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Menopause symptoms and chronic pain in a national sample of midlife women veterans

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Abstract

Objective: Women are more likely than men to suffer chronic pain, with the highest rates seen in midlife. The symptoms that characterize menopause broadly affect health and well-being, but their contribution to chronic pain risk during this period is poorly understood. To address this gap in knowledge, we examined relationships between indicators of menopause symptoms and chronic pain among midlife women veterans, a population with prevalent chronic pain diagnoses and elevated risk for bothersome menopause symptoms.

Methods: This is a cross-sectional analysis of national Veterans Health Administration medical and pharmacy records. Using national medical and pharmacy records from women veterans aged 45 to 64 with at least one VA encounter during 2014 and/or 2015 (n = 200,901), we developed multivariable logistic regression models to examine associations between menopause symptoms (defined by menopause symptom-related diagnoses on ≥2 encounters and/or menopause hormone therapy use) and chronic pain outcomes, adjusting for age, race, body mass index, mental health diagnoses, and substance use disorders.

Results: In this national sample of midlife women veterans (mean age 54.3 ± 5.4), 26% had menopause symptoms, 52% had chronic pain, and 22% had ≥2 distinct chronic pain diagnoses. In multivariable analyses, women with menopause symptoms had nearly two-fold odds of chronic pain (odds ratio 1.89, 95% confidence interval 1.85-1.94, $P < 0.001$) and multiple chronic pain diagnoses (odds ratio 1.86, 95% confidence interval 1.83-1.90).

Conclusions: These findings raise the possibility within this vulnerable critical period, midlife women with a higher menopause symptom burden may be most vulnerable for chronic pain.

Key Words: Chronic pain – Menopause symptoms – Veterans.

Women are disproportionately affected by chronic pain.[1] Not only are women more likely than men to report common chronic pain conditions, including back pain, fibromyalgia, arthritis, and osteoarthritis,[2] but women with these conditions also report greater pain severity and pain-related disability than their male counterparts.[1] Although chronic pain contributes to morbidity and disability across the lifespan, risk for common conditions that cause or exacerbate pain is highest among women in midlife.[2]

The etiology underlying chronic pain risk among women in midlife is not well understood. Biological and behavioral changes related to the menopause transition broadly affect health and well-being in midlife and may play a role in the experience of chronic pain. Estrogen and other reproductive hormones have complex interactions with pain modulation and pain sensitivity,[3] and the characteristic fluctuations and decline in estrogen in perimenopause and into postmenopause may influence vulnerability to the development and exacerbation of pain conditions during this period. Hormonal changes, along with age-related declines in health and health behaviors, affect health and symptom experience in midlife. Common changes related to menopause and aging include weight gain and decreased physical activity, which may further contribute to chronic pain morbidity, and impaired sleep and negative mood, which are known to affect symptom sensitivity and pain tolerance.[4,5] These factors all influence the experience of other somatic symptoms related to

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menopause and aging common in midlife and beyond, including hot flashes, night sweats,[6] and genitourinary symptoms.[7]

Although hormonal changes are universal for women traversing the menopause transition, the symptom experience of women during and after this period is highly variable. Between 25% and 50% of women never experience menopause symptoms,[8] whereas others experience menopause symptoms for years or even decades leading up to and after menopause.[9,10] Among women who do report menopause symptoms, the frequency, severity, and duration of these symptoms, and the bother attributed to them, varies widely.[6] A minority of women report that these symptoms significantly impair quality of life and daily functioning, and only a fraction of those seek treatment for them.[8,11] In addition to hormonal changes and aging, the factors that predict not only having menopause symptoms, but finding them particularly bothersome, include comorbid health conditions, health risk behaviors, and negative mood symptoms,[6] which are also shared risk factors for chronic pain.[12] Therefore, within this critical period, women with a higher menopause symptom burden may be most vulnerable for chronic pain.

In this study, we examined associations between evidence of menopause symptoms in the medical record and chronic pain within a large national sample of midlife women who receive care in the Veterans Health Administration (VA) health care system. This population has a high rate of mental health and medical comorbidities,[13,14] and prevalent risk factors that may contribute to both menopause symptoms and a high prevalence of chronic pain complaints.[15-20] We anticipated that those women who have a generally high menopause symptom burden in midlife will also be at greatest risk for chronic pain. Therefore, we hypothesized that even after accounting for age and other known risk factors, treatment and diagnoses indicating menopause symptoms would be associated with increased odds of diagnosed chronic pain and chronic pain multimorbidity.

METHODS

Data source

Data for this cross-sectional study were drawn from VA administrative data sources, including the Decision Support System's National Data Extract of pharmacy data, a comprehensive database of medications dispensed through VA pharmacies, and the VA National Patient Care Database, which contains VA visit dates and associated *International Classification of Diseases, Ninth Revision Clinical Modification (ICD-9-CM)* diagnostic codes derived from electronic medical records generated during clinical visits. For this study, a primary analytic sample of women Veterans aged 45 to 64 with at least one outpatient VA encounter in 2014 and/or 2015 was created. This age range was selected to be comparable with midlife age categorization in reported rates of chronic pain and other comorbidities from national VA data,[14] and to limit assessment to the age range that menopause symptoms are most commonly reported.[21] 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

Menopause symptoms were assessed by data abstraction from pharmacy and medical records in 2014 and 2015. Patients were categorized with menopause symptoms if they had menopause-related diagnoses (see Appendix, Supplemental Digital Content 1, http://links.lww.com/MENO/A399, which details the diagnoses and ICD-9-CM codes used to categorize menopause symptoms and chronic pain) indicating treatment seeking for menopause symptoms on at least two encounters, or prescribed menopausal hormone therapy on at least one encounter, as treatment of menopause symptoms is the primary indication for this prescription. Because some hormone preparations can be used for other indications (eg, contraception, sex-affirming hormone therapy), expert clinician review (A.J.H.) was used to distinguish oral, transdermal, and vaginal hormone preparations primarily used for menopause symptoms. Although 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 healthcare provider. Menopause-related diagnoses and hormone therapy use were also categorized separately for descriptive and exploratory analyses.

Chronic pain was defined as the presence of ICD-9-CM codes (see Appendix, Supplemental Digital Content 1, http://links.lww.com/MENO/A399, which details the diagnoses and ICD-9-CM codes used to categorize menopause symptoms and chronic pain) indicating the same pain diagnosis category on two or more outpatient encounters spanning at least 90 days in the observed period. This approach has been used in prior studies using administrative data to detect chronic pain, which have documented associations between chronic pain, traumatic brain injury, and mental health comorbidities.[22] Chronic pain multimorbidity was defined as chronic pain criteria met for two or more unique pain diagnoses during the observed period.

Demographic and health-related covariates were obtained from outpatient medical records during 2014 and 2015. All covariates were selected a priori due to known relationships with chronic pain.[23] Age (continuous) was defined as age on January 1, 2014, based on the birth date documented in the medical record. Race was categorized as white, black, other, or missing, based on self-reported race documented in the medical record. Race categories combined in the ''other'' category each comprised $\leq$1% of the overall sample. Body mass index (BMI) was identified from physical examination measurements from each patient's first documented outpatient encounter and categorized as underweight/normal (<25), overweight (25-29.9), and obese (30+), or missing if no BMI was available. Mental health comorbidities were defined as the presence of ICD-9 codes indicating depressive disorder, anxiety disorder, and/or posttraumatic stress disorder on more than one encounter in the observed period. These

diagnoses were selected as the most common mental health diagnoses among women veterans, with known associations with chronic pain.[24] Substance use disorders were defined as the presence of ICD-9 codes indicating alcohol use disorder and/or substance use disorder on more than one encounter in the observed period.

Statistical analyses

Descriptive statistics were used to summarize key variables and covariates in the sample, including frequencies and percentages for categorical data and means and standard deviations for continuous data. Separate multivariable logistic regression models were used to examine associations between evidence of menopause symptoms in the medical record and chronic pain, and chronic pain multimorbidity. Additional exploratory analyses were also conducted with evidence of menopause symptoms categorized only by ICD-9 codes to examine potential differences in the pattern of results affected by hormone therapy use. All models were adjusted for age, race, BMI, mental health comorbidities, and substance use disorder diagnoses. All analyses were performed using SAS 9.4 (SAS Institute Inc, 2013, Cary, NC) and Stata 14 (StataCorp, 2015, College Station, TX). Reported P values are two sided, and $P < 0.001$ was considered statistically significant.

RESULTS

Characteristics of the sample

The final analytic sample comprised 200,901 women veterans (mean age 54.3 ± 5.4 years). Overall, the sample was largely white (58%) and overweight (25%) or obese (41%). Posttraumatic stress disorder was the most common mental health diagnosis, documented for 18% of women in the sample; 13% had a depressive disorder diagnosis; 15% had an anxiety diagnosis; 5% had documented alcohol use disorder; and 4% documented substance use disorder. Fifteen percent of women had two or more comorbid mental health diagnoses. The prevalence of overweight/obesity and all mental health diagnoses was higher among women with chronic pain and chronic pain multimorbidity relative to women without chronic pain (Table 1).

Menopause symptoms and chronic pain

Evidence of menopause symptoms in the medical record was observed for 26% of women in the overall sample. More than half (52%) of all women in the sample had chronic pain, and 22% had chronic pain multimorbidity, or multiple distinct chronic pain diagnoses. Relative to women without chronic pain, indicators of menopause symptoms were more prevalent in women with chronic pain and chronic pain multimorbidity (18% vs 33% and 37%, respectively; $P < 0.001$) (Table 1).

In multivariable analyses adjusted for age, race, BMI, mental health comorbidities, and substance use disorder diagnoses, women with medical record–documented evidence of menopause symptoms had higher odds of being diagnosed with chronic pain (odds ratio [OR] 1.89, 95% confidence interval [CI] 1.85-1.94) and chronic pain multimorbidity (OR 1.86, 95% CI 1.83-1.90). Increased odds of both chronic pain and chronic pain multimorbidity were also seen among women who were older, black, overweight, or

TABLE 1. *Characteristics of the sample*

	Total (n = 200,901)	No chronic pain (n = 95,917, 47.7%)	Chronic pain[a] (n = 104,984, 52.3%)	Chronic pain multimorbidity[b] (n = 43,843, 21.8%)
Age (mean, SD)	54.3 (5.4)	54.1 (5.4)	54.5 (5.4)	54.2 (5.3)
VA clinical encounters				
1 in observed period	4,060 (2.0%)	4,060 (4.2%)	0 (0.0%)	0 (0.0%)
>2 in observed period	196,841 (98.0%)	91,857 (95.8%)	104,984 (100.0%)	43,843 (100.0%)
Evidence of menopause symptoms	51,730 (25.8%)	17,510 (18.3%)	34,220 (32.6%)	16,378 (37.4%)
Menopause symptom diagnoses	10,501 (5.2%)	3,210 (3.4%)	7,291 (6.9%)	3,536 (8.1%)
Hormone therapy use	47,951 (23.9%)	16,199 (16.9%)	31,752 (30.2%)	15,272 (34.8%)
Race				
White	116,128 (57.8%)	55,526 (57.9%)	60,602 (57.7%)	25,436 (58.0%)
Black or African American	65,215 (32.5%)	29,892 (31.2%)	35,323 (33.7%)	14,690 (33.5%)
Other	7,420 (3.7%)	3,544 (3.7%)	3,876 (3.7%)	1,678 (3.8%)
Missing	12,138 (6.0%)	6,955 (7.3%)	5,183 (4.9%)	2,039 (4.7%)
Body mass index				
Underweight/normal (<25)	34,583 (17.2%)	16,106 (16.8%)	18,477 (17.6%)	7,590 (17.3%)
Overweight (25-29.9)	49,622 (24.7%)	21,742 (22.7%)	27,880 (26.6%)	11,890 (27.1%)
Obese (30+)	81,907 (40.8%)	32,688 (34.1%)	49,219 (46.9%)	21,249 (48.5%)
Missing	34,789 (17.3%)	25,381 (26.5%)	9,408 (9.0%)	3,114 (7.1%)
Mental health diagnoses				
Anxiety	30,783 (15.3%)	9,898 (10.3%)	20,885 (19.9%)	10,882 (24.8%)
Depression	25,262 (12.6%)	7,711 (8.0%)	17,551 (16.7%)	9,536 (21.8%)
PTSD	35,132 (17.5%)	10,768 (11.2%)	24,364 (23.2%)	13,223 (30.2%)
Alcohol use disorder	9,398 (4.7%)	3,627 (3.8%)	5,771 (5.5%)	2,630 (6.0%)
Substance use disorder	7,902 (3.9%)	2,478 (2.6%)	5,424 (5.2%)	2,837 (6.5%)

PTSD, posttraumatic stress disorder; SD, standard deviation.

[a]Chronic pain was defined as the presence of ICD-9 codes indicating the same or similar pain diagnosis category on ≥2 encounters spanning at least 90 days in 2014 and/or 2015.

[b]Chronic pain multimorbidity was defined as chronic pain criteria met for ≥2 unique pain diagnoses in 2014 and/or 2015.

TABLE 2. *Results of multivariable regression models: associations between chronic pain, evidence of menopause symptoms in the medical record, and sample characteristics*

	Chronic pain[a] OR, 95% CI	Chronic pain multimorbidity[b] OR, 95% CI
Evidence of menopause symptoms	1.89 (1.85-1.94)[c]	1.86 (1.83-1.90)[c]
Age	1.01 (1.01-1.01)[c]	1.01 (1.00-1.01)[c]
Race		
White	Referent	Referent
Black or African American	1.12 (1.09-1.14)[c]	1.09 (1.07-1.11)[c]
Other	1.02 (0.97-1.07)	1.03 (0.99-1.08)
Body mass index[d]		
Underweight/normal (<25)	Referent	Referent
Overweight (25-29.9)	1.12 (1.09-1.16)[c]	1.13 (1.10-1.16)[c]
Obese (30+)	1.33 (1.30-1.37)[c]	1.31 (1.27-1.34)[c]
Any mental health diagnosis	2.19 (2.14-2.23)[c]	2.33 (2.28-2.37)[c]
Alcohol or substance use disorder	1.13 (1.09-1.18)[c]	1.12 (1.08-1.16)[c]

CI, confidence interval; OR, odds ratio.
[a]Referent: no chronic pain.
[b]Referent: 0-1 chronic pain diagnoses.
[c]$P < 0.001$.
[d]Data not shown: missing body mass index (n = 34,789).

obese, and those with mental health comorbidities and substance use disorder diagnoses. Increased odds of chronic pain and chronic pain multimorbidity related to menopause symptoms were less than those related to mental health diagnoses, but significantly greater than all other known risk factors assessed (Table 2). In exploratory analyses, the association between menopause symptoms as defined solely by diagnostic codes and chronic pain was equivalent (OR 1.90, 95% CI 1.82-1.99), and the association between menopause symptoms and chronic pain multimorbidity remained significant but attenuated (OR 1.33, 95% CI 1.27-1.40) (data not shown).

DISCUSSION

In this study, we used national VA medical record data to examine the association between evidence of menopause symptoms in the medical record and chronic pain among midlife women Veterans. Independent of established risk factors, women with evidence of menopause symptoms had almost two-fold increased odds of being diagnosed with both chronic pain and multiple distinct chronic pain conditions.

Although a causal explanation cannot be established from these data, these findings add to a limited literature suggesting a relationship between menopause and chronic pain among women in midlife. Previous studies have demonstrated links between menopause status and self-reported chronic pain diagnoses and symptoms, highlighting the potential role of menopause-related hormonal change in chronic pain experience. In a large longitudinal cohort of women with rheumatoid arthritis, menopause had a detrimental impact on the level and rate of functional decline over time.[25] Other epidemiological studies have identified increased risk of onset and worsening symptoms for fibromyalgia related to natural[26] and surgical[27] menopause, with earlier age at menopause linked to higher fibromyalgia-related pain interference.[28] In addition, self-reported arthralgias,[29] general bodily pain,[30] and multiple pain conditions[31] worsened following menopause and over the years of the menopause transition[30,31] in several retrospective and longitudinal cohort studies. The current study is novel in examining chronic pain diagnoses verified by medical record documentation rather than self-report, and evidence of menopause symptoms rather than menopause status among women in the age range typically encompassing the menopause transition.

The posited role of menopause in chronic pain has traditionally centered on the hormonal changes inherent to the peri- and postmenopause. Our findings suggest that during this vulnerable period, menopause symptom burden may also be related to chronic pain experience, which may be explained by multiple pathways. Menopause symptoms perceived as bothersome may reflect general somatic symptom sensitivity,[6] influencing symptom tolerance, symptom experience, and treatment-seeking for both menopause symptoms and chronic pain. Chronic pain and pharmacological chronic pain management may also exacerbate menopause symptoms.[12] Both chronic pain and menopause symptoms are strongly and consistently associated with psychosocial factors and health risk behaviors prevalent in and after the menopause transition. These include sleep difficulty,[6] physical and mental health comorbidities,[6,32] and health risk behaviors such as limited physical activity,[7,33] which may underlie or exacerbate both menopause symptoms and chronic pain experience.[4,12,34,35] We, however, accounted for several of these factors that were common in this population, including mental health comorbidity and overweight/obesity, and the strong and independent association between menopause symptoms and chronic pain remained.

These findings should be interpreted in light of several limitations. Although several established risk factors for chronic pain were included in analyses, observed relationships may be due in part to unmeasured confounders. Longitudinal trends such as the duration or chronicity of menopause symptoms and chronic pain cannot be determined with these cross-sectional data. In addition, the temporal relationship between menopause symptoms and chronic pain is unknown; it remains unclear whether menopause symptoms contribute to chronic pain, chronic pain contributes to menopause symptom burden and/or reporting, or whether shared etiology underlies both experiences. We also cannot determine menopause status, or if observed chronic pain diagnoses were present before and/or worsened over the menopause transition. This study was drawn from midlife women veterans who use VA health care, who have prevalent risk factors for menopause symptoms and high rates of chronic pain diagnoses; results may not be generalizable to the larger population of women veteran who do not use VA care, or to midlife women in the general population. Reliance on ICD-9 codes likely underrepresents diagnoses and experiences, particularly those related to menopause which may be infrequently discussed and/or documented in the VA setting. Women who use hormone therapy and/or have documented menopause-related diagnoses may be particularly proactive patients willing to discuss sensitive and often stigmatized

symptoms with their providers, which may also contribute to increased reporting of symptoms related to chronic pain diagnoses. Some factors related to both chronic pain and menopause that may have influenced the observed relationships, such as sleep disturbance, could not be accounted for due to limited documentation in VA medical records.[36]

Despite these limitations, this study has multiple strengths. These include the use of a large, diverse, nationally representative sample of midlife and older women Veterans, an understudied population at elevated risk for chronic pain conditions. We accounted for a range of demographic and clinical factors to assess for independent relationships and limit effects of confounding. We used an established measure of chronic pain[22] and a novel approach to characterize varied aspects of menopause symptom experience, defined by electronic medical record data to enhance the reliability of diagnoses examined in this study. Despite inherent limitations, the use of this real-world data allows for examination of indicators of menopause symptoms and chronic pain diagnoses as documented and managed within a large, integrated health care system. These findings may inform comprehensive gender-sensitive care both within and outside of VA settings.

These findings have important clinical considerations. Chronic pain is a common and often debilitating diagnosis among women in midlife, contributing to morbidity and disability during this vulnerable period in the trajectory of aging. Understanding health factors related to chronic pain, and the health-related context in which they occur, is essential for providing adequate, effective, and comprehensive care. In the current study, evidence of menopause symptoms in the medical record was strongly and independently associated with chronic pain, meriting assessment in the clinical setting. The magnitude of the relationship between menopause symptoms and chronic pain was significantly larger than the modest associations seen with known risk factors including older age and higher BMI, and approached that of mental health comorbidities known to influence both menopause and pain experience. Menopause symptoms can be chronic and progressive, representing potentially long-lasting and under-recognized factors that may influence chronic pain experience and care among midlife and older women. The menopause transition may be seen as a period of opportunity to anticipate changes in pain experience and plan for comprehensive assessment and treatment, particularly among women who present with a high menopause symptom burden or elevated risks for these concerns. Consideration should be given to integrated approaches to comprehensive care for midlife and older women with chronic pain, such as targeted cognitive behavioral therapy coordinated with interdisciplinary care providers. Integrated practices may help to mitigate both menopause symptoms[37] and chronic pain.[38]

CONCLUSIONS

Among midlife women veteran VA users, evidence of menopause symptoms in the medical record were associated with an almost two-fold increased odds of chronic pain and chronic pain multimorbidity, independent of age, mental health status, and other known risk factors. These findings raise important questions about the relationships between menopause symptoms and chronic pain among women in midlife.

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