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Gender and the Association between Long-Term Prescription Opioid Use and New Onset Depression

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Abstract

Women have a higher prevalence of chronic non-cancer pain conditions and report more severe pain, yet, it is not known if the association between long term opioid analgesic use (OAU) and risk of a new depression episode (NDE) differs by gender. We analyzed patient data from the Veterans Health Administration (VHA; 2000 to 2012; n=70,997) and a large private-sector health care organization (2003 to 2012; n=22,981) to determine whether long-term OAU and risk of NDE differed by gender. Patients were free of depression and OAU for two years prior to baseline. OAU duration was defined as 1–30, 31–90 and >90 days, and NDE was defined by ICD-9 codes.

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Gender-stratified Cox proportional hazard models estimated hazard ratios. Propensity scores and subsequent inverse probability of treatment weighting controlled for confounding. In the VHA, >90 compared to 1–30 day OAU was more strongly associated with NDE among females than males (female: HR=1.79; 95%CI:1.45–2.22 vs. male HR=1.25; 95%CI:1.16–1.34, $p=0.002$). In private sector patients, there was no gender difference in the association between >90 day OAU and NDE (female HR=1.97; 95%CI:1.64–2.37 vs. male HR=1.99; 95%CI:1.44–2.74). Risk of NDE following long-term OAU is similar in men and women in private-sector patients but may differ for VHA patients. Future prospective studies are needed to identify mechanisms for the association between longer OAU and NDE.

Keywords

opioids; depression; gender; pain; epidemiology

Introduction

The evidence for greater pain sensitivity in women compared to men is well documented. In both private sector and Veterans Health Administration (VHA) patient populations, women are more likely to report current pain, have a higher prevalence of non-cancer pain conditions, report more severe pain associated with these conditions and are more likely to have persistent pain ^{2,13,18,44}. Yet, this literature is mixed because others have reported female veterans are more likely to report moderate to severe pain but not persistent pain ¹². In addition to higher pain prevalence, women also have twice the odds of depression compared to men ¹⁶, thus, it is not surprising that comorbid pain and depression are significantly more common among women ⁴.

The literature on gender differences in prescription opioid analgesic use (OAU) is inconsistent. Women with non-cancer pain in the VHA are less likely to receive long-term opioid prescriptions ^{14,44}. However, women in non-VHA samples, especially those over age 45, are more likely to have long term opioid use ⁵ and to overdose ^{8,21}. Further, some studies ^{8,21} but not others ^{15,19,20} report women receive higher doses than males.

While there is abundant evidence for a bi-directional association between prescription OAU and depression that is independent of pain ^{31,39}, the evidence for gender differences in this association is sparse and inconclusive. Research from a community-based, longitudinal study reveals both men and women reporting use of analgesics not specific to opioids compared to those with no analgesic use were more likely to experience incident depression ⁴. In contrast, others have found less depression among women receiving opioids compared to women who did not receive opioids and more depression among men receiving opioids vs men not receiving opioids ⁹. These studies did not determine whether depression symptoms associated with opioid use were independent of pain.

It remains uncertain whether women receiving prescription opioids for non-cancer pain have a greater risk of new-onset depression than men. Previous reports indicate long-term prescription OAU is associated with significant increased risk of a new depression episode (NDE) in VHA and private-sector patient cohorts after rigorous control for confounding by

indication^{30,34}. We previously reported descriptive statistics indicating VHA and private sector female patients were more likely to develop NDE, and we observed VHA male patients but not private sector male patients were significantly more likely to have >90 day OAU³⁴. This pattern suggested a potential for gender differences in the OAU-NDE association. However, we have yet to formally conduct sub-group comparisons. The present study fills this gap in the literature by determining if there is a gender difference in the risk of NDE following long-term prescription opioid use in large VHA and private-sector patients.

Methods

This retrospective cohort analysis used electronic medical record data obtained from the VHA and a private health care system, the Henry Ford Health System (HFHS). The HFHS used data from the Health Care Systems Research Network Virtual Data Warehouse²⁸. Data included ICD-9-CM diagnostic codes, inpatient and outpatient visits, prescription fill records, vital signs and demographic information from January 1, 2000 to December 31, 2012 for the VHA and January 1, 2003 to December 31, 2012 for HFHS. The project was approved by the institutional review boards of participating institutions.

Cohort Identification

Samples were restricted to patients aged 18 to 80 years (n=500,000 for VHA and n=122,145 for HFHS). Patients must have been cancer- and HIV-free, had at least one visit in each of the 2 washout years (2000–2001 for VHA and 2003–2004 for HFHS), and at least one visit in follow-up, defined as January 1, 2002 to December 31, 2012 for VHA and January 1, 2005 to December 31, 2012 for HFHS. As this was a new opioid user design with the outcome NDE, patients with any OAU or a diagnosis of depression in the 2 washout years were excluded. Among patients with new OAU in follow-up, those who started OAU on or after NDE, or started on the last clinical encounter for those without NDE were excluded. Finally, patients must have had complete demographic data available leaving an eligible cohort of 70,997 for the VHA and 22,981 for HFHS. Detailed descriptions of cohort eligibility have been described elsewhere³⁴.

Follow-up time

Follow-up time was defined as months from January 1, 2002 for VHA or January 1, 2005 for HFHS to either date of NDE or censor date. Censor date was date of last clinical encounter in the follow-up period (2002–2012 for VHA and 2005–2012 for HFHS) for those without an NDE.

Opioid use – duration and dose

New OAU began with the date of initial prescription fill during follow-up for any of the following opioids: codeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, morphine, oxycodone, oxymorphone, and pentazocine. Both short- and long-acting release formulations were included. Fill information included number of pills dispensed or liquid volume, unit dose in milligrams (mg), and ‘days supply’ which is the number of days required to finish medication if taken as prescribed.

OAU duration was defined using each patient's initial continuous use period and accounted for early refills and any overlaps. Patients were considered continuous users if no gap >30 days occurred between the end of one prescription and the start of another. OAU duration in days was calculated from the initial fill date to either the start of a >30-day gap or end of follow-up. Patients were classified into 1–30 day, 31–90 day, or >90 days of OAU.

Morphine equivalent dose (MED) was calculated using standard conversion tables mapping the amount of morphine equivalent to a given type of drug and dose. Assuming medication was taken as prescribed, the 'days supply' and quantity variables were used to calculate daily MED for each day of use in the continuous use period. The maximum daily MED in the initial continuous OAU period was used to assign patients to one of three MED groups: 1–50 mg, 51–100 mg, or >100 mg.

Outcome – New depression episode

New depression episode (NDE) was defined by a primary ICD-9-CM diagnosis of 296.2x, 296.3x or 311 in follow-up. Diagnostic codes had to occur in either one inpatient stay or at least two outpatient visits in the same 12-month period for a positive depression diagnosis. This algorithm is a valid and reliable measure of depression using administrative medical record data ^{10,36}.

Covariates

All variables, with the exception of pain scores and marital status not available in HFHS, were measured the same way in each patient cohort. Demographics included age, gender, race (white vs other), marital status (married vs other), and insurance coverage. Insurance coverage was defined as federal coverage only (VHA only and Medicare, coded separately in VHA and HFHS) vs. other sources. The volume of healthcare utilization variable was used to control for detection bias and was defined by the average number of outpatient visits per month in follow-up. Quartiles of healthcare utilization classified patients as either high (>75th percentile) or low utilizers (< 75th percentile).

All comorbidities were selected for their theoretical or prior evidence for an association with OAU or depression. Comorbid conditions were defined using ICD-9-CM codes. Psychiatric comorbidities included: posttraumatic stress disorder; any other anxiety disorder (a composite of panic disorder, generalized anxiety disorder, social phobia, obsessive compulsive disorder, and anxiety disorder not otherwise specified); alcohol abuse or dependence; any illicit drug abuse or dependence; and nicotine dependence. Metabolic and cardiovascular comorbidities included: type 2 diabetes mellitus, hypertension, cerebrovascular disease, obesity and cardiovascular disease (a composite of hyperlipidemia, ischemic heart disease, disease of pulmonary circulation, other heart disease, hypertensive heart disease and myocardial infarction). Other conditions included low testosterone and sleep apnea.

Five separate painful condition variables, arthritis, back pain, headaches, musculoskeletal pain and neuropathic pain, were derived from over 900 ICD-9-CM codes for which an opioid could be prescribed ^{30,35}. For the VHA, patient-reported pain scores obtained during

routine clinical care were available. Scores range from 0 to 10, where higher scores indicate more pain. The maximum pain score before end of follow-up was used in analysis.

Propensity Scores and Inverse Probability of Treatment Weighting (IPTW)

Since bias by indication may confound the association between OAU duration and NDE, we balanced potential confounders across levels of OAU duration. A propensity score is the conditional probability that a patient will be in a given OAU duration group, given covariates. A multinomial logistic regression model with OAU duration as the outcome (1–30 day vs 31–90 day vs >90 day) was used to generate a propensity score given covariates. Inverse probability of treatment weighting (IPTW) approaches were applied to propensity scores to create stabilized weights^{6,7,11,17,26,27,38,45}. The stabilized weight is the marginal probability of exposure, i.e. probability of a patient receiving 1–30 days, 31–90 days or >90 days of OAU given no covariates, divided by the propensity score. Weighting results in pseudo-populations such that covariate distributions are similar across OAU duration groups as if groups had been randomized, thereby obtaining analyses that are not confounded by factors predicting OAU duration. IPTW weighted analyses obtain unbiased estimates of the population average treatment effect, do not result in any reductions in sample size like propensity score matching methods, and analyses are generalizable to the entire population from which the sample was derived^{1,3}. Propensity models perform well if covariates achieve balance across groups and stabilized weights have a mean near one and do not fall outside a maximum of 10³⁸. This analysis stratified by gender a priori, therefore, propensity score calculation and weighting were done separately for males and females to create gender-specific weights. This strategy has been used successfully in other publications from our group examining OAU and multiple depression outcomes^{29,32–34}.

Statistical Analysis

All analyses were performed separately for each healthcare system with SAS v9.4 (SAS Institute, Cary, NC) at an alpha of 0.05. Prior to weighting data, bivariate analysis using independent samples t-tests for continuous variables and chi-square tests for categorical variables assessed the relationship of gender with covariates. Similarly, ANOVA and chi-square tests were used to assess the relationship of OAU duration with covariates separately for males and females within each healthcare system. Bivariate analyses of OAU duration and covariate relationships were repeated after IPTW to ensure covariate balance across OAU duration groups within each gender. Also, a chi-square test and Poisson regression model were used to compare crude incidence proportion and incidence rate (in person-years) across OAU duration groups, respectively.

Gender-stratified Cox proportional hazard models estimated crude and weighted hazard ratios with 95% confidence intervals for the relationship of OAU duration and NDE, treating OAU exposure as time-dependent. A fully adjusted, weighted model added additional time-dependent covariates to control for pain diagnoses and maximum pain scores that could have onset or changed after opioid initiation. Time-dependent variables allow ascertainment of time under exposure and any change in exposure status (e.g., a new pain diagnosis). Tests of the proportional hazards assumption for OAU exposure and pain covariates, including interactions of each covariate with follow-up time, were computed using the SAS PHREG

procedure. The proportional hazard assumption was met for all covariates and OAU exposure among both males and females in each healthcare system (all $p > 0.05$). Prior to stratification, a fully adjusted, overall weighted Cox proportional hazard model assessed the interaction effect of gender and OAU duration to evaluate whether gender-specific hazard ratios were different.

Results

Distributions of covariates and outcomes by gender in each healthcare system are shown in Table 1. The VHA sample was 93.9% male and the HFHS sample was 39.9% male. In the VHA, females had a higher incidence rate of NDE than males (23.2/1000PY vs. 12.7/1000PY). Males had a significantly longer OAU duration ($p < 0.0001$) and MED ($p = 0.003$) than females. In the VHA, all other covariates were significantly related to gender (see Table 1).

In the HFHS, females had a higher incidence rate of NDE than males (20.3/1000PY vs. 10.9/1000 PY). OAU duration was not significantly related to gender but males had a higher maximum OAU MED ($p = 0.013$). In HFHS, all other covariates, with the exception of PTSD and cerebrovascular disease, were significantly associated with gender (see Table 1).

Among female VHA patients ($n = 4300$), 81.2% had 1–30 day, 11.6% had 31–90 day, and 7.2% had >90 day OAU. NDE incidence rate increased with OAU duration from 21.3/1000PY among 1–30 day OAU, 25.6/1000PY among 31–90 day OAU to 36.7/1000PY in >90 day OAU ($p < 0.0001$). Among female VHA patients, longer OAU duration was significantly associated with older age, white race, high healthcare utilization, higher maximum MED, and presence of PTSD and other anxiety diagnosis, nicotine and any illicit drug abuse/dependence, higher pain score, and arthritis and back pain diagnosis. See Table 2.

Table 2 also shows that among male VHA patients ($n = 66,697$), 77.7% had 1–30 day, 12.2% had 31–90 day, and 10.1% had >90 day OAU. NDE incidence rate increased with OAU duration from 12.0/1000PY among those with 1–30 day OAU, 14.5/1000PY among those with 31–90 day OAU to 15.4/1000PY among those with >90 day OAU ($p < 0.0001$). Longer OAU duration was significantly associated with older age, white race, other forms of insurance, and higher maximum MED. Longer OAU duration was significantly associated with all comorbidities with the exception of obesity, sleep apnea and headaches.

Table 3 shows relationship of OAU duration and covariates within gender for HFHS. For females in the HFHS ($n = 13,814$), 88.9% had 1–30 day, 7.5% had 31–90 day, and 3.6% had >90 day OAU. NDE incidence rate increased with increasing OAU duration from 19.2/1000PY among those with 1–30 day OAU, 27.3/1000PY among those with 31–90 day OAU to 33.9/1000PY among those with >90 day OAU ($p < 0.0001$). Among female HFHS patients, longer OAU duration was significantly associated with older age and Medicare use as well as psychiatric, metabolic/cardiovascular, and pain comorbidities but not with other anxiety disorders or headaches. See Table 3.

For males in the HFHS (n=9167; Table 3), 89.6% had 1–30 day, 7.1% had 31–90 day, and 3.3% had >90 day OAU. NDE incidence rate increased from 10.3/1000PY to 13.0/1000 PY to 21.8/1000 PY with each increasing OAU duration group ($p<0.0001$). Increasing OAU duration was associated with older age, Medicare use, and increasing OAU MED. Longer OAU duration was significantly associated with all comorbidities with the exception of low testosterone and headaches.

Gender-specific propensity score models and IPTW stabilized weights were successful in balancing all covariates across OAU duration categories among males and females in both healthcare systems (all $p>0.05$; results shown in supplementary material, e-Table 1 for VHA and e-Table 2 for HFHS).

Results of unadjusted and unweighted gender-stratified Cox proportional hazards models are shown in Table 4. In unweighted models, in both VHA and HFHS female patients, 31–90 day OAU vs. 1–30 day OAU was associated with a significantly increased risk of NDE. Compared to 1–30 day OAU, >90 day OAU among females was associated with a significantly increased risk of NDE in VHA and HFHS patients (VHA: HR=1.76, 95%CI=1.42–2.18; HFHS: HR=1.79, 95%CI=1.48–2.17).

For males, 31–90 day OAU vs. 1–30 day OAU was significantly associated with increased risk of NDE in VHA (HR=1.22; 95%CI=1.15–1.31) but not in HFHS (HR=1.26, 95%CI=0.96–1.65). Among males, >90 day OAU vs. 1–30 day OAU was significantly associated with increased risk of NDE in VHA (HR=1.29, 95%CI=1.21–1.39) and HFHS (HR=2.15, 95%CI=1.58–2.91).

After weighting data and adjusting for painful conditions and maximum pain score after OAU initiation (see Table 4), an assessment of the interaction of OAU duration and gender showed that gender-specific hazard ratios for the association of OAU duration and NDE were significantly different for female and male VHA patients ($p=0.003$). In both female and male patients, 31–90 day OAU vs. 1–30 day OAU was significantly associated with a 36% and 16% increased risk of NDE, respectively, but there was no significant difference by gender ($p=0.114$). However, >90 day OAU was more strongly associated with NDE among VHA females than males, such that females had 1.8 times the risk of NDE compared to males with 1.3 times the risk of NDE (female: HR=1.79; 95%CI:1.45–2.22 vs. male HR=1.25; 95%CI:1.16–1.34, $p=0.002$).

In the HFHS, gender-specific hazard ratios for the relationship of OAU duration and NDE were found to be similar (interaction $p=0.534$). In HFHS patients, 31–90 day OAU vs. 1–30 day OAU was significantly associated with a 42% increased risk of NDE in females, but not significantly associated in males (HR=1.42; 95%CI:1.22–1.65 and HR=1.26; 95%CI:0.96–1.66, respectively). In HFHS patients, >90 day OAU vs. 1–30 day OAU was significantly associated with approximately two times the risk of NDE in females and males (HR=1.97; 95%CI:1.64–2.37 and HR=1.99; 95%CI:1.44–2.74, respectively).

Discussion

In two large patient populations we observed >90 day OAU compared to 1–30 day OAU was associated with significant increased risk of NDE in males and females. These findings confirm our previous reports demonstrating longer OAU duration is associated with NDE in VHA and private sector patient groups³⁴. However, evidence that the association between duration and NDE differed by gender was mixed. Significant gender difference in risk of NDE among patients with long-term OAU was observed only in VHA patients who used OAU for >90 days. Female VHA patients with >90 days OAU had a 79% increased risk of NDE which was a significantly larger increased risk than the 25% increase seen in male VHA patients with >90 day OAU vs. 1–30 day OAU. No gender differences in the association between longer OAU and NDE were seen in HFHS men and women, where gender-specific hazard of NDE were similar for those who used opioids for 31–90 days or >90 days.

In our prior study of the association of long-term OAU and NDE in VHA and private sector patients³⁴, we did not stratify by gender and observed >90 day OAU, compared to 1–30 day OAU, was associated with a 35% increased risk of NDE in VHA patients and 105% increased risk in HFHS patients. When compared to the present gender specific results in VHA patients, it appears that female gender partly moderates the >90 day OAU-NDE association. However, in HFHS patients we found both female and male patients with >90 day OAU were about two times more likely to develop NDE which is not significantly different than the estimate obtained for non-stratified results in our prior study³⁴.

To our knowledge, there is no existing literature on whether the association between longer OAU duration and NDE differs by gender. Calvo-Perxas and colleagues⁴ study of incident depression and pain in a population-based sample revealed self-reported use of analgesics, compared to no analgesic use, was associated with a 100% and 58% increased odds of incident depression in female and male participants, respectively. Although this is largely consistent with our results, it is not known if these findings are due to opioids or other self-reported analgesics. In a cross-sectional study of patients treated in a specialty pain clinic, the average score on the Beck Depression Inventory (BDI) somatic subscale was not different for males and females with medical record-confirmed opioid use vs. non-use⁹. However, this same study revealed a significant gender by opioid use interaction for the BDI affective distress subscale in which male opioid users vs. non-users had higher affective distress and female opioid users vs. non-users had lower affective distress⁹. Fillingim and colleagues' opioid measure was a binary indicator of taking opioids (i.e., yes vs. no) and comparisons were limited to bivariate analysis⁹; therefore, methodological differences may account for inconsistent results on gender differences in the opioid-depression association.

We observed male VHA patients were more likely than women to use opioids for >90 days, and a higher proportion of men than women had a daily MED >50 mg. There was no gender difference in duration of OAU in HFHS patients, however, women were significantly less likely to have a maximum MED >50 mg. These gender patterns are consistent with previous studies of prescription opioid use in the VHA which indicate less opioid exposure among women^{14,44}. The lack of gender differences in OAU duration in HFHS patients is consistent

with prior studies reporting no gender difference in receipt of opioids for non-cancer pain in non-veteran patients^{15,19} while diverging from evidence that women over 45 are more likely to have long-term opioid use⁵.

We speculate the significantly smaller magnitude of association between OAU duration and NDE in male veterans compared to female veterans is related to evidence that differences in patient characteristics are more pronounced in female vs. male veterans compared to civilian females and males. In the present study, female veterans were about 10 years younger than male veterans while females and males in HFHS were of similar age. The prevalence of OAU >90 days was less common in female vs. male veterans but similar in HFHS males and females. Although PTSD and nicotine dependence were much more common in veterans compared to the civilian sample, both diagnoses were less prevalent among females vs. males in VHA patients. In HFHS, the prevalence of PTSD was quite similar in women and men. It is possible that the higher prevalence of long-term OAU, PTSD and nicotine dependence is associated with a higher prevalence of unmeasured and undetected symptoms of depression and other conditions associated with those disorders. If true, this would reduce the strength of association between OAU and depression in males.

Community survey results indicate male veterans compared to non-veterans are more often obese but obesity did not differ in female veterans vs. female civilians³⁷. PTSD is more common among female veterans but male veterans experience more trauma exposure⁴⁰. This may be explained by females' greater exposure to sexual trauma which is a stronger risk factor for PTSD than other forms of trauma²⁵. Military sexual trauma is associated with obesity²⁴ which in turn is associated with depression²², persistent pain²³, and consequently, opioid use. As more women veterans are using VHA for care, the differences between men and women found in this study may dissipate in the future.

Limitations should be considered when interpreting the present study. NDE diagnoses may not be reliable as these datasets lack inter-rater reliability information. However, this limitation is minimal as the algorithm used to identify NDE cases has been shown to have 99% positive predictive value compared to chart-reviewed diagnoses³⁶ and 88% positive predictive value and 71% negative predictive value compared to self-reported lifetime depression¹⁰. Also, we do not know if patients took their opioid medications as prescribed. We do not have symptom-level data other than pain scores, and it is possible that longer OAU worsened subclinical depression which then led to a diagnosis. Indeed, a recent study found that intermittent or regular/higher dose opioid use as opposed to minimal or no use was associated with higher PHQ-8 depressive symptom scores and a higher prevalence of elevated scores (i.e. PHQ-8 ≥ 10) indicating probable clinical depression⁴³. While findings for female patients are consistent across VHA and HFHS, results may not generalize to non-VHA health patients in regions of the country other than southeastern Michigan. The potential for misclassification of depression exists, however, the VHA and HFHS both have implemented routine depression screening, which limits the chance of misclassifying patients as not having NDE. We have previously reported the patient characteristics in VHA and HFHS³⁴. VHA patients were more often prescribed >90 day OAU than HFHS patients and both physical and psychiatric comorbidity was substantially more common in VHA than HFHS patients. We control for these confounding factors but it is possible that the strong

association between comorbid psychiatric disorders and NDE and overall greater burden of disease mitigates the effect size in VHA compared to HFHS patients.

Some elements of criteria for causation have been observed in our series of studies on OAU and depression^{29,30,32–34}, including consistency, temporal order of exposure and outcome, and evidence of a dose-response relationship. Also, in post-hoc analysis of VHA patients, not stratified by gender, we explored evidence for dose-response and found unadjusted incidence of NDE increased from 8.6/1000PY in non-OAU exposed to 12.6/1000 PY in 1–30 day OAU, 15.4/1000 PY in 31–90 day OAU and 16.3/1000 PY in >90 day OAU. However, we do not claim our study establishes a causal relationship because we have several measurement limitations including the lack of data on detailed pain interference measures, repeated depression symptom measures and information on lifetime depression. These, and other factors, could moderate or mediate the association between long term OAU and new depression episodes.

Conclusions

The opioid epidemic is still an urgent public health concern in the United States with >200 million opioid prescriptions dispensed per year⁴¹ and about 2 million people suffering from substance use disorder related to prescription opioids⁴². Based on prior studies, long-term OAU is associated with NDE as well as treatment-resistant depression^{33,34}. We found some evidence of a lower magnitude of risk in male compared to female veterans, but risks for NDE were equivalent in both genders in the civilian patient population. However, both genders are vulnerable for depression with longer OAU. Screening for depression in long-term users may contribute to early detection and aggressive treatment. Prospective data collection is warranted to identify factors that may be in the causal pathway from long-term OAU to NDE.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Perspective

Existing research is mixed regarding gender differences in outcomes following long-term prescription opioid use. This study found both genders have increased risk of a new depression episode following >90 day opioid use. Women and men may benefit from closer monitoring of mood associated with chronic opioid use.¹

Highlights

- Increased risk of depression following >90 days opioid use for both genders.
- Female vs. male veterans have greater depression risk after >90 days opioid use.
- No gender difference in opioid-depression risk was found in the private sector.
- Need closer monitoring of mood associated with chronic opioid use for some groups.

Table 1

Characteristics of new OAU users, males vs. females by healthcare organization

Variable, n (%)	VHA (n=70,997)			HFHS (n=22,981)		
	Female (n=4,300)	Male (n=66,697)	p-value	Female (n=13,814)	Male (n=9,167)	p-value
<u>Outcome</u>						
NDE, incidence %	905 (21.1)	7707 (11.6)	<.0001	1911 (13.8)	680 (7.4)	<.0001
NDE, incidence rate	23.2/1000PY	12.7/1000PY	<.0001	20.3/1000PY	10.9/1000PY	<.0001
<u>Covariates</u>						
Age, mean (sd)	45.4 (13.3)	56.1 (12.7)	<.0001	47.4 (14.9)	48.3 (13.6)	<.0001
Race: White	2924 (68.0)	50866 (76.3)	<.0001	6043 (43.8)	4653 (50.8)	<.0001
Insurance: VHA only	1304 (30.3)	23497 (35.2)	<.0001	---	---	---
Insurance: Medicare	---	---	<.0001	3253 (23.6)	2007 (21.9)	.004
Marital status: Married	1704 (39.6)	37372 (56.0)	<.0001	---	---	---
High Healthcare utilization	1049 (24.4)	18543 (27.8)	<.0001	2931 (21.2)	2051 (22.4)	.037
OAU, duration (days)						
1–30	3490 (81.2)	51816 (77.7)		12278 (88.9)	8209 (89.6)	
31–90	499 (11.6)	8141 (12.2)	<.0001	1033 (7.5)	652 (7.1)	.257
> 90	311 (7.2)	6740 (10.1)		503 (3.6)	306 (3.3)	
MED, maximum (mg)						
1–50	3939 (91.6)	60046 (90.0)		10703 (77.5)	6961 (75.9)	
51–100	265 (6.2)	4950 (7.4)	.003	2685 (19.4)	1928 (21.0)	.013
> 100	96 (2.2)	1701 (2.6)		426 (3.1)	278 (3.0)	
Psychiatric comorbidities						
PTSD	495 (11.5)	9862 (14.8)	<.0001	82 (0.6)	41 (0.5)	.136
Other anxiety ^A	664 (15.4)	7719 (11.6)	<.0001	1422 (10.3)	635 (6.9)	<.0001
Nicotine dependence	1463 (34.0)	28712 (43.1)	<.0001	2813 (20.4)	2461 (26.9)	<.0001
Alcohol abuse/dependence	394 (9.2)	13919 (20.9)	<.0001	298 (2.2)	712 (7.8)	<.0001
Any illicit drug abuse/dependence	309 (7.2)	8418 (12.6)	<.0001	234 (1.7)	391 (4.3)	<.0001
Metabolic/Cardiovascular comorbidities						
Diabetes Type II	1051 (24.4)	28895 (43.3)	<.0001	4037 (29.2)	3064 (33.4)	<.0001
Hypertension	2686 (62.5)	55930 (83.9)	<.0001	9351 (67.7)	6506 (71.0)	<.0001

Variable, n (%)	VHA (n=70,997)			HFHS (n=22,981)		
	Female (n=4,300)	Male (n=66,697)	p-value	Female (n=13,814)	Male (n=9,167)	p-value
Cardiovascular disease #	3095 (72.0)	58285 (87.4)	<.0001	10108 (73.2)	7336 (80.0)	<.0001
Cerebrovascular disease	433 (10.1)	14505 (21.8)	<.0001	2099 (15.2)	1461 (15.9)	.128
Obesity diagnosis	2083 (48.4)	25538 (38.3)	<.0001	4432 (32.1)	2090 (22.8)	<.0001
Other comorbidities						
Low Testosterone	---	2165 (3.2)	---	---	310 (3.4)	---
Sleep apnea	311 (7.2)	7252 (10.9) ^c	<.0001	598 (4.3)	985 (10.8)	<.0001
Painful conditions						
Arthritis	3665 (85.2)	54839 (82.2)	<.0001	11198 (81.1)	7183 (78.4)	<.0001
Back pain	3134 (72.9)	43458 (65.2)	<.0001	9809 (71.0)	6106 (66.6)	<.0001
Headaches	1815 (42.2)	12574 (18.8)	<.0001	5872 (42.5)	2519 (27.5)	<.0001
Musculoskeletal pain	3173 (73.8)	41644 (62.4)	<.0001	11634 (84.2)	7639 (83.3)	.073
Neuropathic pain	1319 (30.7)	21676 (32.5)	.013	3341 (24.2)	1871 (20.4)	<.0001
Maximum pain score, mean (sd)	8.7 (1.9)	8.4 (2.2)	<.0001	---	---	---

Note: OAU = opioid analgesic use; MED=morphine equivalent dose; VHA = Veterans Health Administration; HFHS = Henry Ford Health System; NDE=New depression episode; PY=person-years

^a Other anxiety disorders = panic disorder, OCD, social phobia, GAD, Anxiety NOS

[#] Cardiovascular disease = hyperlipidemia, ischemic heart disease, diseases of pulmonary circulation, other heart disease, hypertensive heart disease, myocardial infarction

Table 2

VHA: Characteristics of new OAU users by OAU duration, stratified by gender (n=70,997)

VHA (n=70,997)								
Variable, n (%)	Females (n=4,300)			Males (n=66,697)				
	OAU 1–30 days (n=3490)	OAU 31–90 days (n=499)	OAU > 91 days (n=311)	p-value	OAU 1–30 days (n=51816)	OAU 31–90 days (n=8141)	OAU > 91 days (n=6740)	p-value
<i>Outcome</i>								
NDE, incidence %	681 (19.5)	128 (25.6)	96 (30.9)	<.0001	5737 (11.1)	1050 (12.9)	920 (13.7)	<.0001
NDE, incidence rate	21.3/1000PY	29.3/1000PY	36.7/1000PY	<.0001	12.0/1000PY	14.5/1000PY	15.4/1000PY	<.0001
<i>Covariates</i>								
Age, mean (sd)	45.0 (13.0)	47.1 (14.4)	47.1 (14.2)	<.001	55.9 (12.8)	56.5 (12.6)	56.4 (12.3)	<.001
Race: White	2329 (66.7)	344 (68.9)	251 (80.7)	<.0001	38878 (75.0)	6315 (77.6)	5673 (84.2)	<.0001
Insurance: VHA only	2444 (70.0)	350 (70.1)	202 (64.9)	.170	33718 (65.1)	5269 (64.7)	4213 (62.5)	<.001
Insurance: Medicare	---	---	---	---	---	---	---	---
Marital status: Married	1380 (39.5)	199 (39.9)	125 (40.2)	.968	28941 (55.8)	4562 (56.0)	3869 (57.4)	.055
High Healthcare utilization	820 (23.5)	140 (28.1)	89 (28.6)	.017	14207 (27.4)	2456 (30.2)	1880 (27.9)	<.0001
MED, maximum (mg)								
1–50	3295 (94.4)	431 (86.4)	213 (68.5)		48249 (93.1)	7017 (86.2)	4780 (70.9)	
51–100	156 (4.5)	53 (10.6)	56 (18.0)	<.0001	2969 (5.7)	832 (10.2)	1149 (17.1)	<.0001
> 100	39 (1.1)	15 (3.0)	42 (13.5)		598 (1.2)	292 (3.6)	811 (12.0)	
Psychiatric comorbidities								
PTSD	393 (11.3)	50 (10.0)	52 (16.7)	.008	7427 (14.3)	1265 (15.5)	1170 (17.4)	<.0001
Other anxiety ^	517 (14.8)	83 (16.6)	64 (20.6)	.019	5623 (10.8)	1050 (12.9)	1046 (15.5)	<.0001
Nicotine dependence	1162 (33.3)	162 (32.5)	139 (44.7)	<.0001	21779 (42.0)	3677 (45.2)	3256 (48.3)	<.0001
Alcohol abuse/dependence	311 (8.9)	46 (9.2)	37 (11.9)	.216	10647 (20.6)	1810 (22.2)	1462 (21.7)	.001
Any illicit drug abuse/dependence	243 (7.0)	31 (6.2)	35 (11.3)	.013	6400 (12.4)	1065 (13.1)	953 (14.1)	<.0001
Metabolic/Cardiovascular comorbidities								
Diabetes Type II	841 (24.1)	131 (26.3)	79 (25.4)	.531	22229 (42.9)	3629 (44.6)	3037 (45.1)	<.001
Hypertension	2150 (61.6)	334 (66.9)	202 (64.9)	.046	43238 (83.5)	6883 (84.6)	5809 (86.2)	<.0001
Cardiovascular disease #	2492 (71.4)	371 (74.4)	232 (74.6)	.221	45160 (87.2)	7156 (87.9)	5969 (88.6)	.002
Cerebrovascular disease	341 (9.8)	64 (12.8)	28 (9.0)	.085	11143 (21.5)	1900 (23.3)	1462 (21.7)	.001

VHA (n=70,997)

Variable, n (%)	Females (n=4,300)			p- value	Males (n=66,697)			p- value
	OAU 1–30 days (n=3490)	OAU 31–90 days (n=499)	OAU > 91 days (n=311)		OAU 1–30 days (n=51816)	OAU 31–90 days (n=8141)	OAU > 91 days (n=6740)	
Obesity diagnosis	1678 (48.1)	260 (52.1)	145 (46.6)	.195	19769 (38.2)	3179 (39.1)	2590 (38.4)	.293
Other comorbidities								
Low Testosterone	---	---	---	---	1638 (3.2)	243 (3.0)	284 (4.2)	<.0001
Sleep apnea	247 (7.1)	46 (9.2)	18 (5.8)	.134	5620 (10.9)	929 (11.4)	703 (10.4)	.147
Painful conditions								
Arthritis	2944 (84.4)	440 (88.2)	281 (90.4)	.002	42099 (81.3)	6901 (84.8)	5839 (86.6)	<.0001
Back pain	2505 (71.8)	369 (73.9)	260 (83.6)	<.0001	32715 (63.1)	5642 (69.3)	5101 (75.7)	<.0001
Headaches	1462 (41.9)	227 (45.5)	126 (40.5)	.257	9747 (18.8)	1584 (19.5)	1243 (18.4)	.253
Musculoskeletal pain	2568 (73.6)	380 (76.2)	225 (72.4)	.396	32255 (62.3)	5285 (64.9)	4104 (60.9)	<.0001
Neuropathic pain	1046 (30.0)	176 (35.3)	97 (31.2)	.055	16270 (31.4)	2868 (35.2)	2538 (37.7)	<.0001
Maximum pain score, mean (sd)	8.6 (1.9)	9.0 (1.7)	9.1 (1.4)	<.0001	8.3 (2.2)	8.7 (1.8)	8.7 (1.9)	<.0001

Cells with < 5 patients are reported as '<5' to protect patient privacy and confidentiality

Note: OAU = opioid analgesic use; MED=morphine equivalent dose; VHA = Veterans Health Administration; NDE=New depression episode; PY=person-years

[^] Other anxiety disorders = panic disorder, OCD, social phobia, GAD, Anxiety NOS

[#] Cardiovascular disease = hyperlipidemia, ischemic heart disease, diseases of pulmonary circulation, other heart disease, hypertensive heart disease, myocardial infarction

Table 3

HFHS: Characteristics of new OAU users by OAU duration, stratified by gender (n=22,981)

HFHS (n=22,981)								
Variable, n (%)	Females (n=13,814)			Males (n=9,167)				
	OAU 1–30 days (n=12278)	OAU 31–90 days (n=1033)	OAU > 91 days (n=503)	p- value	OAU 1–30 days (n=8209)	OAU 31–90 days (n=652)	OAU > 91 days (n=306)	p- value
<i>Outcome</i>								
NDE, incidence %	1607 (13.1)	192 (18.6)	112 (22.3)	<.0001	578 (7.0)	58 (8.9)	44 (14.4)	<.0001
NDE, incidence rate	19.2/1000PY	27.3/1000PY	33.9/1000PY	<.0001	10.3/1000PY	13.0/1000PY	21.8/1000PY	<.0001
<i>Covariates</i>								
Age, mean (sd)	46.6 (14.7)	52.3 (15.0)	55.4 (14.3)	<.0001	48.0 (13.7)	50.8 (13.2)	52.4 (12.7)	<.0001
Race: White	5361 (43.7)	465 (45.0)	217 (43.1)	.676	4174 (50.8)	339 (52.0)	140 (45.8)	.174
Insurance: VHA only	---	---	---	---	---	---	---	---
Insurance: Medicare	2628 (21.4)	386 (37.4)	239 (47.5)	<.0001	1703 (20.8)	186 (28.5)	118 (38.6)	<.0001
Marital status: Married	---	---	---	---	---	---	---	---
High Healthcare utilization	2627 (21.4)	198 (19.2)	106 (21.1)	.242	1829 (22.3)	141 (21.6)	81 (26.5)	.201
MED, maximum (mg)								
1–50	9684 (78.9)	681 (65.9)	338 (67.2)		6335 (77.2)	427 (65.5)	199 (65.0)	
51–100	2244 (18.3)	308 (29.8)	133 (26.4)	<.0001	1645 (20.0)	195 (29.9)	88 (28.8)	<.0001
> 100	350 (2.9)	44 (4.3)	32 (6.4)		229 (2.8)	30 (4.6)	19 (6.2)	
Psychiatric comorbidities								
PTSD	65 (0.5)	14 (1.4)	< 5	.004	34 (0.4)	< 5	5 (1.6)	.006
Other anxiety ^	1239 (10.1)	122 (11.8)	61 (12.1)	.084	534 (6.5)	73 (11.2)	28 (9.2)	<.0001
Nicotine dependence	2349 (19.1)	302 (29.2)	162 (32.2)	<.0001	2107 (25.7)	227 (34.8)	127 (41.5)	<.0001
Alcohol abuse/dependence	252 (2.1)	28 (2.7)	18 (3.6)	.031	590 (7.2)	80 (12.3)	42 (13.7)	<.0001
Any illicit drug abuse/dependence	174 (1.4)	35 (3.4)	25 (5.0)	<.0001	308 (3.8)	47 (7.2)	36 (11.8)	<.0001
Metabolic/Cardiovascular comorbidities								
Diabetes Type II	3471 (28.3)	356 (34.5)	210 (41.8)	<.0001	2695 (32.8)	244 (37.4)	125 (40.9)	.001
Hypertension	8127 (66.2)	781 (75.6)	443 (88.1)	<.0001	5742 (69.9)	518 (79.5)	246 (80.4)	<.0001
Cardiovascular disease #	8862 (72.2)	821 (79.5)	425 (84.5)	<.0001	6529 (79.5)	553 (84.8)	254 (83.0)	.002
Cerebrovascular disease	1768 (14.4)	204 (19.8)	127 (25.3)	<.0001	1248 (15.2)	130 (19.9)	83 (27.1)	<.0001

HFHS (n=22,981)								
Variable, n (%)	Females (n=13,814)			p- value	Males (n=9,167)			
	OAU 1-30 days (n=12278)	OAU 31-90 days (n=1033)	OAU > 91 days (n=503)		OAU 1-30 days (n=8209)	OAU 31-90 days (n=652)	OAU > 91 days (n=306)	
Obesity diagnosis	3887 (31.7)	358 (34.7)	187 (37.2)	.006	1837 (22.4)	173 (26.5)	80 (26.1)	.019
Other comorbidities								
Low Testosterone					284 (3.5)	14 (2.2)	12 (3.9)	.177
Sleep apnea	501 (4.1)	71 (6.9)	26 (5.2)	<.0001	858 (10.5)	92 (14.1)	35 (11.4)	.014
Painful conditions								
Arthritis	9814 (79.9)	927 (89.7)	457 (90.8)	<.0001	6351 (77.4)	564 (86.5)	268 (87.6)	<.0001
Back pain	8547 (69.6)	841 (81.4)	421 (83.7)	<.0001	5355 (65.2)	502 (77.0)	249 (81.4)	<.0001
Headaches	5231 (42.6)	444 (43.0)	197 (39.2)	.295	2246 (27.4)	174 (26.7)	99 (32.4)	.142
Musculoskeletal pain	10222 (83.3)	947 (91.7)	465 (92.5)	<.0001	6798 (82.8)	567 (87.0)	274 (89.5)	<.0001
Neuropathic pain	2849 (23.2)	317 (30.7)	175 (34.8)	<.0001	1588 (19.3)	174 (26.7)	109 (35.6)	<.0001
Maximum pain score, mean (sd)								

Cells with < 5 patients are reported as '<5' to protect patient privacy and confidentiality

Note: OAU = opioid analgesic use; MED=morphine equivalent dose; HFHS = Henry Ford Health System; NDE=New depression episode; PY=person-years

[^] Other anxiety disorders = panic disorder, OCD, social phobia, GAD, Anxiety NOS

[#] Cardiovascular disease = hyperlipidemia, ischemic heart disease, diseases of pulmonary circulation, other heart disease, hypertensive heart disease, myocardial infarction

Results from Cox Proportional Hazards Models stratified by gender, measuring the association between OAU duration and NDE, weighted by inverse probability of OAU duration, two healthcare sites

Table 4

Variable	VHA (n=70,997)				HFHS (n=22,981)			
	Female		Male		Female		Male	
	Unweighted Female (n=4,300)	weighted Female (n=4,300)	Unweighted Male (n=66,697)	weighted Male (n=66,697)	Unweighted Female (n=13,814)	Weighted Female (n=13,814)	Unweighted Male (n=9,167)	weighted Male (n=9,167)
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
OAU, duration (days)								
1–30	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
31–90	1.39 (1.15–1.68)	1.36 (1.12–1.64)	1.22 (1.15–1.31)	1.16 (1.08–1.23) ^a	1.43 (1.23–1.66)	1.42 (1.22–1.65)	1.26 (0.96–.65)	1.26 (0.96–1.66) ^c
> 90	1.76 (1.42– 2.18)	1.79 (1.45– 2.22)	1.29 (1.21– 1.39)	1.25 (1.16– 1.34) ^b	1.79 (1.48– 2.17)	1.97 (1.64– 2.37)	2.15 (1.58– 2.91)	1.99 (1.44–2.74) ^d
Arthritis		1.11 (0.91– 1.34)		1.18 (1.11– 1.25)		1.42 (1.25– 1.61)		1.27 (1.05–1.54)
Back pain		1.49 (1.27– 1.75)		1.49 (1.42– 1.57)		1.39 (1.25– 1.54)		1.45 (1.23–1.72)
Headache		1.42 (1.24– 1.62)		1.54 (1.46– 1.62)		1.49 (1.36– 1.63)		1.34 (1.13–1.59)
Musculoskeletal pain		1.44 (1.22– 1.69)		1.27 (1.21– 1.34)		1.29 (1.13– 1.48)		1.12 (0.91–1.38)
Neuropathy		1.15 (0.99– 1.33)		1.13 (1.07– 1.19)		1.28 (1.16– 1.43)		1.36 (1.13–1.64
Maximum pain score		1.22 (1.15– 1.29)		1.25 (1.23– 1.27)		---		---
OAU *gender, p-value		.003				.534		

Note: OAU = opioid analgesic use; VHA = Veterans Health Administration; HFHS = Henry Ford Health System; NDE=New depression episode; HR=hazard ratio; CI=confidence interval; PH=proportional hazards

^aVHA 31–90 days Male vs. Female HR contrast p=.114

^bVHA > 90 days Male vs Female HR contrast p=.002

^cHFHS 31–90 days Male vs Female HR contrast p=.536

^dHFHS > 90 days Male vs Female HR contrast p=.379