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National Study of Discontinuation of Long-Term Opioid Therapy among Veterans

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Abstract

Introduction—Veterans have high rates of chronic pain and long-term opioid therapy (LTOT). Understanding predictors of discontinuation from LTOT will clarify the risks for prolonged opioid use and dependence among this population.

Methods—All veterans with at least 90 days of opioid use within a 180 day period were identified using national Veteran's Health Affairs (VHA) data between 2009 and 2011. Discontinuation was defined as 6 months with no opioid prescriptions. We utilized Cox proportional hazards analysis to determine clinical and demographic correlates for discontinuation.

Results—A total of 550,616 met criteria for LTOT. The sample was primarily male (93%), and white (74%), with a mean age of 57.8 years. The median daily morphine equivalent dose was 26 mg and 7% received high-dose (>100 mg MED) therapy. At one year after initiation, 7.5%

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(N=41,197) of the LTOT sample had discontinued opioids. Among those who discontinued (20%, N=108,601), the median time to discontinuation was 317 days. Factors significantly associated with discontinuation included both younger and older age, lower average dosage and receiving less than 90 days of opioids in the previous year. While tobacco use disorders decreased the likelihood of discontinuation, co-morbid mental illness and substance use disorders increased the likelihood of discontinuation.

Conclusions—LTOT is common in the VHA system and is marked by extended duration of use at relatively low daily doses with few discontinuation events. Opioid discontinuation is more likely in veterans with mental health and substance use disorders. Further research is needed to delineate causes and consequences of opioid discontinuation.

Introduction

Up to 40% of Veteran's receiving care in the Veteran's Health Affairs (VHA) system have received long-term opioid therapy (LTOT) for chronic non-cancer pain (CNCN) [8,21,34]. Veterans have high rates of chronic pain and high rates of comorbid mental illness and substance use disorders that may increase the likelihood of both long-term opioid use and misuse [10,20,28,29]. Prior studies have noted high rates of opioid-related morbidity and mortality from overdose among VHA samples as well as the general population [12,23,24,29].

Among veterans receiving prescription opioids, many receive long-term opioid therapy (LTOT) for the treatment of CNCN defined by greater than 90 days of opioid use per year, [10,29]. A recently released draft report from the Agency for Health Research and Quality on "The Effectiveness and Risks of Long-term Opioid Treatment of Chronic Pain" concluded: "Evidence on long-term opioid therapy for chronic pain is very limited, but suggests an increased risk of serious harms that appears to be dose-dependent [2]." Risks associated with prolonged use of opioid therapy in addition to abuse and overdose include opioid-induced hyperalgesia, endocrine dysregulation, sleep-disordered breathing, depression, bone fractures and constipation [4]. In previous research, less than half of chronic opioid users in commercially insured and Medicaid populations were found to discontinue therapy when followed up to five years [22]. Factors associated with continuation of long-term therapy in the civilian population include prior exposure to opioids, high average daily doses, nicotine use and mental illness [16,18,30]. Consequently, those at highest risk for adverse events on opioid therapy have traditionally been the most likely to continue with high doses and long-term use, a form of adverse selection.

In spite of increased attention to the adverse effects associated with LTOT, little is known about factors that predict discontinuation of LTOT. Unlike short-term opioid therapy, which naturally ends as an acute injury heals, there is no natural endpoint to LTOT. The identification of relevant clinical, sociodemographic or opioid use factors associated with likelihood of opioid discontinuation may help guide clinical decisions concerning long-term opioid use or dose reduction, or support the implementation of programs that promote opioid discontinuation.

This analysis investigates the demographic, clinical and opioid use characteristics of discontinuation of LTOT among a national sample of Veterans enrolled in the VHA system.

Methods

Sample Population

Potential participants were obtained from the VHA Pharmacy Benefits Management Service (PBM) database of all veterans receiving a prescription for an opioid analgesic between October 1st, 2008 and September 30th, 2012. The PBM contains records of all prescription medications dispensed through the VHA, including medication name, strength, number dispensed, days supplied and date dispensed. Data from the PBM was linked using a scrambled social security number (SSN) to data from the VHA Corporate Data Warehouse (CDW) which contains records from the VHA electronic health record of inpatient and outpatient episodes of care, ICD-9 CM codes associated with care and demographic information. The study sample consisted of all adult veterans receiving 90 days or greater supply of non-parenteral opioids with less than a 30-day gap in supply within a 180-day period between October 1st, 2009 and September 30th 2011. The index date was defined as the first day of this 90-day period. A minimum of two prior encounters in the year preceding the index date were required to document enrollment and evaluate for additional exclusionary criteria and relevant co-variables. Veterans with an ICD-9 cancer diagnosis (with the exception of non-melanoma skin cancers) and administrative codes for nursing home use, hospice or palliative care services in the 360 days before and after the index date were excluded. Additionally, veterans with incomplete opioid prescription data (unknown dosages or types), receipt of parenteral, suppository or trans-mucosal opioid therapies or enrolled in a VA opioid replacement programs (methadone maintenance programs) at any time were excluded.

Given high rates of interrupted or episodic use among chronic opioid users and to maintain consistency in definitions with other studies, discontinuation was defined as the first day of a minimum 180-day period with no opioid prescriptions after their index date [3,10,13,22]. In sensitivity analyses, we explored the effect of defining discontinuation as a 90-day period with no opioid prescription. In order to distinguish clearly between disenrollment from VHA and opioid discontinuation, participants without any VA service use in the 90 days after discontinuation were excluded.

Demographic data included age, sex, race (white/Caucasian, African American, multiracial, unknown/declined and other), marital status and geographic location, determined by postal code and classified as urban, suburban, rural and isolated-rural [19]. Co-morbid mental health, substance use and medical conditions were collected via International Classification of Diseases-9th Revision (ICD-9) codes generated through healthcare contacts in the year prior to the index date. Mental health classifications included depressive disorders (e.g.: major depressive disorder and all relevant subtypes, dysthymia, depressive disorder not-otherwise-specified), anxiety disorders, Post-Traumatic Stress Disorder (listed separately from anxiety disorders), schizophrenia and psychotic-spectrum illnesses, bipolar affective disorders and Traumatic Brain Injury. Lists of these ICD-9 codes to generate these groupings can be made available upon request. Similarly, substance use disorder

classifications included tobacco, alcohol, opioid and non-opioid use disorders. The Charlson Comorbidity Index (CCI) was calculated to measure overall burden of medical co-morbidities with allowances for the exclusion of cancer diagnoses [6]. Mental health and substance use diagnoses were based on definitions utilized by the VA Northeast Program Evaluation Center (NEPEC, available upon request). A mental health or substance use diagnosis was defined as having at least two outpatient encounters with any mental health or substance use code in a diagnostic field with the requirement that at least one of the outpatient encounters be face-to-face. Each unique Veteran could receive more than one mental health or substance use diagnosis.

Chronic non-cancer pain conditions were identified through ICD-9 codes and grouped into five broad categories encompassing the most common chronic pain conditions, similar to prior analyses [13]. These groupings included neck pain, back pain, arthritis/joint pain, headache/migraine and neuropathic pain. Clinical self-reported pain intensity scores, ranging from 0 to 10, were averaged over the 90-day period post-initiation of LTOT. These scores have been used in prior VA LTOT studies, and have been correlated with other patient self-reported measures of pain [10,15].

VHA pharmacy data was used to generate relevant characteristics of the opioid prescribed and to convert prescriptions to daily dosage mean in morphine equivalents. Each opioid prescription was converted to a morphine equivalent dose (MED) by multiplying the medication strength and the quantity dispensed by a published conversion factor [33]. If any two prescriptions overlapped by greater than 20% or greater than ten days, the overlapping portions of the prescription were assumed to be taken concurrently and the overlapping days were only included once in the opioid days calculation. If the overlap was 20% and 10 days, the second prescription was shifted and the overlapping days from both the first and second prescription were included in the opioid days' calculation. Veterans average daily use was divided into three groups, 0 – median MED, median to 100 mg MED and greater than 100 mg MED (classified as high-dose), clinically significant cutoffs which have been correlated with adverse events [14]. In sensitivity analyses, we explored the effect of adjusting for shorter (30 days) or longer (180 days) of pre-index opioid use on model associations to attempt to account for the spectrum of baseline opioid use. Since these different definitions of pre-index opioid use did not significantly affect the direction or magnitude of associations with other variables in survival analyses, we proceeded with a dichotomous variable identifying veterans with greater than 90-days' supply of opioid therapies in the year prior to index date to allow for adjustment of prior use based on previous research identifying prior use as a significant predictor of LTOT [22].

Service utilization during the period of chronic opioid therapy initiation was calculated as the total number of mental health encounters, substance use encounters and all other VA encounters abstracted from outpatient Stop Codes in the 90 days post-index. This analysis was approved by the Institutional Review Board of University of Arkansas for Medical Sciences and the Central Arkansas Veterans Healthcare System. A data use agreement was executed with each data repository.

Statistical Analysis

Descriptive statistics were calculated for demographic and clinical variables comparing veterans with a discontinuation event at one year vs. those who continued on LTOT for greater than one year. Chi-squared and t-tests were used to compare these two groups across the range of covariates. Two Cox proportional hazards survival analyses were performed utilizing demographic data, mental health and substance abuse categories, CNCP conditions (a summed count of 0-3 or > 3 categories), average pain score, Charlson Comorbidity Index (CCI), opioid use characteristics and service utilization, with time to discontinuation as the main dependent variable. In order to meet criteria for discontinuation of a gap of 180 days, the first discontinuation events occurred a minimum of 150 days after the index date. The first model entered each mental health and substance abuse diagnostic category as an independent co-variable, while the second model entered a cumulative sum of mental health (range 0 to 5) and substance abuse diagnostic categories (range 0 to 3) as two variables to test the degree to which cumulative mental health or substance abuse burden was associated with discontinuation of therapy. Because the association between tobacco use and LTOT was opposite that of all other mental health and substance use variables in model 1, and traumatic brain injury incorporates multiple disciplines beyond traditional mental health, these were intentionally kept as separate covariates in model 2. Censoring occurred at death, nursing home or hospice care enrollment, or end of the study period. Year of index date was included to account for temporal shifts in opioid prescribing patterns or VHA policy that may have impacted the chronicity of opioid therapy during the study period. Kaplan-Meier plots were generated for overall time to discontinuation and stratified for presentation of clinically relevant findings, available upon request. All analyses were considered significant at the $P < 0.05$ level and performed using SAS version 9.1 [26].

Results

Sample Characteristics

Out of 1,827,279 individuals with an opioid prescription in the VA between FY 2009 and 2011, a total of 814,311 (44.6%) met criteria for LTOT. After exclusions were applied, 550,616 (67.6% of LTOT) were eligible for analysis and 530,964 were entered into survival models. 7,705 (1.4%) were excluded due to missing data, primarily the absence of reliable rural/urban coding. 11,947 were excluded due to missing pain intensity scores.

Table 1 displays one-year discontinuation rates for the total sample by demographics, opioid use, clinical characteristics and service use. The sample was primarily male (93%), white (74%) and urban-dwelling (69%), with a mean age of 57.8 years and 52% were married. At one year after their index prescription date, only 7.5% of the LTOT sample had discontinued opioids. The majority of the total sample (59%) received at least 60 days' supply of medications in the 90-day period at the end of their first year of LTOT. Of those who continued LTOT at one year, the average number of days of opioids supplied in the last 90 days of the year was 63 (standard deviation, 30.0) with an average daily morphine equivalent dose (MED) of 44.8 mg (standard deviation, 67.6 mg).

The majority of the LTOT sample suffered from at least one chronic, non-cancer pain condition (82.3%) with just over a quarter of the sample with conditions in two chronic pain categories (26.7%), and the average pain intensity score post-opioid-initiation was 4.04 (out of 10). Similarly, 62.3% of the sample had a mental health diagnosis, the most common being depressive disorders (29.7%). Only 14.5% were found to have a non-tobacco related substance use disorder, while 25.6% of the total sample used tobacco. The mean number of total clinical encounters in 90-days post-index was almost 9 (mean 8.9, SD 11.0), with mental health or substance use encounters accounting for just over one of these encounters on average (mean 1.4, SD 5.35).

The mean daily MED was 41 mg (SD 61.7 mg) among the LTOT recipients, though the median was 23.5 mg and only 7% received greater than 100 mg daily morphine equivalent dose. Nearly all received short-acting opioids (97.1%). Over half (57%) had received greater than 90 days total opioid supply in the year preceding their index date.

Survival Analysis

Table 2 shows the hazard ratios (HR) and 95% confidence intervals associated with each covariate for model 1. The maximum time available for follow-up was 1,129 days (3.1 years), and of those who discontinued (20%, N=106,542), the median time to discontinuation was 317 days (445 days after index, SD 298.37, mean: 381, or 531 after index). Though the majority of the sample continued use through the end of follow-up, demographic variables associated with higher rates of discontinuation included younger and older age compared with those aged 50-65 (18-30 years HR = 1.53, 95% CI 1.48 to 1.58 and > 65 years HR = 1.34, 95% CI 1.32 to 1.36), non-married status (HR 1.06, 95% CI 1.05 to 1.08) and African American race (HR 1.04, 95% CI 1.02 to 1.06). Compared with those in an isolated rural setting, those in an urban setting were significantly more likely to discontinue (HR 1.07, 95% CI 1.05 to 1.10).

Veterans with higher average daily doses of opioids were less likely to discontinue therapy compared to those in the lowest average dose category (HR 0.82, 95% CI 0.81 to 0.83 for median to 100 mg range, HR 0.63, 95% CI 0.61 to 0.65 for greater than 100 mg daily dose). Those with greater than 90 days use of opioids in the prior year were significantly less likely to discontinue (HR 0.69, 95% CI 0.68 to 0.70). Analyses using 30 days or 180 days of opioid use in the year pre-index did not yield significantly different hazard ratios. Persons with higher levels of medical comorbidity were less likely to discontinue, and persons with higher average post-index pain scores were slightly less likely to discontinue.

Each mental health and substance use disorder category is also listed in Table 2. In general, mental health diagnoses were all associated with greater likelihood of discontinuation, with schizophrenia and bipolar diagnoses associated with nearly 20% greater likelihood of discontinuation (HR 1.20, 95% CI 1.16 to 1.25 for schizophrenia and HR 1.19, 95% CI 1.16 to 1.23 for bipolar). Alcohol (HR 1.10, 95% CI 1.08 to 1.12), opioid (HR 1.09, 95% CI 1.05 to 1.13) and non-opioid use disorders (HR 1.22, 95% CI 1.19 to 1.26) were all significantly associated with higher rates of discontinuation. In contrast to other mental health and substance use predictors, tobacco use disorders were associated with significantly lower rates of opioid discontinuation (HR 0.96, 95% CI 0.94 to 0.98).

Model 2 consolidated the mental health and substance use disorder categories, finding that those with successively higher numbers of mental health or substance use disorder types were more likely to discontinue (Table 3). The demographic and clinical covariate point estimates in model 2 were unchanged with regards to significance or magnitude in these models.

The number of encounters for mental health, substance abuse, and non-mental health/substance abuse were weakly associated with rates of discontinuation. Each substance abuse or mental health encounter decreased the rates of discontinuation by about 1%, whereas each additional non-mental health/substance abuse encounter increased discontinuation rates by 1% (Table2).

Discussion

In a national sample of veterans receiving a 90-day continuous supply of opioids, nearly 80% did not achieve opioid discontinuation when followed for up to 3.5 years. The factors that were most significantly associated with discontinuation included both younger and older age, lower average dosage and receiving less than 90 days of opioids in the previous year. Unlike previous studies, co-morbid mental illness and substance use disorders increased the chance of discontinuation in a dose-response fashion, except for tobacco use disorders, which were significantly associated with continuation of therapy.

The rates of discontinuation identified in this study are similar to prior analyses of civilian populations. A previous sample demonstrated prescription coverage for an average of 234 days out of the year for veterans receiving greater than 90 consecutive days of opioids [11]. The TROUP study followed a sample of more than 30,000 Medicaid and privately insured enrollees on chronic opioid therapy, finding nearly two-thirds remained on therapy when followed for up to 4.5 years [22], and a more recent analysis of LTOT within a civilian population reported over 80% still receiving high-dose therapy after one year of follow-up in spite of measured concerns or perceived helpfulness [32]. Requiring a 180 day period of no opioid prescriptions to qualify as discontinuation of opioids is stringent, but protects against counting commonly occurring intermittent use as discontinuations [17]. Using a 90-day discontinuation definition did not change our hazard ratios significantly.

The finding that lower doses of opioid therapy are associated with greater likelihood of discontinuation is consistent with previous research. For this sample, those within the highest opioid doses were 34% less likely to discontinue. This almost exactly matches what was found in the TROUP sample [22], further validating the association between relatively high-dose use and failure to discontinue. The risk of accidental death, overdose or emergency department visit has also been associated with average daily opioid dose, meaning that those patients receiving the highest doses are more likely to receive long-term therapy, subjecting them to these risks over longer periods [31].

While prior research has identified a far greater likelihood of LTOT initiation among those with co-morbid substance abuse and mental health diagnoses, our analysis identified a consistent modest association between nearly all mental health and substance abuse

diagnoses and greater likelihood of discontinuation [27]. Additionally, the association appears to exist in a dose-response pattern, with greater levels of co-morbidity associated with greater likelihood of discontinuation even after controlling for chronic pain conditions, patient reported average pain-intensity scores, medical comorbidity, demographics and service utilization. The finding that both younger and older age groups were more likely to discontinue may also point to more appropriate prescribing practices, because these two groups carry higher risks for diversion, substance use or serious medical side effects respectively. It is of note that many factors commonly found to predict LTOT initiation in samples of Veterans are also associated with discontinuation of LTOT in the present study. This may be the first evidence that large-scale efforts within the VA population, the largest healthcare system in the country, to appropriately limit long-term opioid therapy in those at greatest risk may be having a measurable effect.

Prior studies of long-term opioid therapy have found increased rates of opioid use and misuse with tobacco use and initiation with therapy and continuation with therapy in veterans [7,10]. The reinforcing effects of nicotine have been found to be due, in part, to effects in the endogenous opioid system and anti-nociception [1,5,25]. Though other classes of substance use may also be modulated through the opioid system [9], smoking may carry less stigma and may be under-recognized for its role in addiction co-morbidity. For persons on LTOT, nicotine may activate the endogenous opioid system and pain relief, thus compounding opioid or nicotine withdrawal effects and reinforcing the association we observed between tobacco use and LTOT.

Interestingly, the number of total encounters and mental health and substance use specific encounters in the 3 months post-index, though significant, had very minimal effect on discontinuation from LTOT after adjustment. Given the chronicity of LTOT in our sample, service utilization in the first 90 days may not completely reflect a veteran's service utilization pattern over the entire course of LTOT, and future investigations could examine service utilization in the time leading up to discontinuation, which may be more predictive.

Several limitations should be considered when reviewing our results. Our study was retrospective and made use of administrative data for diagnoses, service utilization and pharmacy records. Opioids received outside of the VA system were not accounted for, though use of anchoring visits prior to the index date and after the date of discontinuation helped to ensure that subjects received care within the VA throughout their LTOT episode. We were unable to control for the receipt of concurrent psychoactive therapies, such as sedative-hypnotics, which may confound the association between LTOT discontinuation, mental illness and substance abuse, though our models adjusted for co-morbid substance use and mental health diagnoses which may serve as a proxy at times for sedative-hypnotic use. Comparisons made between our national sample of primarily white, middle-aged male veterans may not be applicable in different sub-regions or populations. Our ability to exactly describe daily opioid use patterns was limited by the nature of the pharmacy data. We did require that, for a given prescription time period to be valid, the quantity must cover at least half of the days specified, resulting in a fair likelihood of near daily use in our cohort. Finally, our criteria for 90-day supply of opioids with less than 30-day gap to qualify for LTOT and the requirement of 180-days' gap in opioid prescriptions to qualify as

discontinuation is somewhat arbitrary, but hazard ratios were not significantly altered in sensitivity analyses that used alternate definitions.

Though our analysis highlighted the nature of LTOT within the VA and identified some key demographic, clinical and pharmacological variables associated with discontinuation, additional research is needed to further classify the causes and consequences of opioid discontinuation. As an example, are the factors we associated with discontinuation indicative of a mutually informed provider-patient decision to stop therapy or a consequence of forced discontinuation resulting from suspected diversion, misuse or harm? The results of opioid discontinuation on pain levels, functional status, and health care utilization are also of interest. Further study on the effects of mental health or substance abuse treatment, or systematic differences in the VHA system of healthcare (including a shared electronic medical record), may further enhance knowledge regarding associations with long-term opioid use and successful discontinuation, offering guidance on the development of programs that could enhance successful LTOT discontinuation.

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Glossary

MED	Morphine Equivalent Dose per day in mg
STD	Standard Deviation
Dx	Diagnosis
PTSD	Post-Traumatic Stress Disorder
SUD	Substance Use Disorder
MH	Mental Health
CNCP	Chronic Non-Cancer Pain categories
TBI	Traumatic Brain Injury

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Summary

Veterans on continuous opioids with lower doses were more likely to stop. Mental illness and substance use increased the likelihood of discontinuation.

Table 1

Demographic, Comorbidity, Drug and Treatment Variables Amongst Chronic VA Opioid Users Stratified by Discontinuation at 1 Year, 2009-2011

Variable	Categories	Total (%)	Discontinued (%)	Continued (%)
Total	All	550,616 (100.0%)	41,197 (7.48%)	509,419 (92.52%)
Age Category	18-30	16,852 (3.06%)	1,976 (11.73%)	14,876 (88.27%)
	30-50	104,747 (19.02%)	7,974 (7.61%)	96,773 (92.39%)
	50-65 (Reference)	294,272 (53.44%)	19,793 (6.73%)	274,479 (93.27%)
	>=65	134,745 (24.47%)	11,454 (8.50%)	123,291 (91.50%)
	Mean (STD)	57.76 (12.92)	57.90 (14.44)	57.75 (12.79)
Age*				
Gender	Male	514,373 (93.42%)	38,230 (7.43%)	476,143 (92.57%)
Race	White	406,284 (73.79%)	30,300 (7.46%)	375,984 (92.54%)
	Black	84,686 (15.38%)	6,876 (8.12%)	77,810 (91.88%)
	Other	10,509 (1.91%)	757 (7.20%)	9,752 (92.80%)
	Multiracial	3,934 (0.71%)	313 (7.96%)	3,621 (92.04%)
	Unknown/Declined	45,203 (8.21%)	2,951 (6.53%)	42,252 (93.47%)
Marital Status	Married	286,663 (52.06%)	20,389 (7.11%)	266,274 (92.89%)
Index Year	2009	350,050 (63.57%)	22,812 (6.52%)	327,238 (93.48%)
	2010	106,073 (19.26%)	10,465 (9.87%)	95,608 (90.13%)
	2011	94,493 (17.16%)	7,920 (8.38%)	86,573 (91.62%)
Residential Setting	Urban	374,682 (69.01%)	28,843 (7.70%)	345,839 (92.30%)
	Isolated Small Rural (Reference)	39,166 (7.21%)	2,599 (6.64%)	36,567 (93.36%)
	Large Rural	82,211 (15.14%)	5,751 (7.00%)	76,460 (93.00%)
	Small Rural	46,853 (8.63%)	3,175 (6.78%)	43,678 (93.22%)
	Any Mental Health Diagnoses	342,954 (62.29%)	26,183 (7.63%)	316,771 (92.37%)
Mental Health Dx	PTSD	100,820 (18.31%)	8,122 (8.06%)	92,698 (91.94%)
	Anxiety	89,176 (16.20%)	7,252 (8.13%)	81,924 (91.87%)
	Depression	163,267 (29.65%)	12,942 (7.93%)	150,325 (92.07%)
	Bipolar	23,269 (4.23%)	2,207 (9.48%)	21,062 (90.52%)
	Schizophrenia	11,670 (2.12%)	1,105 (9.47%)	10,565 (90.53%)
	0	207,662 (37.71%)	15,014 (7.23%)	192,648 (92.77%)
	1	157,246 (28.56%)	11,057 (7.03%)	146,189 (92.97%)
	2	101,058 (18.35%)	7,742 (7.66%)	93,316 (92.34%)
	3	58,002 (10.53%)	4,820 (8.31%)	53,182 (91.69%)
	4	20,771 (3.77%)	1,896 (9.13%)	18,875 (90.87%)
	5	5,877 (1.07%)	668 (11.37%)	5,209 (88.63%)
	TBI	10,160 (1.85%)	1,026 (10.10%)	9,134 (89.90%)
Any Substance Use Diagnoses (not including Tobacco)		79,743 (14.4%)	7,425 (9.3%)	72,318 (90.7%)
Substance Use Disorder	Alcohol	57,487 (10.44%)	5,463 (9.50%)	52,024 (90.50%)
	Non-Opioid	39,755 (7.22%)	4,068 (10.23%)	35,687 (89.77%)
	Opioid	15,490 (2.81%)	1,590 (10.26%)	13,900 (89.74%)
	Tobacco*	140,825 (25.58%)	10,293 (7.31%)	130,532 (92.69%)

Variable	Categories	Total (%)	Discontinued (%)	Continued (%)
Opioid Characteristics	0	470,865 (85.52%)	33,769 (7.17%)	437,096 (92.83%)
	1	53,633 (9.74%)	4,571 (8.52%)	49,062 (91.48%)
	2	19,255 (3.50%)	2,021 (10.50%)	17,234 (89.50%)
	3	6,863 (1.25%)	836 (12.18%)	6,027 (87.82%)
	Mean Daily Dose (mg MED); (STD)	40.70 (61.66)	30.29 (39.75)	41.54 (63.03)
	0 - Median	275,307 (50.00%)	24,845 (9.02%)	250,462 (90.98%)
	Median to 100	236,718 (42.99%)	14,880 (6.29%)	221,838 (93.71%)
	Greater than 100 mg	38,591 (7.01%)	1,472 (3.81%)	37,119 (96.19%)
	Long-Acting Formulations	16,094 (2.92%)	774 (4.81%)	15,320 (95.19%)
	Short-Acting Formulation	534,522 (97.08%)	40,423 (7.56%)	494,099 (92.44%)
	Greater than 90 day Pre-Index Opioid Use	313,813 (56.99%)	16,516 (5.26%)	297,297 (94.74%)
	Average Number of Days Covered in 90 days between day 270 and 360 Post-Index (STD)	58.89 (32.29)	12.18 (21.39)	62.66 (29.99)
	Average MED in Days 270-360 Post-Index (STD)	44.35 (66.91)	30.00 (37.70)	44.80 (67.57)
Any CNCP [*]		453,198 (82.31%)	33,715 (7.44%)	419,483 (92.56%)
Chronic Pain Category Count	0	97,418 (17.69%)	7,482 (7.68%)	89,936 (92.32%)
	1	241,041 (43.78%)	18,436 (7.65%)	222,605 (92.35%)
	2	146,930 (26.68%)	10,594 (7.21%)	136,336 (92.79%)
	>=3	65,227 (11.85%)	4,685 (7.18%)	60,542 (92.82%)
	Charlson Co-Morbidity Index Mean (STD)	0.72 (0.89)	0.76 (0.93)	0.72 (0.89)
Service Intensity	Mean Pain Intensity Score in 90-days Post-Index (STD)	4.03 (2.46)	3.89 (2.44)	4.04 (2.47)
	Mean 90-Day Encounter Count (STD)	8.92 (11.01)	11.03 (13.01)	8.75 (10.82)
	Combined Mental Health/SUD Encounter Count (STD)	1.37 (5.35)	1.92 (6.61)	1.32 (5.23)
	Mean 90-Day MH Encounter Count Post Index (STD)	1.09 (3.89)	1.46 (4.53)	1.06 (3.83)
	Mean 90 Day SUD Encounter Count Post-Index (STD)	0.28 (3.03)	0.46 (3.99)	0.26 (2.94)

MED: Morphine Equivalent Dose per day in mg, STD: Standard Deviation, Dx: Diagnosis, PTSD: Post-Traumatic Stress Disorder, SUD: Substance Use Disorder, MH: Mental Health, CNCP: Chronic Non-Cancer Pain categories, TBI: Traumatic Brain Injury

* All associations significant at the $p < 0.0001$ level except for Age, $p = 0.0208$, Tobacco, $p = 0.0043$ and any CNCP: 0.0095

Table 2

Adjusted Hazard Ratios and 95% Confidence Intervals Associated with Discontinuation for Each Predictor (Model 1)^f

Covariate		Hazard Ratio	95% Confidence Interval	
Age 18-30		1.53	1.48	1.58
Age 30-50		1.09	1.07	1.11
Age 50-65 (ref)		1.00	--	--
Age >65		1.34	1.32	1.36
Female		1.05	1.02	1.07
Married		0.94	0.93	0.95
Race	Caucasian (ref)	1.00	--	--
	African American	1.04	1.02	1.06
	Other	0.98	0.94	1.03
	Multiracial	1.05	0.97	1.12
	Unknown/Declined	0.91	0.88	0.93
Location	Urban	1.07	1.05	1.10
	Large Rural	1.02	0.99	1.05
	Small Rural	0.99	0.96	1.02
	Isolated Small Rural (ref)	1.00	--	--
Index Year	2009 (ref)	1.00	--	--
	2010	0.92	0.90	0.93
	2011	0.67	0.65	0.68
Bipolar		1.19	1.16	1.23
Anxiety Disorder		1.07	1.05	1.09
Depressive Disorders		1.08	1.06	1.09
PTSD		1.09	1.07	1.10
Schizophrenia		1.20	1.16	1.25
Alcohol SUD		1.10	1.08	1.12
Non-Opioid SUD		1.22	1.19	1.26
Opioid SUD		1.09	1.05	1.13
Tobacco SUD		0.96	0.94	0.97
TBI		1.12	1.08	1.17
Pre-Index Opioid > 90 d		0.69	0.68	0.70
Opioid Dosage Range	0 – Median (~24 mg MED, ref)	1.00	--	--
	Median to 100 mg	0.82	0.81	0.83
	Greater than 100 mg	0.63	0.61	0.65
Short-Acting Opioid		1.00	0.96	1.04
Chronic Pain Category Count (ref = 0)	0	1.00	--	--
	1	1.00	0.98	1.02

Covariate	Hazard Ratio	95% Confidence Interval	
2	0.97	0.95	0.99
3	0.97	0.95	0.99
Charlson Comorbidity Score	1.07	1.06	1.07
90-Day Non MH/SUD Encounter Count	1.01	1.01	1.01
90-Day SUD Encounter Count	0.99	0.99	0.99
90-Day MH Encounter Count	0.99	0.99	0.99
90-Day Average Pain Score Post-Index	1.00	0.99	1.00

Abbreviations - Ref: Reference category, PTSD: Post-Traumatic Stress Disorder, SUD: Substance Use Disorder, MH: Mental Health, CNCP: Chronic Non-Cancer Pain categories, TBI: Traumatic Brain Injury, MED: Morphine-Equivalent Dose

¹ All associations are significant at the $P < 0.0001$ level except for chronic pain count ($p = 0.0003$, significant), short-acting opioid therapy ($P = 0.8412$, NS) and 90-Day average pain score ($P = 0.0027$, significant).

Table 3

Adjusted Hazard Ratios and 95% Confidence Intervals Associated with Discontinuation for the Number of Mental Health or Substance Use Disorder Categories (Model 2)¹

Mental Health/Substance Use Count		Hazard Ratio	95% Hazard Ratio	Confidence Intervals
Mental Health Category Counts (Reference 0)	1	1.07	1.05	1.09
	2	1.18	1.16	1.21
	3	1.25	1.22	1.28
	4	1.30	1.26	1.35
	5	1.42	1.35	1.50
Substance Use Disorder Category Counts (Reference 0)	1	1.13	1.11	1.16
	2	1.31	1.27	1.35
	3	1.40	1.34	1.47

¹ All associations are significant at the P<0.0001 level.