Menopausal Symptoms and Higher Risk Opioid Prescribing in a National Sample of Women Veterans with Chronic Pain

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BACKGROUND: The greatest increases in long-term opioid use and opioid-related overdose mortality in recent years have been among women in midlife. Common menopausal symptoms broadly affect health and health care utilization in midlife, but their contribution to chronic pain management during this period is unknown.

OBJECTIVE: To examine relationships between menopausal symptoms and long-term opioid prescription patterns among midlife women with chronic pain.

DESIGN: Cross-sectional analysis of national Veterans Health Administration medical and pharmacy records (2014–2015).

PARTICIPANTS: Women Veterans aged 45–64 with ≥ 1 outpatient visit and chronic pain diagnoses spanning $\geq$ 90 days.

MAIN MEASURES: Long-term opioids (prescribed oral opioids for ≥ 90 days), high-dose long-term opioids (> 50 mg average morphine equivalent daily dose), and long-term opioids co-prescribed with central nervous system depressants (benzodiazepine and non-benzodiazepine sedative-hypnotics, gabapentin/pregabalin, muscle relaxants). Multivariable logistic regression models were used to examine associations between outcomes and menopausal symptoms (menopausal symptom–related diagnoses (i.e., "symptomatic menopausal states") on ≥ 2 encounters and/or menopausal hormone therapy, adjusting for race, age, body mass index, and mental health and substance use disorder diagnoses.

KEY RESULTS: In this national sample of 104,984 midlife women Veterans with chronic pain (mean age 54.5, SD 5.4 years), 17% had evidence of menopausal symptoms, 51% were prescribed long-term opioids, 13% were prescribed high-dose long-term opioids, and 35% were co-prescribed long-term opioids and central nervous system depressants. In multivariable analyses, women with menopausal symptoms had increased odds of long-term opioids (OR 1.21, 95% CI 1.18–1.26), high-dose long-term opioids (OR 1.08, 95% CI 1.02–1.13), and long-term opioids co-prescribed with central nervous system depressants (sedative-hypnotics OR 1.25, 95% CI 1.22–1.30; gabapentin/pregabalin OR 1.23, 95% CI 1.20–1.27; muscle relaxants OR 1.24, 95% CI 1.20–1.28).

CONCLUSIONS: Among midlife women Veterans with chronic pain, evidence of menopausal symptoms was associated with potentially risky long-term opioid prescription patterns, independent of known risk factors.

KEY WORDS: women's health; menopause; opioids; chronic pain; Veterans.

INTRODUCTION

Women are disproportionately affected by the ongoing opioid epidemic.[1] This is a particular concern in the Veterans Health Administration (VA),[2] where women Veterans are a growing population with complex care needs, including higher rates of chronic pain, opioid receipt, and mental health comorbidities than their male peers.[3] Across health care settings, women are more likely than men to have chronic pain,[3, 4] to be prescribed opioids,[1, 5, 6] and to have opioid prescription patterns linked to misuse and overdose risk. These include being prescribed opioids at higher doses,[7] for a longer duration,[8] and co-prescribed with central nervous system (CNS) depressants.[1] These patterns are pronounced among women in their 40s, 50s, and into their 60s.[8]

Over the past two decades, the greatest increases in long-term opioid use[1] and opioid-related overdose mortality[8, 9] have been among women in midlife. This may be related to changes in pain experience and pain management over the menopausal transition. Chronic health comorbidities[10] and hormonal changes[11] related to menopause and aging increase risk for chronic pain and pain sensitivity. Common menopausal symptoms, including hot flashes, mood symptoms, and sleep difficulty, may share etiologic mechanisms with and/or exacerbate chronic pain,[10, 12] affecting pain management. Among women with chronic pain treated with opioids, pharmacological

treatment of menopausal symptoms with CNS depressants, including sedative-hypnotics for anxiety and insomnia;[13] gabapentin for mood symptoms,[14] insomnia,[13] and hot flashes and night sweats;[15] and muscle relaxants for arthralgia,[15] may lead to potentially high-risk polypharmacy.[16] Within this vulnerable period, women with chronic pain and menopausal symptoms may be at elevated risk for potentially problematic opioid prescribing patterns.

In this study, we used national VA medical record data from midlife women Veterans with chronic pain, a leading diagnosis within the largest age group of women served by VA,[17] to compare long-term opioid prescription patterns between those with and without menopausal symptoms. We hypothesized that independent of known risk factors, women with menopausal symptoms would have higher odds of being prescribed long-term opioids, high-dose long-term opioid, and co-prescribed CNS depressants.

METHODS

Data Source

Data for this cross-sectional study were drawn from VA administrative data sources: (1) the Decision Support System's National Data Extract of pharmacy data, a comprehensive database of medications dispensed through VA pharmacies, and (2) the VA National Patient Care Database, containing *International Classification of Diseases, Ninth Revision Clinical Modification (ICD-9-CM)* diagnostic codes from electronic medical records generated during clinical visits. The primary analytic cohort includes women Veterans aged 45–64 with chronic non-cancer pain and at least one VA outpatient encounter between January 1, 2014, and December 31, 2015. This age range was selected to be comparable with midlife age categorization in previous studies of opioid prescribing,[1] and to limit assessment to the age range that menopausal symptoms are most commonly reported.[18] Chronic pain was defined by ICD-9 codes indicating the same pain diagnosis category (online appendix) on at least two encounters spanning ≥ 90 days during the observed period, an approach used in prior VA administrative data studies.[19] The study was approved by the institutional review boards of the University of California, San Francisco, and the Research and Development Committee of the San Francisco VA Health Care System.

Variables

Menopausal symptoms were assessed by data abstraction from pharmacy and medical records in 2014–2015. Menopausal symptoms were categorized by (1) menopause-related diagnoses including postmenopausal atrophic vaginitis, specified and unspecified menopausal disorders, and symptomatic menopausal states including hot flashes and sleep difficulty (online appendix) on at least two encounters, or (2) menopausal hormone therapy prescriptions filled at least once during the

observed period, as treatment of menopausal symptoms is the primary indication for this prescription. Since some hormone preparations can be used for other indications (e.g., contraception, gender-affirming hormone therapy), expert clinician review (AH) was used to distinguish oral, transdermal, and vaginal hormone preparations primarily used for menopausal symptoms. While this approach does not capture unreported symptoms, it allows for detection of symptoms that are considered severe enough to warrant discussion, evaluation, documentation, and/or treatment by a health care provider.

Opioid prescriptions were derived from pharmacy records of dispensed medications during 2014–2015. Long-term opioids were defined as prescribed oral opioid medications for ≥ 90 days over the observed period, consistent with past definitions using VA data.[20] Patch formulations and buprenorphine were not included, as these are non-formulary in the VA with use restricted to treatment of cancer/palliative care pain (fentanyl) and opioid use disorder (buprenorphine, oral or patch). High-dose long-term opioids were defined as long-term opioids with a mean morphine equivalent daily dose (MEDD) ≥ 50 mg, calculated from the average dose of all long-term opioid use over the observed period. This threshold was chosen based on dosage risk profiles and VA guideline recommendations.[21] MEDD was also categorized as < 20 mg, 20 to < 50 mg, 50 to < 100 mg, and ≥ 100 mg for descriptive analyses. Long-term opioids co-prescribed with CNS depressants were defined as long-term opioids with a prescription for a ≥ 5-day supply of (1) sedative-hypnotics (benzodiazepines and non-benzodiazepine sedative-hypnotics including alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, flurazepam, lorazepam, oxazepam, temazepam, triazolam, zolpidem, eszopiclone, zaleplon, and ramelteon), (2) gabapentin or pregabalin, or (3) muscle relaxants (baclofen, carisoprodol, cyclobenzaprine, methocarbamol, tizanidine, and metaxalone) overlapping for 1+ day in the observed period. These were chosen as medications commonly prescribed to women in midlife for indications related to menopausal symptoms,[13–15] with known[22] and emerging[23–27] literatures supporting misuse and mortality risk in combination with opioids.

Demographic and health-related covariates were obtained from outpatient medical records during 2014–2015. All covariates were selected a priori due to known relationships with chronic pain management.[3, 20, 28, 29] Age was defined as age on January 1, 2014, based on medical record-documented birth date. Race was categorized as white, black, other, or missing (if not available), based on self-reported race in the medical record. Race categories combined in the "other" category each comprised ≤ 1% of the overall sample. Body mass index (BMI) was identified from physical examination measurements from outpatient encounters, categorized as underweight/normal (< 25), overweight (25–29.9), and obese (30+), or missing if unavailable. Mental health diagnoses (posttraumatic stress disorder, depression, anxiety disorder) and substance use disorders (substance use disorder, alcohol

use disorder) were defined by ICD-9 codes on more than one encounter in the observed period (online appendix).

Statistical Analyses

Descriptive statistics were used to summarize key variables and covariates, including frequencies and percentages for categorical data and means and standard deviations for continuous data. Chi-square analyses were used to examine unadjusted differences in (1) long-term opioid patterns and (2) long-term opioid dosages (restricted to any long-term opioids) between women with and without medical record evidence of menopausal symptoms.

Multivariable logistic regression models were used to examine associations between menopausal symptoms and long-term opioids (referent, no long-term opioids), high-dose long-term opioids (referent, 0–50 mg MEDD), and long-term opioids co-prescribed with CNS depressants (benzodiazepine and non-benzodiazepine sedative-hypnotics, gabapentin/pregabalin, and muscle relaxants; referent, no long-term opioids or long-term opioids without co-prescription). Associations between menopausal symptoms and each outcome were assessed in separate models. All models were adjusted for age, race, BMI, any mental health diagnosis, and any substance use disorder diagnosis. All analyses were performed using SAS 9.4 (SAS Institute Inc., 2013; Cary, NC) and Stata 14 (StataCorp, 2015; College Station, TX).

RESULTS

Characteristics of the Sample

The final analytic sample was comprised of 104,984 midlife women Veterans with chronic pain (mean age 54.5 ± 5.4 years). Overall, the sample was largely white (58%), and overweight (27%) or obese (47%). PTSD was documented for 23% of women in the sample; 17% had depression, 20% had an anxiety disorder, and 11% had an alcohol or substance use disorder. Evidence of menopausal symptoms in the medical record was observed for 17% of women. Over half of all women in the sample were prescribed long-term opioids, and one in ten women in the sample was prescribed long-term opioids ≥ 50 mg MEDD. Among all women in the sample, over a third received long-term opioids were co-prescribed with a CNS depressant (Table 1). Although not examined as an outcome, co-prescription with multiple CNS depressants was also common (i.e., 22% co-prescribed opioids, sedative-hypnotics, and gabapentin/pregabalin; data not shown).

Menopausal Symptoms and Long-term Opioids

In unadjusted analyses, evidence of menopausal symptoms was more prevalent in women with all higher risk opioid prescribing patterns (data not shown). Among women prescribed long-term opioids, those with medical record evidence of menopausal symptoms were more likely to be prescribed $\geq$ 100 mg MEDD (Fig. 1).

In multivariable analyses adjusted for age, race, BMI, and mental health and substance use disorder diagnoses, women with evidence of menopausal symptoms had increased odds of long-term opioids (vs. no long-term opioids), high-dose long-term opioids (vs. 0–49 MEDD), and long-term opioids co-prescribed with CNS depressants (vs. no opioids or long-term opioids with no co-prescribed CNS depressants). Women also had increased odds of long-term opioids and long-term opioids co-prescribed with CNS depressants if they were older, were black, were overweight or obese, or had mental health and substance use disorders. Age, mental health, and substance use disorders were also associated with increased odds of high-dose long-term opioids (Table 2).

DISCUSSION

In this national sample of midlife women Veterans with chronic pain, we examined associations between long-term opioid prescription patterns and evidence of menopausal symptoms. One in two women was prescribed long-term opioids, one in ten was prescribed high-dose long-term opioids, and one in three were co-prescribed long-term opioids and CNS depressants at some point during the 2-year observed period. Independent of established demographic and clinical risk factors, the odds of each of these potentially high-risk prescription patterns were up to 25% higher among women with menopausal symptoms.

These novel findings suggest that menopausal symptoms may be related to problematic opioid prescribing among women in midlife with chronic pain, a population with dramatically increasing rates of opioid use[1] and opioid-related overdose mortality.[8, 9] Although menopause affects pain experience in midlife,[10, 30, 31] the role of menopausal symptoms in chronic pain management has not been previously examined. To our knowledge, this study is the first to identify associations between indicators of menopausal symptoms and long-term and high-dose long-term opioid prescription patterns, which may be explained by multiple pathways. Long-term opioid use may lower estrogen levels, potentially precipitating or exacerbating menopausal symptoms.[32] Menopausal symptoms perceived as bothersome may reflect general somatic symptom sensitivity,[33] influencing treatment-seeking and treatment decisions for both pain and menopausal symptoms. Common correlates of menopausal symptoms, including physical and mental health comorbidities[33, 34] and health risk behaviors such as limited physical activity,[35, 36] also present known challenges to pain management[29, 37, 38] that may influence provider decisions to prescribe long-term and high-dose long-term opioids.

Of note, mental health conditions related to menopausal symptoms[33] have been linked to higher rates of opioid receipt and long-term use.[29, 39] Opioid use may attenuate emotional

Table 1 Characteristics of 104,984 Midlife Women Veterans with Chronic Pain Diagnoses

Long-term opioids				Any long-term opioids + CNS depressants[‡]		
	No long-term opioids (n = 51,921, 49.5%)	Any long-term opioids* (n = 53,063, 50.5%)	Long-term opioids ≥ 50 mg MEDD[†] (n = 13,858, 13.2%)	Long-term opioids + sedative-hypnotics (n = 33,147, 31.6%)	Long-term opioids + gabapentin/ pregabalin (n = 33,349, 31.8%)	Long-term opioids + muscle relaxants (n = 42,265, 40.3%)
Menopausal symptoms	7944 (15.3%)	9693 (18.3%)	2753 (19.9%)	6670 (20.1%)	6471 (19.4%)	7985 (18.9%)
Age, in years (mean, SD)	54.3 (5.4)	54.7 (5.3)	55.1 (5.2)	54.7 (5.3)	54.7 (5.3)	54.6 (5.3)
Race						
White	30,295 (58.4%)	30,307 (57.1%)	8910 (64.3%)	20,186 (60.9%)	19,400 (58.2%)	23,904 (56.6%)
Black	16,744 (32.3%)	18,579 (35.0%)	3859 (27.9%)	10,417 (31.4%)	11,439 (34.3%)	15,094 (35.7%)
Other	2009 (3.9%)	1867 (3.5%)	532 (3.8%)	1143 (3.5%)	1150 (3.5%)	1468 (3.5%)
Body mass index (kg/m^2)						
Underweight/ normal (<25)	9699 (18.7%)	8778 (16.5%)	2739 (19.8%)	5789 (17.5%)	5502 (16.5%)	6881 (16.3%)
Overweight (25–29.9)	14,145 (27.2%)	13,735 (25.9%)	3646 (26.3%)	8713 (26.3%)	8639 (25.9%)	10,993 (26.0%)
Obese (30+)	22,969 (44.2%)	26,250 (49.5%)	6551 (47.3%)	16,098 (48.6%)	16,699 (50.1%)	21,059 (49.8%)
Mental health diagnoses						
Depression	6719 (12.9%)	10,832 (20.4%)	3567 (25.7%)	8730 (26.3%)	8007 (24.0%)	9253 (21.9%)
Anxiety	8921 (17.2%)	11,964 (22.6%)	3779 (27.3%)	9692 (29.2%)	8450 (25.3%)	10,039 (23.8%)
Posttraumatic stress disorder	9862 (19.0%)	14,502 (27.3%)	4751 (34.3%)	11,711 (35.3%)	10,410 (31.2%)	12,246 (29.0%)
Alcohol use disorder	2285 (4.4%)	3486 (6.6%)	1094 (7.9%)	2547 (7.7%)	2527 (7.6%)	2865 (6.8%)
Substance use disorder	1621 (3.1%)	3803 (7.2%)	1653 (11.9%)	2956 (8.9%)	2980 (8.9%)	3290 (7.8%)

All opioid and CNS depressant prescriptions dispensed during observed period, 2014 and 2015
MEDD, morphine equivalent daily dose
Data not shown: race (n = 5183), body mass index (n = 9408) categorized as missing
Prescribed oral opioid medications for ≥ 90 days
[†]*Average dose of all long-term opioids ≥ 50 mg morphine equivalent daily dose (MEDD)*
[‡]*Long-term opioids and overlapping prescription (≥ 1 day) of CNS depressants (> 5-day supply)*

distress by dampening neural activity in the limbic system and related structures that process both emotional and physical pain,[40] which may explain increased use among women with
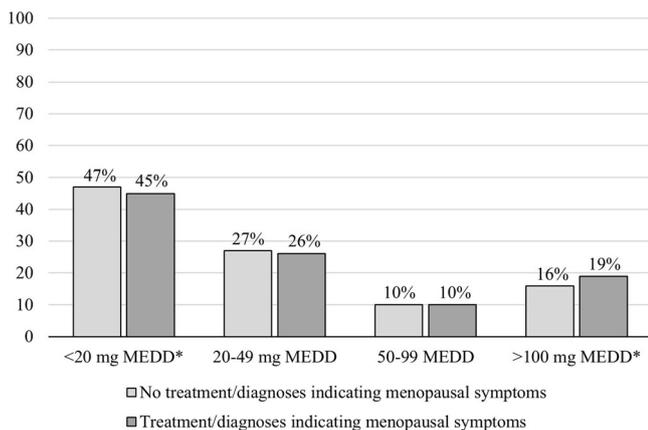
Figure 1 Mean morphine equivalent dose (MEDD) categories among women Veterans with chronic pain prescribed long-term opioids (n = 53,063). MEDD calculated as average dose of all long-term opioids over observed period. Among women with any long-term opioids during observed period, chi-square analyses were used to compare unadjusted prevalence rates of long-term opioids between women with and without evidence of menopausal symptoms. p < .001 for overall comparisons across dosage categories; *p < .001 for comparisons within dosage categories.

mental health comorbidities.[39] Although opioids have not been studied, recommended, or FDA-approved for these indications, these findings suggest that long-term and high-dose opioids may be inadvertently prescribed to manage inadequately treated menopausal symptoms among midlife women with chronic pain.

Among midlife women with chronic pain treated with opioids, concurrent treatment of menopausal symptoms may contribute to potentially high-risk polypharmacy. In this study, women with menopausal symptoms were more likely to be co-prescribed long-term opioids with CNS depressants, including benzodiazepine and non-benzodiazepine sedative-hypnotics, gabapentin/pregabalin, and muscle relaxants. Although the intended indications for these prescriptions cannot be verified with these data, these co-prescribed medications are commonly used for menopause-related indications.[15, 41, 42] Specifically, sedative-hypnotics are often prescribed for anxiety and/or sleep difficulties, common in the peri- and postmenopause,[42] and muscle relaxants are used to treat menopausal arthralgia.[41] Similarly, gabapentin/pregabalin is prescribed for neuropathic pain and fibromyalgia,[43] common among women in midlife, and increasingly prescribed off-label for mood symptoms, sleep difficulty,[14] and menopausal hot flashes and night sweats.[15, 44] Each of these medications have abuse potential,[24,

Table 2 Adjusted Odds of Opioid Prescription Patterns by Menopausal Symptoms

	Long-term opioids		Long-term opioids + CNS depressants ¶		
	Any long-term opioids[§] OR (95% CI)	Long-term opioids ≥ 50 mg MEDD[‖] OR (95% CI)	+Sedative-hypnotics OR (95% CI)	+Gabapentin/ pregabalin OR (95% CI)	+Muscle relaxants OR (95% CI)
Menopausal symptoms	1.21 (1.18–1.26)	1.08 (1.02–1.13)*	1.25 (1.22–1.30)	1.23 (1.22–1.30)	1.24 (1.20–1.28)
Age	1.02 (1.01–1.02)	1.02 (1.01–1.02)	1.01 (1.01–1.02)	1.01 (1.01–1.02)	1.01 (1.00–1.02)
Race					
White	Referent	Referent	Referent	Referent	Referent
Black	1.14 (1.11–1.17)	0.67 (0.64–0.70)	1.03 (1.02–1.06)**	1.11 (1.08–1.13)	1.16 (1.13–1.19)
Other	0.94 (0.88–1.01)	0.97 (0.87–1.08)	0.90 (0.85–0.96)**	0.93 (0.87–0.99)[†]	0.95 (0.89–1.01)[††]
Body mass index					
Underweight/normal (< 25)	Referent	Referent	Referent	Referent	Referent
Overweight (25–29.9)	1.09 (1.05–1.13)	0.86 (0.81–0.91)	1.07 (1.03–1.11)	1.09 (1.06–1.13)	1.10 (1.06–1.14)
Obese (30+)	1.30 (1.25–1.34)	0.82 (0.78–0.87)	1.24 (1.20–1.28)	1.29 (1.25–1.34)	1.29 (1.25–1.34)
Any mental health diagnosis	1.64 (1.60–1.69)	1.61 (1.55–1.68)	2.10 (2.05–2.15)	1.78 (1.73–1.82)	1.71 (1.67–1.75)
Substance/alcohol use disorder	1.59 (1.52–1.67)	1.60 (1.51–1.70)	1.60 (1.53–1.67)	1.68 (1.60–1.75)	1.56 (1.49–1.63)

MEDD, morphine equivalent daily dose
All models adjusted for age, race, body mass index, any mental health diagnosis, and substance/alcohol use disorder
Any mental health diagnosis includes depressive disorders, anxiety disorders, and/or posttraumatic stress disorder
Data not shown: race, body mass index categorized as missing
*p = .004, *p = .01, †p = .02, ‡p = .08; all other values shown significant at p < .001
[§]*Referent: no long-term opioids*
[‖]*Referent: < 50 mg MEDD (including no opioids)*
[¶]*Referent: no long-term opioids or long-term opioids without co-prescribed CNS depressants*

[41, 42] particularly when used concomitantly with opioids,[45] and contribute to opioid-related mortality.[26, 46] These findings extend past research demonstrating higher rates of co-prescribed opioids and sedative-hypnotics in women,[1] identifying a gender-specific risk factor for co-prescription and highlighting other understudied but potentially high-risk combinations in this population.

These findings have important clinical implications. The long-term opioid prescription patterns associated with menopausal symptoms in this study can contribute to risk for opioid misuse, opioid-related overdose mortality, and other adverse health outcomes. Observed odds were independent from those of previously identified risk factors, including comorbid mental health and substance use disorder diagnoses.[29, 47] Risk of developing opioid use disorder[48] and risk for opioid overdose[49] are elevated with long-term use and higher doses, and dramatically increased when opioids are co-prescribed with CNS depressants.[49] When co-prescribed with CNS depressants, opioids are often prescribed for a longer duration and at higher doses than when prescribed alone.[49] Misuse, dependence, and disability related to sedative-hypnotics independent of opioid use have been well-documented,[42] and benzodiazepines are implicated in 30% of opioid-related overdose deaths.[49] A growing literature also describes the abuse potential of gabapentin[23] and muscle relaxants,[41] with misuse of each increased in the context of comorbid opioid use.[23, 41, 46] While patient behaviors cannot be determined from this data, these findings suggest provider-driven treatment decisions that may contribute to risk for misuse, disability, and overdose, even when medications are taken as prescribed.

The clinical risks related to these long-term opioid prescription patterns may be particularly high for midlife and older women with chronic pain. Long-term opioid use with and without co-prescribed CNS depressants augments risk for primary health concerns in aging populations, including cognitive impairment,[48, 50] fracture risk,[48, 50] physical dependence,[51] and poor health outcomes.[52] Additionally, common aging-related chronic health conditions, such as obstructive sleep apnea, increase risk for overdose mortality.[50] Even among women with a seemingly acceptable safety profile in midlife, the long-term nature of opioid prescribing for chronic pain may result in increasing risk for adverse health outcomes and opioid-related misuse and overdose with age.

Racial differences in prescribing may further augment these relationships among black women, who had greater odds of being prescribed long-term opioids both alone and co-prescribed with CNS depressants than white women in this study. This finding contradicts past reports of higher opioid prescribing among whites relative to racial/ethnic minorities.[28, 53, 54] However, racial differences in prescribing by gender may not have been observed in the absence of gender-stratified or gender-specific samples, frequently drawn from largely male populations such as the VA.[53, 54] Further, some research suggests that racial differences in prescribing patterns may be reversed in older adults,[28] which may be reflected in this sample.

These findings should be interpreted with caution. Longitudinal trends including the duration of hormone therapy, menopausal diagnoses, or opioid receipt, as well as temporal relationships between them, cannot be determined with these cross-sectional data. Given the large sample size, small differences that may not be clinically significant may be statistically significant. This study uses data from midlife women Veterans who use VA healthcare, a population at elevated risk for

chronic pain and long-term opioid use with high rates of medical and mental health comorbidities.[17] Results may not be generalizable to women Veterans who do not use VA healthcare, or to women in the general population. We cannot confirm the validity or chronicity of diagnoses in the medical record. Reliance on ICD-9-CM codes likely underrepresents diagnoses related to menopausal symptoms, which may be infrequently discussed and/or documented in VA settings. Although hormone therapy also served as a proxy for menopausal symptoms, only a fraction of symptomatic women use hormone therapy.[15] Women with documented menopausal symptoms may differ in their willingness to discuss sensitive, often stigmatized, symptoms with their providers. These patient characteristics may also lead to increased reporting of symptoms related to chronic pain, and subsequent receipt of opioids to treat chronic pain.

Pharmacy data was limited to VA records, and we cannot account for non-VA prescriptions. We can only ascertain prescription patterns based on dispensed medications, not actual use or misuse of those medications. Finally, the VA implemented opioid safety initiatives in 2013, and national changes in opioid prescribing have been observed since that time.[55] We are unable to describe or account for any changes that may have occurred since 2015. Of note, VA opioid safety initiatives have not focused on women, and gender-specific changes in prescribing patterns since their implementation have not been examined.

Despite these limitations, this study has multiple strengths. To our knowledge, this is the first study to examine menopausal symptoms in relation to long-term opioids in midlife women, a population with increasing rates of opioid use[1] and opioid-related overdose mortality.[8, 9] We examined a large, diverse, nationally representative sample of midlife women Veterans who utilize VA care, and accounted for a wide range of demographic and clinical factors to assess for independent relationships and limit confounding. We characterized varied long-term opioid prescription patterns among patients with chronic pain, defined by electronic medical record and pharmacy data to enhance diagnostic validity. Despite inherent limitations, the use of this real-world data allows for examination of menopausal symptoms and chronic pain treatment as documented and managed within a large, integrated health care system. These findings identify a novel indicator for potentially problematic opioid prescription patterns within a high-risk period in the lifespan, which may help to inform interventions to improve comprehensive care for women with chronic pain.

CONCLUSIONS

Among midlife women Veterans with chronic pain, those with evidence of menopausal symptoms had increased odds of long-term opioids, high-dose long-term opioids, and long-term opioids co-prescribed with CNS depressants,

independent of known demographic and clinical risk factors. Although rates of opioid use[1] and opioid-related mortality[8] have risen dramatically among midlife women over the past two decades, drivers of increased risk in this vulnerable population had not been previously identified. These findings raise the possibility that menopausal symptoms are an under-recognized indicator of risk among midlife women with chronic pain, influencing treatment decisions that enhance risk for opioid-related disability and mortality. Safe and effective comprehensive care for midlife women with chronic pain should include recognition of the potential role of menopause in pain experience and management, and the possibility that pharmacological treatments for menopausal symptoms may inadvertently put women with chronic pain treated with long-term opioids at increased risk for opioid misuse and overdose.

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Compliance with Ethical Standards:

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