.83	[0.78, 0.89]	0.78	[0.67, 0.90]
Misuse score>=4	0.80	[0.67, 0.95]	0.89	[0.61, 1.25]
>=30 opioids days in pre-index period	0.55	[0.53, 0.58]	0.76	[0.70, 0.82]
CNCP: back only	—	—	0.98	[0.87, 1.11]
CNCP: neck only	—	—	0.84	[0.60, 1.15]
CNCP: joint only	—	—	1.01	[0.89, 1.15]
CNCP: head only	—	—	1.01	[0.82, 1.23]
CNCP: 2 or more	—	—	0.82	[0.73, 0.91]
Referent: No CNCP				
Charlson score	0.97	[0.95, 1.00]	1.06	[1.03, 1.09]
class II short only	0.72	[0.59, 0.86]	—	—
class II long only	1.14	[1.01, 1.28]	—	—
non-class II+class II short	1.08	[0.94, 1.24]	—	—
non-class II+class II long	1.15	[1.05, 1.27]	—	—
class II short+long	0.99	[0.83, 1.17]	—	—
All 3 types	1.06	[0.86, 1.30]	—	—
Referent: non – class II only				
Opioid daily dose: median-120	0.92	[0.88, 0.97]	0.87	[0.80, 0.94]
Opioid daily dose: >120	0.66	[0.57, 0.76]	0.66	[0.50, 0.85]
Referent: Opioid daily dose < median				
RX: pre-index sedative/hypnotics	0.89	[0.85, 0.94]	—	—
RX: post-index Cox-2 s	1.08	[1.01, 1.15]	—	—
RX: post-index muscle relaxants	0.91	[0.87, 0.96]	—	—
RX: post-index SSRI/SNRIs	0.94	[0.89, 0.99]		
RX: post-index anti-migraine drugs	0.82	[0.74, 0.91]	—	—
Referent: No exposure to other analgesic drugs				
MH: personality disorder	1.76	[1.05, 2.74]	—	—
MH: mood disorder	—	—	1.15	[1.04, 1.27]
Referent: No mental health diagnoses				
SA: alcohol	1.22	[1.00, 1.47]	1.33	[1.06, 1.64]

Referent: No substance abuse diagnoses
Cox2s-Cyclooxygenase 2 inhibitors; SSRIs—Selective Serotonin Reuptake Inhibitors; SNRIs – Serotonin–Norepinephrine Reuptake Inhibitors

many persons who are prescribed intermittent opioids are gradually titrated up to daily or near-daily COT.

Other strong predictors of opioid continuation were daily opioid doses over 120 mg MED and possible opioid misuse. The effect of high dose opioids on discontinuation is consistent with a study of workers with back injury where the maximum dose of opioids in the first three months after injury was the strongest prognostic factor for continued opioid use at one year.[18] Though the mechanisms of opioid analgesic tolerance are still unclear,[19] the association between high daily doses and longer durations suggest that opioid tolerance and withdrawal symptoms may drive escalating doses and longer durations of therapy. Opioid dose may be a marker for more difficult to treat pain conditions or other comorbidities; however, it remained significant in multivariable models that attempted to control for a range of comorbidities. This association of high dose COT and continuation is of concern since prescribed daily opioid dose over 100 mg MED has been associated with increased risks of overdose[11] fracture,[12] dependence [13] and death.[20]

Patients with possible opioid misuse were also significantly less likely to discontinue opioid therapy, but probable misuse was not significantly associated with longer durations of opioid therapy in the AR Medicaid sample; this is likely due to the relatively small number of patients (n=98) in this category. Our misuse score is derived from excess days supplied of opioid, multiple opioid prescribers and multiple opioid pharmacies and may reflect "doctor shopping", diversion or other aberrant medication behaviors; this measure has been shown to be associated with substance abuse diagnoses,[16] but may also reflect legitimate care delivered by multiple providers. Nevertheless, the 20% increase in the time until opioid discontinuation

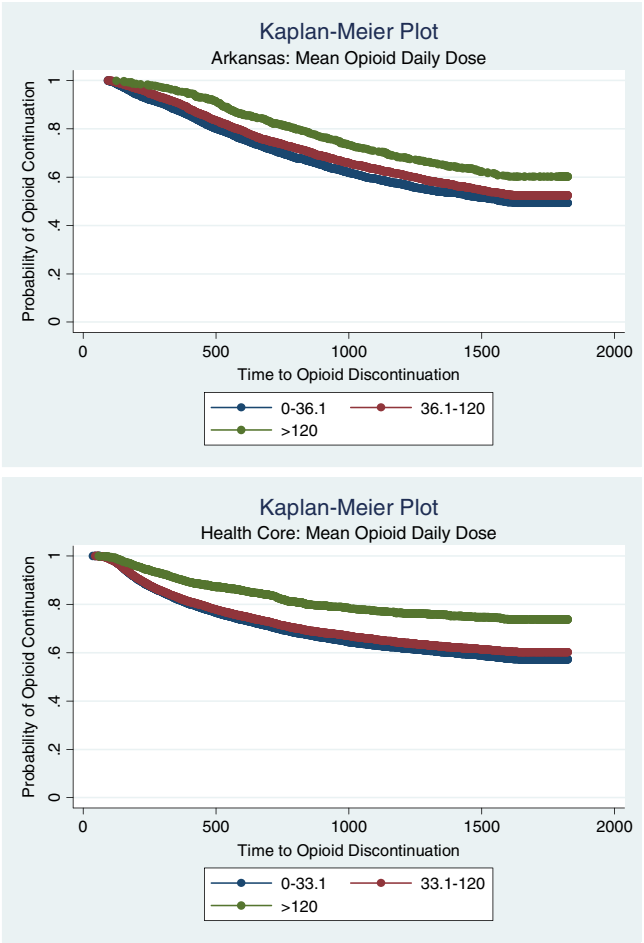

Figure 2. Days until opioid discontinuation by mean daily opioid dose for Arkansas Medicaid and healthcore, 2001–2005.

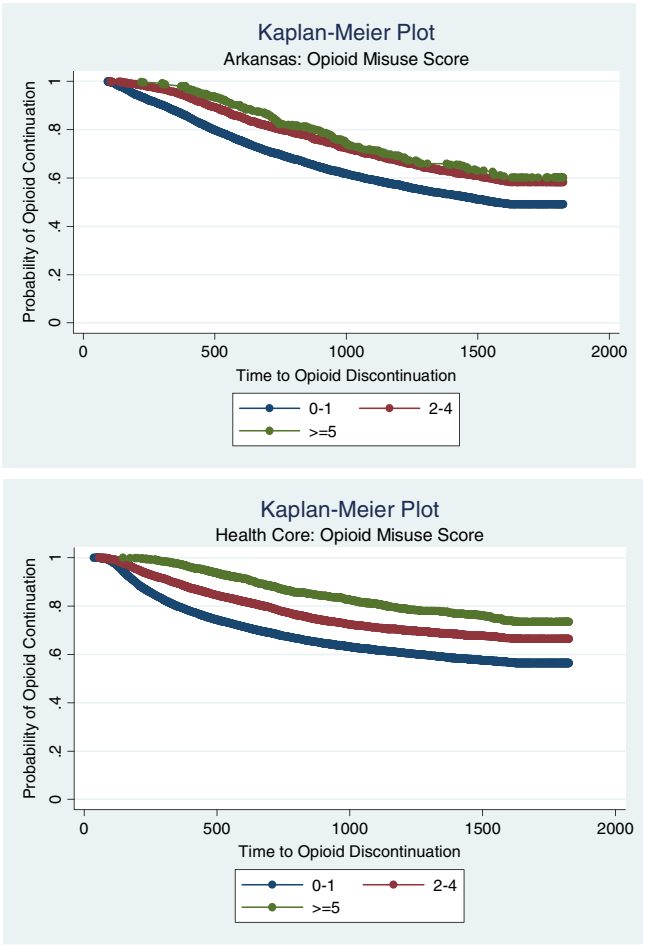

Figure 3. Days until opioid discontinuation by misuse score for Arkansas Medicaid and healthcore, 2001–2005.

associated with possible misuse in both samples is worrisome since higher daily opioid doses and opioid misuse have been associated with adverse outcomes of COT. Overall, these data show that approximately 1 in 7 persons on COT potentially misuse opioids and these patients take opioids for durations that are measured in years. With the increase in prescription monitoring programs throughout the U.S., some of the measures with which our misuse score were derived can be monitored in order to deter aberrant opioid behaviors but future research will be needed to assess the effectiveness of these strategies.

Recipient demographics had modest and variable effects on the time until discontinuation. Younger persons 18–30 years old were relatively more likely to discontinue than middle aged persons. This might be due to the increased risk for misuse and abuse of opioids among younger persons,[13,21] which may lead to greater vigilance of prescribers and pharmacists or may reflect less persistent and severe pain. Persons with prior non-opioid drug or alcohol abuse were also more likely to discontinue, which might also suggest greater vigilance in this higher risk group. The lack of consistent associations between most mental health disorders and discontinuation is surprising given previous studies demonstrating increased use of COT for CNCP among persons with mental health disorders and substance use disorders.[22–26] Nearly 40% of the COT users in both samples also had a sedative hypnotic prescribed and in the Health Core sample, these drugs were associated with a lower discontinuation rate. The high rate of co-prescribing of sedative hypnotics to COT raises safety concerns as benzodiazepines are the most frequent co-intoxicants in opioid related deaths.[27]

Although long-acting opioids are often recommended in COT guidelines,[2,5] we found that only 13–15% of COT recipients used a long acting opioid and did not find that long-acting opioids were associated with COT continuation. In the HealthCore sample, recipients using only short-acting schedule II opioids in the first six months of their opioid episode were less likely to discontinue COT. Furthermore, over three quarters of COT recipients received non-schedule II opioids as their primary opioid in the initial six months of COT. While recent federal efforts in responding to the prescription drug abuse problem have focused on the risks of long-acting opioids,[28] our data suggest that this would only address 1 in 6 COT recipients.

These data should be interpreted in light of the following limitations to our study. First, all the recipients in this sample were prescribed a minimum of 90 days of supply of continuous opioid therapy over a 6 month period. Rates of discontinuation are likely higher for persons exposed to shorter or less continuous opioid therapy. Future work could determine if there is a duration threshold, beyond which discontinuation becomes much less likely. Second, our definition of discontinuation relied on the absence of any opioid prescription claims for at least 182 days. Recipients who used opioids intermittently or had gaps of less than 182 days between opioid prescriptions

were not classified as discontinuations. This long period to define discontinuation minimizes, but does not eliminate the chances that a person continued to use opioids that they "stockpiled". The data were drawn from two disparate sources, a geographically dispersed commercial population and a single state's Medicaid population and it is unknown to what extent these findings can be generalized to other settings. We found differences between the samples for some of the factors associated with discontinuation which suggest these weaker factors may be less generalizable; however, the relative consistency of the rates of discontinuation and the associations with dose and prior use common in both samples are more likely to be representative of long term opioid use in the U.S. We used stepwise procedures to identify the significant factors in our Cox models; this can lead to model mis-specification errors which may exclude relevant variables and include spurious factors; however, model mis-specification errors are less likely for those factors identified in both samples. When inspecting the Kaplan Meier curves (Figs. 2 and 3), the key variables appear to meet the proportional hazards assumption; however, interactions between time and key variables were significant in models checking the proportional hazards assumption, which suggests that the hazard ratios we report represent the average effect and this may not be strictly proportional throughout the follow-up period. Lastly, because we did not have links between diagnoses and prescriptions nor have patient reported data, it was not possible to identify the specific reason for COT or the pain severity level; this makes it difficult to interpret some of our associations, particularly for high daily opioid doses and lower discontinuation rates.

CONCLUSIONS

Over half of persons prescribed 90 days of opioid therapy over a six-month period remained on opioids years later and these rates of extended use should be considered and discussed with patients prior to initiating a course of COT. The factors most strongly associated with opioid continuation were prior opioid exposure, daily opioid doses of 120 mg MED per day, and possible misuse; however the data from which these associations were observed did not have clinical measures such as pain or disease severity. Additional caution and monitoring is advised for those who receive more than 90 days of continuous opioid therapy, particularly those who are on high doses or exhibit patterns of potential misuse.

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