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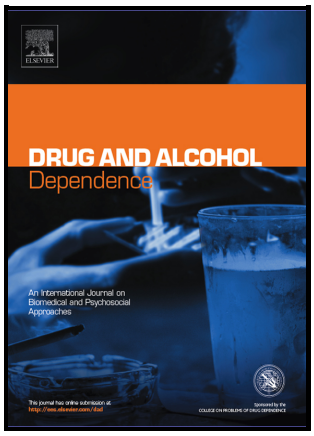


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# Impact of Transitioning from Long-Term to Intermittent Opioid Therapy on the Development of Opioid-Related Adverse Outcomes: A Retrospective Cohort Study

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**Abstract**

*Background:* Increasing pressures exist to reduce or discontinue opioid use among patients currently on long-term opioid therapy (LTOT). It is essential to understand the potential effects of opioid reduction.

*Methods:* This retrospective cohort study was conducted among veterans with chronic pain and on LTOT. Using 1:1 propensity score-matched samples of veterans switching to intermittent opioid therapy and those continuing LTOT, we examined the development of subsequent substance use disorders (SUD composite; individual SUD types: opioid, non-opioid drug, and alcohol use disorders) and opioid-related adverse outcomes (ORAO composite; individual ORAO types: accidents resulting in wounds/injuries, opioid-related and alcohol/non-opioid medication-related accidents and overdoses, self-inflicted and violence-related injuries). Sensitivity analyses were conducted using logistic regression with stabilized inverse probability of treatment weighting (SIPTW) and instrumental variable (IV) models.

*Results:* A total of 29,293 veterans switching to intermittent therapy were matched to veterans continuing LTOT. With matched samples, no differences were found in composite SUDs and ORAOs between the groups. With SIPTW, veterans switching to intermittent opioid therapy had higher odds of composite SUDs and ORAOs (SUDs aOR=1.12, 95%CI: 1.07,1.17; ORAOs aOR=1.05, 95%CI:1.00,1.09). IV models found lower risks for composite SUDs and ORAOs among veterans switching to intermittent

opioid therapy (SUDs: β=-0.38, 95%CI:-0.63,-0.13; ORAOs: β=-0.27, 95%CI:-0.50,-0.04).

*Conclusions:* There were no consistent associations between transitioning patients from LTOT to intermittent opioid therapy and the risk of SUDs and ORAOs.

*Keywords:* opioids, long-term opioid therapy, chronic non-cancer pain, intermittent opioid therapy, opioid-related adverse outcomes, substance use disorders

## 1. Introduction

Many initiatives are underway in the U.S. and specifically Veterans Health Administration (VHA) to decrease opioid prescribing rates. The Centers for Disease Control and Prevention has published opioid prescribing guidelines for primary care settings that encourage use of non-opioid therapies for managing chronic pain (Dowell et al., 2016). In 2017, the U.S. Department of Health and Human Services declared the opioid crisis a public health emergency and announced a 5-point strategic plan to combat the opioid epidemic, which includes decreasing reliance on opioid therapy for pain management (HHS, 2017). In 2013, VHA launched the Opioid Safety Initiative (OSI) due to its rise in opioid prescribing rates (Veterans Health Administration, 2017a).

The OSI developed and disseminated many educational materials on the evidence for opioid therapy as well as guidance for opioid tapering. It also developed an opioid dashboard, based on VHA electronic health record data, to identify patients on long-term opioid therapy (LTOT) and encourage prescribers to re-evaluate the need for LTOT among individual patients (Veterans Health Administration, 2017a). As patients are tapered on their opioid regimens and as opioid prescribing declines, more information is needed on the potential unintended adverse outcomes that may result.

Most of the literature on duration of opioid use shows that longer duration of opioid use increases the risk of opioid-related adverse outcomes (ORAOs) and substance use disorders (SUDs). A retrospective cohort study of commercially-insured patients who received at least one opioid prescription found that increasing duration and regularity of opioid therapy was associated with increased risks for drug abuse and opioid overdose (L. Paulozzi et al., 2014). Another cohort study of patients with polyneuropathy found that patients on LTOT (≥ 90 days) were

more likely to be diagnosed with opioid dependence or opioid overdose (Hoffman et al., 2017). A retrospective cohort study among patients with chronic pain found that duration of opioid therapy was a more important risk factor for opioid use disorder than daily opioid dose (Edlund et al., 2013). Alternately, some studies suggest that variability or changes in prescribed opioids may be associated with greater risk of harms (Glanz et al., 2019; Oliva et al., 2020). Limited evidence exists on the risk of ORAOs and SUDs among patients who transition from regular use of prescribed opioids to intermittent use, which may be more common with current opioid prescribing trends.

The purpose of this study is to compare the risks of ORAOs and SUDs between patients transitioning to intermittent opioid therapy (at least one opioid prescription within 180 days, but not meeting LTOT criteria) compared to those who continued LTOT (defined as >90 days' supply of opioids within 180 days with no gaps >30 days). We hypothesized that SUDs [opioid use disorder (OUD), non-opioid drug use disorder (DUD), alcohol use disorder (AUD)] and ORAOs [accidents resulting in wounds or injuries, self-inflicted injuries, opioid-related accidents and overdoses, alcohol and non-opioid drug-related accidents and overdoses, and violence-related injuries] would be significantly lower among those switching to intermittent opioid therapy compared to those continuing LTOT.

## 2. Material and Methods

### *2.1. Data source*

We extracted data for fiscal years 2008-2015 from the Veterans Health Administration's (VHA) Corporate Data Warehouse (CDW). The extract included records of inpatient and outpatient medical visits, demographic information, and outpatient pharmacy files. The Central Arkansas Veterans Healthcare System's institutional review board approved the study. A

protocol outlining these study aims and methods was pre-specified in our grant (R36DA046717) and institutional review board applications; however, the protocol was not made available in a publicly accessible portal prior to study execution.

*2.2. Study design and subjects*

Veterans diagnosed with at least one chronic non-cancer pain (CNCP; i.e., arthritis, back pain, neck pain, neuropathic pain, or headache/migraine) condition from 10/1/2008 to 9/30/2015 on LTOT were identified (Edlund et al., 2014). Outpatient prescriptions for opioid analgesics were identified using the VA Drug Class Code CN101. LTOT was defined as receiving at least a 90 days' supply of non-parenteral opioids within any 180-day period with no more than a 30-day gap in supply (Vanderlip et al., 2014).

*2.3. Main independent variable*

After the initial 180-day period in which veterans were first determined to be on LTOT, veterans were followed for an additional 180-day period to determine whether they continued LTOT or switched to intermittent opioid therapy. Those continuing LTOT were required to meet the original LTOT definition in the second 180-day period. Intermittent opioid therapy was defined as any opioid use (at least one outpatient, opioid prescription fill) that did not meet the LTOT definition in the second 180-day period. The index date was defined as the first day of the second 180-day block. See Appendix A for a visual representation of the cohort. Veterans could have been on opioid therapy prior to their initial 180-day period of LTOT, which could have been any level of opioid therapy that did not qualify as LTOT (e.g., one prescription, intermittent opioid therapy).

*2.4 Exclusion criteria*

This study focused on adults with reliable opioid prescription data who regularly sought care at the VA without a history of cancer, terminal illnesses, prior SUD, or prior ORAO. Eleven exclusion criteria were applied based on the CDW records within the 12-month period prior to and inclusive of the index date (unless noted otherwise): (1) ≤18 years of age at the index date, (2) index date before 10/1/2009 or after 10/1/2014, (3) diagnosis for an SUD, ORAO, or cancer (except for non-melanoma skin cancer), (4) filled potentially erroneous opioid prescription records [unable to calculate morphine milligram equivalents (MME), average daily dose above 1000 MMEs, or prescription quantity greater than 1000 units] in the 180 days before the index date, (5) receipt of hospice/palliative care or opioid replacement therapy, (6) lacking at least 2 visits at least 30 days apart to any VA facility, (7) more visits with providers outside the VA than with VA providers, (8) fewer than 2 pain scores in the 180 days prior to the index date with 1 of the pain scores being either on or within 90 days prior to the index date, (9) less than 1 pain score in each 90 day period of the 6-month follow-up period (at least 2 pain scores in the follow-up period), (10) death in the 180-day period after the index date, (11) discontinuation of opioid therapy in the second 180-day block.

*2.5. Study outcomes*

*2.5.1. Opioid-related adverse outcomes*

Study outcomes were evaluated over the 12-month period after the index date. ORAOs were based on definitions by Seal et al. (Seal et al., 2012) using International Classification of Diseases, 9$^{th}$ Revision, Clinical Modifications (ICD-9-CM codes) for accidents resulting in wounds/injuries, opioid-related accidents and overdoses, alcohol and non-opioid, drug-related accidents and overdoses, self-inflicted injuries, and violence-related injuries. ORAOs were

assessed as a composite measure (i.e., having received at least one of the five ORAOs evaluated), as in a veteran receiving a diagnosis for any of our ORAOs, and then individually for each of the five ORAOs.

*2.5.2. Substance use disorders*

SUDs were assessed similarly to ORAOs, first as a composite measure, then individually for each of the three types of SUDs. The types of SUDs included opioid use disorders (OUD), non-opioid non-alcohol drug use disorder (DUD), and alcohol use disorders (AUD). Definitions for each of the types of SUDs were derived from ICD-9-CM definitions from the VA Northeast Program Evaluation Center (Greenberg et al., 2012). DUDs included use disorders for stimulants, marijuana, benzodiazepines, and other non-opioid psychoactive substances. Outcome classification was not mutually exclusive, i.e., veterans could be classified as having more than one category of SUDs or ORAOs or both an SUD and ORAO.

*2.6. Covariates*

Baseline covariates were characterized using CDW records from the 12 months before the index date. Demographic covariates included age, race, marital status, sex, and geographic region (WWAMI Rural Health Research Center, 2005). Medical covariates included the enhanced Charlson comorbidity score (Charlson et al., 2008), diagnoses of mental health conditions (schizophrenia, major depressive disorder, post-traumatic stress disorder, anxiety disorders, bipolar disorder, multiple mental health conditions), and diagnoses for CNCP conditions (listed above). Prescriptions for medications that aid in treating pain or increase the risk of ORAOs when combined with opioids were identified using VA Drug Class Codes. These included benzodiazepines, hypnotics/other non-benzodiazepine sedatives, skeletal muscle relaxants, antidepressants, and other non-opioid analgesics (e.g., nonsteroidal anti-inflammatory

agents). These medication classes were characterized as any use in the 12 months before the index date. Opioid medication characteristics for the first 180 days of LTOT were also evaluated including schedule of opioids used (CII-CV), duration of action (long-acting, short-acting), average MME dose, and mean days covered. Using VA stop codes, health care visits (physical therapy, pain clinic, chiropractic care, medicine/primary care, and mental health visits) were characterized in two ways: (1) any visit in the 12-month period prior to the index date, and (2) the number of days with each healthcare visit type. Using the vital sign files, pain scores were characterized as the average, first, and last pain score using the first 180-day period of LTOT. We calculated change in pain score by subtracting the last pain score reading from the first pain score using the first 180-day period of LTOT.

*2.7. Statistical analysis*

Using a 1:1 greedy matching algorithm without replacement, veterans continuing LTOT were matched to veterans switching to intermittent opioid therapy on both the propensity score and index date (within ± 180 days of each other) (Austin, 2008; Parsons, 2008). The balance of covariates between comparison groups before and after matching were assessed using standardized differences. We considered the covariates to be well-balanced when standardized differences were less than 10% between the two groups (Austin, 2011). Logistic regression models were estimated among the propensity score-matched samples. Only the dummy variable for opioid transitional status (continuing LTOT vs. switching to intermittent opioid therapy) and the counts of each type of healthcare visit in the 12 months prior to the index date were included. Healthcare visit counts were included as veterans were balanced on whether they had a visit for each type of healthcare service (e.g., physical therapy, primary care), but were not balanced on the number of healthcare visits by each type. Logistic regression models were estimated for the

two composite outcomes (SUDs, ORAOs) in addition to the individual types. Analyses were conducted using SAS Enterprise Guide 7.1. Significance was determined using a two-sided significance level of 0.05.

*2.8. Sensitivity analysis*

Robustness of the primary analyses was examined in two ways. First, we used a variant of the original propensity score approach called stabilized inverse probability of treatment weighting (SIPTW). Instead of matching on the propensity score, the SIPTW was calculated and the weights were integrated into the logistic regression model. The SIPTW was calculated using publicly available SAS code (Layton, 2013). Veterans in non-overlapping regions of the propensity score distribution were excluded from the analytical sample. Second, instrumental variable (IV) models were estimated to account for potential unobserved confounding (Baiocchi et al., 2014; Lousdal, 2018; Sargan, 1958). A valid IV is a variable that does not directly influence the outcome (e.g. ORAOs or SUDs) and only influences the exposure; in this case, being more likely to switch to intermittent opioid therapy (Baiocchi et al., 2014). We hypothesize that the proposed IV (geographic variation in rates of switching to intermittent opioid therapy) indirectly influences rates of ORAOs and SUDs only through influence on the exposure, i.e., whether or not a patient switches to intermittent opioid therapy.

IVs based on geographic variation of treatment have been shown to be valid and are common in the literature (Fang et al., 2010; Frölich and Lechner, 2004; Ishaq, 1980; Lousdal, 2018). Geographic variation in opioid prescribing practices, dosing, and opioid formulation is prevalent. For example, patients on high-dose opioid therapy in 2012 ranged from 1.9 per 100 persons to 8.8 per 100 persons, suggesting that geographic variation may provide strong influence on the likelihood of switching to intermittent opioid therapy, which is essential to an IV analysis

(Centers for Disease Control and Prevention (CDC), 2016; Curtis et al., 2006; Delgado et al., 2018; McDonald et al., 2012; Paulozzi et al., 2014; Webster et al., 2009). Unfortunately, analysts cannot prove if an IV is unrelated to the outcome except through the influence of the treatment, in this case switching to intermittent opioid therapy. It is recognized that there is also geographic variation in ORAOs and SUDs (Wagner et al., 2007). If geographic variation in ORAO/SUD rates causes prescribers to switch patients to intermittent opioid therapy, then the IV analysis may not be valid. Alternately, if the patient characteristics are unrelated to the likelihood of being switched to intermittent opioid therapy, and the likelihood of being switched to intermittent opioid therapy is not a function of the prevailing ORAO/SUD rates in geographic region, the IV analyses may be able to account for residual confounding that may exist with traditional analyses such as propensity scores. To that end, geographic variation in switching to intermittent opioid therapy was considered a potentially viable IV. Determining whether the IV is viable is a three-step process as described in the next paragraph.

The geographic units used for the IV in this analysis were the proportion of patients switching to intermittent opioid therapy across the 130 VA parent stations throughout the U.S. The parent VA station most commonly used for obtaining opioid prescriptions was considered the parent VA station associated with an individual veteran. For each parent VA station, the proportion of patients switching to intermittent opioid therapy was determined by dividing the number of veterans who switched to intermittent opioid therapy per parent VA station by the sum of those veterans associated with the parent VA stations who continued LTOT and switched to intermittent opioid therapy. Two IV approaches were conducted: (1) calculation of Wald estimators (Brookhart et al., 2010), which do not adjust for covariates and (2) estimation of two-stage least square (2SLS) regression models, which adjust for covariates while assessing the

variation induced by the instrument (Burgess et al., 2017). To evaluate the IVs' validity, three steps were undertaken. First, standardized differences for all covariates were compared between those seeking care in parent VA stations with high rates of patients switching to intermittent opioid therapy and those in parent VA stations with low rates of patients switching to intermittent opioid therapy based on the observed median rate of patients switching to intermittent opioid therapy. Like a randomized study, balance of the covariates between parent VA stations with high and low rates of patients switching to intermittent opioid therapy suggests, though does not prove, that the instrument is unrelated to the outcome except through differences in the treatment received. Second, post-estimation tests were performed (Durbin, Wu-Hausman, and F-tests) among the adjusted 2SLS regression models. Significant Durbin and Wu-Hausman tests indicate endogeneity or residual confounding may be present and therefore indicate that an IV is necessary to account for unobserved selection bias not controlled for by the other covariates (Durbin, 1954; Hausman, 1978; Wu, 1973). Third, the F-test assesses the relative strength of the correlation of the IV with the treatment variable (switching to intermittent opioid therapy). An F statistic > 10 is indicative of a strong IV (Stock and Yogo, 2005; Stock et al., 2002). As an alternative to the 2SLS models, the 2SLS models were re-estimated as a biprobit model since both the treatment (continuing LTOT vs. switching to intermittent opioid therapy) and outcome variables (SUDs and ORAOs) were binary (STATA, 2015). IV models were estimated using STATA 15.1.

## 3. **Results**

### *3.1. Sample derivation and characteristics*

A total of 99,111 veterans were retained in the sample after applying the inclusion and exclusion criteria, 58,927 continued LTOT, and 40,184 switched to intermittent opioid therapy

(Fig. 1). For both groups, approximately two-thirds were white, 90% male, 40-50% between the ages of 50 and 64, and approximately 70% from urban areas (Table 1). Arthritis and back or neck pain were the most common pain conditions. Approximately half of veterans in each group had one or more mental condition diagnoses. Over 70% in each of the groups used non-opioid analgesics.

Prior to matching, age, race, rural/urban status, opioid schedule (e.g., use of Schedule IV opioids only), and average pain scores in the baseline period were different between those who continued LTOT and those who switched to intermittent opioid therapy. Mean days of opioid supply (150.64 days for veterans continuing LTOT; 124.72 for veterans switching to intermittent opioid therapy), use of combinations of long- and short-acting opioids (10.38% of those continuing LTOT; 4.88% of those switching to intermittent opioid therapy), and average daily MME dose (32.21 average daily MME for veterans continuing LTOT; 21.98 average daily MME for veterans switching to intermittent opioid therapy) were higher for those continuing LTOT prior to matching in the 180 days before the index date. Use of short-acting opioids in the 180 days before the index date was lower among those continuing LTOT (87.71% of veterans continuing LTOT; 94.26% of veterans switching to intermittent opioid therapy).

In the 180 days after the index date, the mean days of opioid supply remained similar at 150.16 among veterans continuing LTOT but decreased to 47.45 for those switching to intermittent therapy. After matching, 29,293 veterans continuing LTOT matched to those switching to intermittent opioid therapy (49.7% of veterans continuing LTOT and 72.9% of veterans switching to intermittent opioid therapy). All baseline covariates were well balanced after propensity score matching (all standardized differences <10%; Table 1).

*3.2. Primary analyses*

For the matched samples, composite SUD rates were not different between veterans switching to intermittent opioid therapy compared to those continuing LTOT (Fig. 2, Table 2; aOR=1.02, 95%CI: 0.96, 1.08). Likewise, rates of individual SUDs did not differ between intermittent and continued LTOT groups (OUD aOR=0.88, 95% CI: 0.75, 1.03; DUD aOR=1.02, 95% CI: 0.94, 1.11; AUD aOR=1.06; 95% CI: 0.98, 1.15). Composite ORAO rates were not different between veterans switching to intermittent opioid therapy and those continuing LTOT (Fig. 2, Table 2; aOR=1.03, 95%CI: 0.97, 1.08). Rates of the individual ORAOs did not differ between the two groups.

*3.3 Sensitivity analyses*

*3.3.1. SIPTW logistic regressions*

A total of 99,083 veterans were retained in the SIPTW sample after excluding veterans in non-overlapping regions of the propensity score distribution: 58,905 veterans continuing LTOT and 40,178 veterans switching to intermittent opioid therapy. Since the SIPTW analyses retain most of the sample, the SIPTW point estimates were similar to the propensity score matching point estimates; however, the confidence intervals were narrower, reflecting greater precision. Veterans switching to intermittent opioid therapy had higher odds of the composite SUD outcome (Fig. 2, Table 2; aOR=1.12, 95% CI: 1.07, 1.17), OUDs (aOR=1.14, 95% CI: 1.03, 1.26), DUDs (aOR=1.16, 95% CI: 1.10, 1.23), and AUDs (aOR=1.11, 95% CI: 1.05, 1.18) compared to those continuing LTOT. Veterans switching to intermittent opioid therapy were also more likely to have the composite ORAO outcome (aOR=1.05, 95% CI: 1.00, 1.09). Alcohol and non-opioid related adverse outcomes were also higher among veterans switching to intermittent

opioid therapy (aOR=1.32, 95% CI: 1.19, 1.47). None of the other individual types of ORAOs was different between the two groups (Fig. 2 and Table 2).

*3.3.2. IV analyses*

Veterans switched to intermittent therapy 44.6% of the time in the VA stations above the median rate of 39.5%, and 35.3% switched to intermittent therapy in the VA stations below the median. The distribution of the covariates between veterans getting care at VA stations above the median versus those getting care at VA stations below the rate were well-balanced, with a few important exceptions (Appendix B). Veterans at VA stations with higher rates of switching to intermittent opioid therapy were more likely to be non-white, use non-opioid analgesics, be prescribed schedule IV opioids, have a lower average MME dose, and be prescribed fewer days of opioids as compared to those receiving care at VA stations with lower rates of switching to intermittent opioid therapy.

The Wald estimator for percentage of veterans switching to intermittent opioid therapy per VA station was insignificant for SUDs (SUDs: β=0.00, 95% CI: -0.04, 0.04) and negative and significant for ORAOs (ORAOs: β=-0.08, 95% CI: -0.12, -0.04), indicating that switching to intermittent opioid therapy had no effect on the risk for SUDs and decreased the risk for ORAOs. However, the 2SLS models showed an increased risk for the development of SUDs (β=0.14, 95% CI: 0.05, 0.23) and no difference in risk for ORAOs (β=-0.01, 95% CI: -0.11, 0.08). Of the individual types of SUDs, DUD (β=0.08, 95% CI: 0.01, 0.14) and AUD (β=0.08, 95% CI: 0.014, 0.15) were higher among veterans switching to intermittent opioid therapy, while OUD was not different between the two groups. None of the individual types of ORAOs was different between veterans switching to intermittent opioid therapy and those continuing LTOT. The biprobit models found a decreased risk for the development of SUDs and ORAOs for veterans switching

to intermittent opioid therapy as compared to veterans continuing LTOT (SUDs: β=-0.38, 95% CI: -0.63, -0.13; ORAOs: β=-0.27, 95% CI: -0.50, -0.04). Bivariate probit models for the individual types of SUDs and ORAOs also found lower risks for OUD (β=-0.72, 95%CI: -0.96, -0.48), DUD (β=-0.35, 95% CI: -0.61, -0.10), opioid-related accidents and overdoses (β=-0.76, 95%CI: -1.14, -0.38), and alcohol- and non-opioid medication-related accidents and overdoses (β=-0.44, 95% CI: -0.72, -0.15). The Durbin and Wu-Hausman tests were significant for composite SUDs, DUD, and AUD (composite SUDs: p=0.0016, DUD: p=0.0225, AUD p=0.0197), indicating endogeneity exists within the treatment variable (switching to intermittent opioid therapy), and therefore, the use of an IV model is suggested. However, the tests were not significant for OUD (OUD: p=0.2773). The Durban and Wu-Hausman tests were not significant for composite ORAOs and each of the individual types of ORAOs (composite ORAOs: p=0.7400, accidents/injuries: p=0.8047, opioid-related accidents and overdoses: p=0.2890, alcohol- and non-opioid medication-related accidents and overdoses: p=0.4230, self-inflicted injuries: p=0.4729, violence-related injuries: p=0.1334). The F-statistic for the strength of the IV was large (F-statistic for percentage of veterans switching to intermittent opioid therapy per VA station=200.41), indicating that intermittent opioid therapy rates by VA parent station was a strong IV.

**4. Discussion**

This study assessed the effect of switching to intermittent opioid therapy after initially being on LTOT in a veteran population with chronic pain. We found approximately 40% transitioned to intermittent opioid therapy in the subsequent 6-month period after initial LTOT. To determine the potential unintended effects of switching to intermittent opioid therapy, we evaluated a broad range of potential risks that might be influenced by changes in opioid therapy including multiple

types of SUDs: OUD, DUD, and AUD, as well as many types of ORAOs: accidents resulting in wounds or injuries, opioid-related accidents and overdoses, alcohol- and non-opioid drug-related accidents and overdoses, self-inflicted injuries, and violence-related injuries.

Among veterans newly prescribed LTOT, nearly 38% were switched from LTOT to intermittent opioid therapy, a change on average of 125 days of opioid therapy to 47 days over two consecutive 6-month periods. There do not appear to be any consistent signals suggesting that transitioning to intermittent therapy increases or decreases the risk of ORAOs such as injury or overdose. In the primary propensity-matched sample, veterans switching to intermittent opioid therapy were not different from veterans continuing LTOT in their likelihood to experience a composite ORAO or any of the individual ORAOs examined. The sensitivity analyses using the SIPTW among the entire sample found a slight increase in the risk of composite ORAOs (aOR=1.05) for those transitioning to intermittent therapy, driven largely by an increased risk of alcohol- and non-opioid medication-related accidents and overdoses (aOR=1.32) among veterans switching to intermittent opioid therapy as compared to veterans continuing LTOT. Conversely, the IV models found lower risks for any ORAO as well as opioid-related and alcohol- and non-opioid medication-related accidents and overdoses among veterans switching to intermittent opioid therapy. Interpreting these findings collectively, it does not appear that transitioning LTOT veterans to intermittent opioids poses a meaningful increase in the risk of opioid adverse events such as injury or drug overdoses, but there are hints based on the IV models that account for unobserved confounding—that this less intense opioid strategy could reduce these ORAO risks. However, the Durbin and Wu-Hausman tests were insignificant for composite ORAOs and each individual type, calling into question the need for an IV approach.

Like the influence of transitions to intermittent therapy on ORAOs, there were no clear signals for SUDs, either. Development of any type of SUD in the 12-month follow-up period was not different for veterans switching to intermittent opioid therapy as compared to veterans continuing LTOT (7.6% vs 7.5%) in our primary analysis, nor were there any significant differences for OUD, DUD, or AUD. Sensitivity analyses using the overall sample with the SIPTW found that transitions to intermittent therapy slightly increased the risk of any SUD (aOR=1.12), OUD (aOR=1.14), DUD (aOR=1.16), and AUD (aOR=1.12), mostly due to tighter confidence intervals. The IV models, however, found that switching to intermittent opioid therapy was associated with a decrease in the development of composite SUDs, OUD, and DUD. Given the conflicting findings of the sensitivity analyses and the null findings of the primary analysis, it is difficult to discern if transitions to intermittent therapy spare or increase the risk of developing SUDs.

Limited evidence exists on the effect of switching to intermittent opioid therapy, or opioid tapering, on the development of ORAOs and SUDs. A Medicaid-based study assessed the impact of the length of opioid tapering and found that longer tapers (time to discontinuation ≥90 days) were associated with fewer emergency department and inpatient admissions due to SUDs or ORAOs (Mark and Parish, 2019). Using administrative claims data from a commercially insured US population, another study evaluated opioid dose trajectories prior to the development of OUD and overdose. They found that, of opioid users, patients tapering their doses (20 to <3 MME) accounted for the lowest percentage of patients developing an OUD/overdose (9.4% of those tapering their dose vs. 34.6% of those on consistent low dose) (Wei et al., 2019). Our study assessed opioid therapy only in the immediate 6-month period after changing to intermittent opioid therapy and not any of the ensuing months; therefore, this study cannot distinguish

transitions to intermittent therapy that reflect opioid tapering ultimately resulting in opioid discontinuation or reflect transitions to acute episodic use. It is likely that this intermittent therapy group consists of a mixture of these strategies, making comparisons of our study with others more challenging. However, it is likely that the relatively slow transitions from LTOT (decrease from 125 to 47 opioid days over a 6-month period) does not increase the rate of SUDs and ORAOs, as most of our findings have shown.

*4.1 Limitations*

Several limitations exist with this study. First, findings from these analyses in veterans may not be generalizable to the civilian population due to their military background and because veterans are mostly white males. Second, history bias may potentially be problematic for this study. History bias becomes a factor when the effects of relevant external events during study progression are not equal between the groups (Naci and Soumerai, 2016). In regard to opioid therapy, many policies within and outside the VA may influence transitional status over time (Centers for Disease Control and Prevention (CDC), 2016b; Dowell et al., 2016; National Harm Reduction Coalition, 2015; Veterans Health Administration, 2015, 2017b). However, since veterans were matched based on the index date in the primary analysis, the effects of any external opioid policies should be balanced across the groups compared in our primary analyses, but the timing of these external effects were not accounted for in our sensitivity analyses. Third, using VA data from CDW does not allow for obtaining information on opioid fills outside of the VA. It is possible and likely that these veterans may seek opioid medications outside of the VA system, particularly after being forced to discontinue LTOT. A recent study has found that 32% of veterans on LTOT received concurrent non-VA opioid prescriptions (Veterans Health Administration, 2017a). To mitigate receipt of opioids outside the VA, our study required

veterans to have more visits to the VA system than fee-for-service visits as well as continuing to visit the VA system at least twice in the 6 months after the index date. Fourth, this study was observational and residual confounding due to selection bias could distort the relationships reported despite the extensive covariate adjustment employed. Fifth, reasons switching to intermittent opioid therapy are not known. For some patients, transitions may be due to improvements in pain, or use of other therapies that may not be gathered from the electronic medical record/measured in this study. Transitions also may have been prompted by detection of opioid misuse or an SUD. Indeed, a recent study of veterans evaluating the reasons for discontinuation of LTOT found that 85% of discontinuations were because of clinician, not patient, decisions. Of those discontinued because of a clinician decision, 75% were discontinued following opioid-related aberrant behaviors (Lovejoy et al., 2017). This creates potential temporal ambiguity where it is unclear if the development of an SUD or AO was the result or the cause of an opioid reduction. We attempted to account for this by excluding persons that experienced an ORAO or SUD in the baseline period; however, since the 6-month window in which intermittent opioid therapy or continued LTOT were assessed overlapped with the first six months of the outcome window, reverse causality cannot be ruled out and our findings should be interpreted as associations.



**5. Conclusions**

There were no consistent associations detected between transitioning patients from LTOT to intermittent opioid therapy and the risk of SUDs and ORAOs. Therefore, it is unclear whether transitioning patients to intermittent opioid therapy is risk increasing or decreasing but these data show that dramatic changes in risk are unlikely. Further research is needed to better understand the effects of transitioning persons from LTOT to less intensive opioid prescribing strategies.

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**Conflicts of Interest**

Dr. Martin receives royalties from TrestleTree LLC for the commercialization of an opioid risk prediction tool, which is unrelated to the current study. Drs. Martin and Li are paid consultants for eMaxHealth Systems for unrelated projects. The remaining authors have no conflicts of interest to disclose.

**Figure 1 Title.** Derivation of the Study Sample.

**Figure 2.** SUD and AO Development comparing Veterans Switching to Intermittent Opioid Therapy to Veterans Continuing Chronic Opioid Therapy with PS Match and SIPTW Samples.

**Figure 2 Legend.** [*]SUD=substance use disorder; [⊗]AO=opioid-related adverse outcome; [Δ]SIPTW=stabilized inverse probability of treatment weighting; [¤]Referent: Continued Chronic Opioid Users; OUD=opioid use disorder; DUD=non-opioid, drug use disorder; AUD=alcohol use disorder; [¥] PS Match=propensity score matched.

**Appendix A Title.** Study Design and Time Frame.

**Appendix B Title.** Baseline Demographic Characteristics of Veterans as Split by the Instrumental Variable.

**Appendix B Legend.** Abbreviation: *Abs Std Diff (%)=absolute standardized differences in percentage form.



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Fig 1

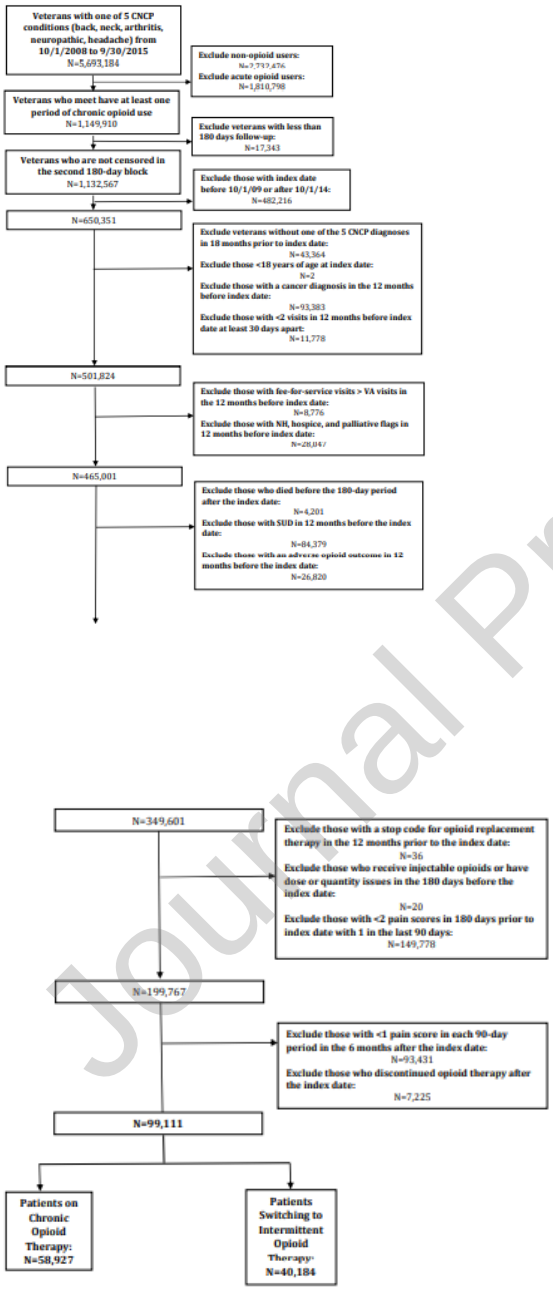


**Fig. 1.**

**Fig2**

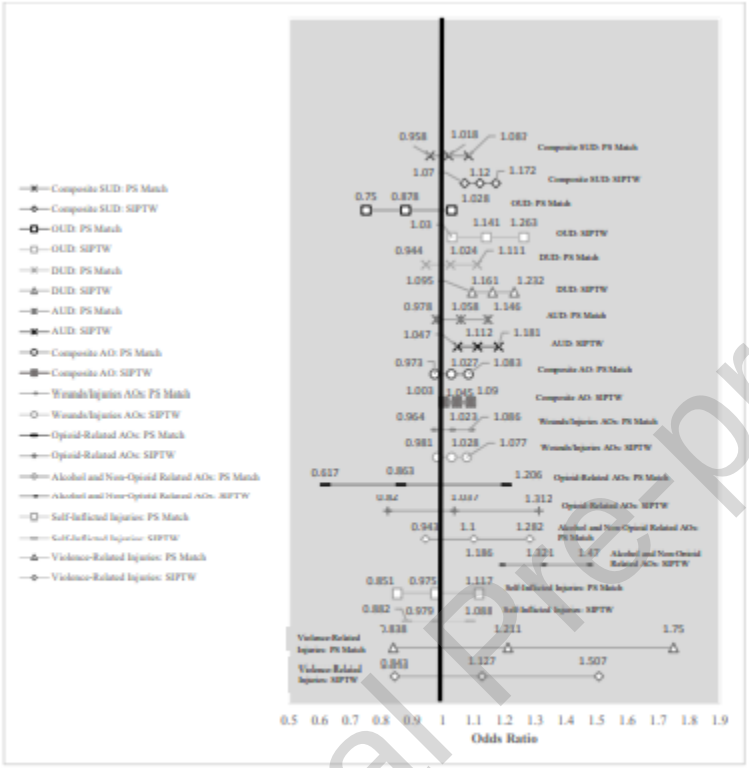


**Fig. 2.**



**Table 1 Title.** Baseline Demographic Characteristics of Veterans Continuing Chronic Opioid Therapy and Switching to Intermittent Opioid Therapy before and after Matching.

| | **Unmatched Sample (N=99,111)** | | | **Matched Veterans Continuing Chronic Opioid Therapy and Switching to Intermittent Opioid Therapy (N=58,586)** | | |
|---|---|---|---|---|---|---|
| | Continuing Chronic Opioid Therapy (N=58,927) | Intermittent Opioid Therapy (N=40,184) | Abs Std Diff (%)✠ | Continuing Chronic Opioid Therapy (N=29,293) | Intermittent Opioid Therapy (N=29,293) | Abs Std Diff (%)✠ |

| | N (Column %) | N (Column %) | | N (Column %) | N (Column %) | |
|---|---|---|---|---|---|---|
| **Race** | | | | | | |
| White | 41557 (70.52) | 25398 (63.20) | 15.6 | 19381 (66.16) | 19422 (66.30) | 0.3 |
| Black | 9674 (16.42) | 8171 (20.33) | 10.1 | 5570 (19.01) | 5560 (18.98) | 0.1 |
| Multiracial | 1966 (3.34) | 1611 (4.01) | 3.6 | 1104 (3.77) | 1128 (3.85) | 0.4 |
| Other | 4007 (6.80) | 3920 (9.76) | 10.7 | 2410 (8.23) | 2359 (8.05) | 0.6 |
| Unknown | 1723 (2.92) | 1084 (2.70) | 1.4 | 828 (2.83) | 824 (2.81) | 0.1 |
| **Age** | | | | | | |
| **Mean and Standard Deviation** | 57.01 ± 13.13 | 59.63 ± 13.67 | | 58.87 ± 13.52 | 58.90 ± 13.46 | |
| 18-30 | 2580 (4.38) | 1431 (3.56) | 4.2 | 1138 (3.88) | 1100 (3.76) | 0.7 |
| 31-49 | 11828 (20.07) | 6742 (16.78) | 8.5 | 5169 (17.65) | 5134 (17.53) | 0.3 |
| 50-64 | 29380 (49.86) | 17886 (44.51) | 10.7 | 13330 (45.51) | 13559 (46.29) | 1.6 |
| ≥65 | 15139 (25.69) | 14125 (35.15) | 20.7 | 9656 (32.96) | 9500 (32.43) | 1.1 |
| **Gender** | | | | | | |
| Male | 53063 (90.05) | 35892 (89.32) | 2.4 | 26173 (89.35) | 26271 (89.68) | 1.1 |
| **Marital Status** | | | | | | |
| Married | 30153 (51.17) | 21700 (54.00) | 5.7 | 15609 (53.29) | 15518 (52.98) | 0.6 |
| **Rural-Urban Commuting Area** | | | | | | |
| Urban | 40883 (69.38) | 27893 (69.41) | 0.1 | 20397 (69.63) | 20388 (69.60) | 0.1 |
| Large Rural | 8474 (14.38) | 5125 (12.75) | 4.8 | 3890 (13.28) | 3952 (13.49) | 0.6 |
| Isolated Small Rural | 8213 (13.94) | 5366 (13.35) | 1.7 | 4060 (13.86) | 4072 (13.90) | 0.1 |
| Missing | 1357 (2.30) | 1800 (4.48) | 12.1 | 946 (3.23) | 881 (3.01) | 1.3 |
| **Enhanced Charlson Comorbidity Index** | | | | | | |
| **Mean and Standard Deviation** | 2.50 ± 1.96 | 2.70 ± 2.04 | | 2.66 ± 2.03 | 2.67 ± 2.03 | |
| 0 | 6862 (11.64) | 3951 (9.83) | 5.9 | 3005 (10.26) | 2949 (10.07) | 0.6 |
| 1 | 14091 (23.91) | 8802 (21.90) | 4.8 | 6642 (22.67) | 6559 (22.39) | 0.7 |
| 2 | 13627 (23.13) | 9098 (22.64) | 1.2 | 6583 (22.47) | 6638 (22.66) | 0.5 |
| 3 | 9779 (16.60) | 6930 (17.25) | 1.7 | 4996 (17.06) | 5023 (17.15) | 0.2 |
| 4 | 6169 (10.47) | 4655 (11.58) | 3.6 | 3248 (11.09) | 3340 (11.40) | 1.0 |
| 5 | 3630 (6.16) | 2791 (6.95) | 3.2 | 2031 (6.93) | 1973 (6.74) | 0.8 |
| ≥6 | 4769 (8.09) | 3957 (9.85) | 6.1 | 2788 (9.52) | 2811 (9.60) | 0.3 |
| **Pain Condition** | | | | | | |
| Back and/or Neck Pain Only | 8036 (13.64) | 4302 (10.71) | 9.0 | 3306 (11.29) | 3352 (11.44) | 0.5 |
| Arthritis Only | 10499 (17.82) | 7829 (19.48) | 4.3 | 5518 (18.84) | 5655 (19.30) | 1.2 |
| Headaches Only | 457 (0.78) | 320 (0.80) | 0.2 | 226(0.77) | 227 (0.77) | 0.0 |
| Neuropathic Pain Only | 921 (1.56) | 588 (1.46) | 0.8 | 449 (1.53) | 435 (1.48) | 0.4 |
| Arthritis and Back and/or Neck Pain Only | 17082 (28.99) | 11509 (28.64) | 0.8 | 8395 (28.66) | 8371 (28.58) | 0.2 |
| Arthritis, Back and/or Neck Pain, and Headaches Only | 3761 (6.38) | 2708 (6.74) | 1.4 | 1985 (6.78) | 1891 (6.46) | 1.3 |
| Neuropathic Pain and One or More Others | 14556 (24.70) | 10366 (25.80) | 2.5 | 7577 (25.87) | 7540 (25.74) | 0.3 |
| All Tracer Pain Conditions | 972 (1.65) | 770 (1.92) | 2.0 | 536 (1.83) | 526 (1.80) | 0.3 |
| Other Multiple Pain Conditions | 2643 (4.49) | 1792 (4.46) | 0.1 | 1301 (4.44) | 1296 (4.42) | 0.1 |
| **Other Medication Use** | | | | | | |
| Antidepressant Use | 32412 (55.00) | 21229 (52.83) | 4.4 | 15705 (53.61) | 15756 (53.79) | 0.4 |
| Skeletal Muscle Relaxant Use | 22765 (38.63) | 15257 (37.97) | 1.4 | 11212 (38.28) | 11161 (38.10) | 0.4 |
| Benzodiazepine Use | 16436 (27.89) | 10099 (25.13) | 6.3 | 7577 (25.87) | 7601 (25.95) | 0.2 |
| Other Non-Opioid Analgesic Use | 42342 (71.86) | 30216 (75.19) | 7.6 | 21917 (74.82) | 21891 (74.73) | 0.2 |
| Hypnotics and Non-Benzodiazepine Sedative Use | 9331 (15.83) | 5849 (14.56) | 3.6 | 4473 (15.27) | 4385 (14.97) | 0.8 |
| **Mental Health Conditions** | | | | | | |
| No Mental Health Conditions | 28128 (47.73) | 19879 (49.47) | 3.5 | 14313 (48.86) | 14383 (49.10) | 0.5 |
| Schizophrenia | 458 (0.78) | 323 (0.80) | 0.3 | 239 (0.82) | 243 (0.83) | 0.2 |
| Major Depressive Disorder | 8225 (13.96) | 5307 (13.21) | 2.2 | 3846 (13.13) | 3919 (13.38) | 0.7 |
| Post-Traumatic Stress Disorder | 3326 (5.64) | 2554 (6.36) | 3.0 | 1826 (6.23) | 1819 (6.21) | 0.1 |
| Bipolar Disorder | 622 (1.06) | 387 (0.96) | 0.9 | 270 (0.92) | 295 (1.01) | 0.9 |
| Anxiety Disorders | 3083 (5.23) | 1829 (4.55) | 3.2 | 1468 (5.01) | 1355 (4.63) | 1.8 |
| Multiple Mental Health Conditions | 15085 (25.60) | 9905 (24.65) | 2.2 | 7331 (25.03) | 7279 (24.85) | 0.4 |
| **Percent with Each of the Following Visit Types in the 12 Months before Index Date** | | | | | | |
| Physical Therapy | 20864 (35.41) | 15132 (37.66) | 4.7 | 10535 (35.96) | 11194 (38.21) | 4.7 |
| Pain Clinic | 9635 (16.35) | 5529 (13.76) | 7.3 | 4146 (14.15) | 4242 (14.48) | 0.9 |
| Chiropractic Care | 954 (1.62) | 766 (1.91) | 2.2 | 498 (1.70) | 573 (1.96) | 1.9 |
| Medicine and Primary Care | 58875 (99.91) | 40149 (99.91) | 0.0 | 29265 (99.90) | 29269 (99.92) | 0.5 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Mental Health Care | 29803 (50.58) | 19400 (48.28) | 4.6 | 14359 (49.02) | 14280 (48.75) | 0.5 |
| **Duration of Action of Opioid Use in 180 Days before Index Date** | | | | | | |
| Long-Acting Only | 1126 (1.91) | 349 (0.87) | 8.9 | 307 (1.05) | 293 (1.00) | 0.5 |
| Short-Acting Only | 51686 (87.71) | 37876 (94.26) | 23.0 | 27305 (93.21) | 27278 (93.12) | 0.4 |
| Combination of Long and Short-Acting | 6115 (10.38) | 1959 (4.88) | 20.8 | 1681 (5.74) | 1722 (5.88) | 0.6 |
| **Schedule of Opioid Use in 180 Days before Index Date** | | | | | | |
| Schedule II Only | 33938 (57.59) | 17183 (42.76) | 30.0 | 13825 (47.20) | 13912 (47.49) | 0.6 |
| Schedule III Only | 1608 (2.73) | 1855 (4.62) | 10.1 | 1167 (3.98) | 1143 (3.90) | 0.4 |
| Schedule IV Only | 10603 (17.99) | 11271 (28.05) | 24.1 | 7200 (24.58) | 7044 (24.05) | 1.2 |
| Schedule V Only | 0 (0.00) | 1 (0.00) | 0.7 | 0 (0.00) | 0 (0.00) | 0.0 |
| Use of Multiple Schedules | 12778 (21.68) | 9874 (24.57) | 6.9 | 7101 (24.24) | 7194 (24.56) | 0.7 |
| | **Mean (SD)** | **Mean (SD)** | | **Mean (SD)** | **Mean (SD)** | |
| **Average Total Days of Opioid Supply** | | | | | | |
| 180 Days before Index Date | 150.64 (23.21) | 124.72 (26.49) | 96.76 | 136.87 (22.90) | 135.38 (23.01) | 6.5 |
| 180 Days after Index Date | 150.16 (25.04) | 47.45 (22.19) | -- | 141.77 (25.71) | 67.02 (32.35) | -- |
| **Average Morphine Equivalent Daily Dose** | | | | | | |
| 180 Days before Index Date | 32.21 (40.68) | 21.98 (19.25) | 32.1 | 23.51 (20.29) | 23.33 (20.44) | 0.9 |
| 180 Days after Index Date | 38.16 (46.50) | 23.44 (19.75) | -- | 28.03 (25.51) | 24.64 (21.43) | -- |
| **Pain Characteristics in 180 Days before Dosage Change Index Date** | | | | | | |
| First Pain Score | 4.98 (3.27) | 4.65 (3.36) | 10.0 | 4.75 (3.32) | 4.75 (3.34) | 0.1 |
| Last Pain Score | 4.27 (3.29) | 3.78 (3.32) | 14.7 | 3.96 (3.32) | 3.96 (3.31) | 0.1 |
| Pain Score Average | 4.51 (2.36) | 4.13 (2.39) | 16.3 | 4.26 (2.38) | 4.26 (2.38) | 0.3 |
| Change from First to Last Pain Score | -0.71 (3.84) | -0.86 (3.93) | 4.0 | -0.79 (3.89) | -0.80 (3.92) | 0.2 |
| **Service Visits in the 12 Months before Dosage Change Index Date Conditional on Use of the Visit Type** | | | | | | |
| Physical Therapy | 4.01 (5.97) | 4.55 (6.61) | -- | 4.11 (5.96) | 4.48 (6.63) | -- |
| Pain Clinic | 3.38 (3.43) | 3.58 (3.81) | -- | 3.45 (3.57) | 3.54 (3.81) | -- |
| Chiropractic Care | 4.34 (4.75) | 4.55 (4.85) | -- | 4.57 (4.96) | 4.48 (4.52) | -- |
| Medicine and Primary Care | 10.91 (7.57) | 11.12 (8.03) | -- | 11.03 (7.74) | 11.17 (8.10) | -- |
| Mental Health Care | 8.35 (11.43) | 8.85 (12.68) | -- | 8.58 (11.88) | 8.92 (12.79) | -- |

Abbreviation: *Abs Std Diff (%)=absolute standardized differences in percentage form.

**Table 2 Title.** SUD and AO Development Comparing Veterans Continuing COT to Veterans Switching to Intermittent Opioid Therapy among the Unmatched Sample and Matched Sample.

| | **Unmatched Sample of Veterans Continuing COT‡ and Switching to Intermittent Opioid Therapy** | | **Matched Sample of Veterans Continuing COT‡ and Veterans Switching to Intermittent Opioid Therapy** | | **Matched Sample (Continuing COT‡ vs Intermittent Opioid Therapy) Odds Ratio (OR) and Confidence Interval (CI)⊠*** | | | **SIPTW⊗ Sample of Veterans Continuing COT‡ and Veterans Switching to Intermittent Opioid Therapy** | | **SIPTW⊗ Sample (Continuing COT‡ vs Switching to Intermittent Opioid Therapy) Odds Ratio (OR) and Confidence Interval (CI)⊠*** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Continuing COT‡ N=58,927 N (%)** | **Intermittent Opioid Therapy N=40,184 N (%)** | **Continuing COT‡ N=29,293 N (%)** | **Intermittent Opioid Therapy N=29,293 N (%)** | **OR** | **Lower 95% CI** | **Upper 95% CI** | **Continuing COT‡ N=59,473.8 N (%)** | **Intermittent Opioid Therapy N=36,616.5 N (%)** | **OR** | **Lower 95% CI** | **Upper 95% CI** |
| **Composite SUDs** | 5278 (9.0) | 2812 (7.0) | 2193 (7.5) | 2237 (7.6) | 1.018 | 0.958 | 1.083 | 4839.01 (8.1) | 3583.24 (9.0) | 1.120 | 1.070 | 1.172 |
| OUD± | 1061 | 342 (0.9) | 336 (1.2) | 296 (1.0) | 0.87 | 0.75 | 1.02 | 870.79 | 662.23 | 1.14 | 1.030 | 1.263 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | (1.8) | | | | 8 | 0 | 8 | (1.5) | (1.7) | 1 | | |
| DUD[⊗] | 2937 (4.98) | 1512 (3.76) | 1196 (4.1) | 1229 (4.2) | 1.02 4 | 0.94 4 | 1.11 1 | 2681.57 (4.5) | 2067.10 (5.2) | 1.16 1 | 1.095 | 1.232 |
| AUD[¥] | 2807 (4.8) | 1682 (4.2) | 1248 (4.3) | 1319 (4.5) | 1.05 8 | 0.97 8 | 1.14 6 | 2640.99 (4.4) | 1945.07 (4.9) | 1.11 2 | 1.047 | 1.181 |
| **Composite AOs** | 5999 (10.2) | 4044 (10.1) | 2946 (10.1) | 3032 (10.4) | 1.02 7 | 0.97 3 | 1.08 3 | 6050.39 (10.2) | 4236.33 (10.7) | 1.04 5 | 1.003 | 1.090 |
| Wounds and Injuries | 4600 (7.8) | 3292 (8.2) | 2360 (8.1) | 2422 (8.3) | 1.02 3 | 0.96 4 | 1.08 6 | 4738.16 (8.0) | 3269.95 (8.3) | 1.02 8 | 0.981 | 1.077 |
| Opioid-Related | 193 (0.3) | 79 (0.2) | 74 (0.3) | 64 (0.2) | 0.86 3 | 0.61 7 | 1.20 6 | 169.90 (0.3) | 118.71 (0.3) | 1.03 7 | 0.820 | 1.312 |
| Alcohol and Non-Opioid Medication-Related | 810 (1.4) | 414 (1.0) | 315 (1.1) | 347 (1.2) | 1.10 0 | 0.94 3 | 1.28 2 | 724.56 (1.2) | 639.03 (1.6) | 1.32 1 | 1.186 | 1.470 |
| Self-Inflicted Injuries | 955 (1.6) | 537 (1.3) | 431 (1.5) | 425 (1.5) | 0.97 5 | 0.85 1 | 1.11 7 | 902.92 (1.5) | 599.26 (1.5) | 0.97 9 | 0.882 | 1.088 |
| Violence-Related Injuries | 94 (0.2) | 71 (0.2) | 52 (0.2) | 63 (0.2) | 1.21 1 | 0.83 8 | 1.75 0 | 106.42 (0.2) | 80.03 (0.2) | 1.12 7 | 0.843 | 1.507 |

Abbreviations: [※]Referent: Veterans continuing chronic opioid therapy; [*] logistic regression models among the matched sample include counts of healthcare service visits as covariates; [‡]COT=chronic opioid therapy; [±]OUD=opioid use disorder; [⊗]DUD=non-opioid drug use disorder; [¥]AUD=alcohol use disorder; [⊗]SIPTW=stabilized inverse probability of treatment weighting.



**CRediT authorship contribution statement**

CJH, EEK, JB, CL, TJH, and BCM made substantial contributions to this manuscript. CJH performed data analyses and wrote the first draft of the work. BCM secured the IRB approval and data access as well as provided intellectual guidance on study design. CL provided guidance on statistical models. CJH, EEK, JB, CL, TJH, and BCM provided input on study design and reviewed, edited, and approved the final manuscript.

**Highlights**

- Switching to intermittent opioid therapy is common in VA.
- Primary analyses did not find differences in opioid-related risks.
- Sensitivity analyses found mixed results in opioid-related risks.

- It is unclear if switching to intermittent therapy increases or decreases risks.