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Depressive Symptoms and Menopausal Burden in the Midlife

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Abstract

Objective—The goal of this study was to assess whether menopausal symptoms were more common and/or more severe among women with depressive symptoms.

Methods—A cross-sectional survey of 1,358 women, ages 45–70, at 2 large integrated health plans (Seattle; Boston) was performed. Information on demographics, medical and reproductive history, medication use, menopausal experience and depressive symptoms (PHQ-8) were collected. Women taking HT were excluded. Logistic regression models adjusted for age and body mass index tested the associations between menopausal symptoms (hot flashes, night sweats, vaginal dryness and dyspareunia) and presence of moderate/severe depressive symptoms.

Results—770 women were included; 98 (12.7%) had moderate/severe depressive symptoms and 672 (87.3%) had no/mild depressive symptoms. Women with moderate/severe depressive symptoms were almost twice as likely to report recent vasomotor symptoms (hot flashes and or night sweats) versus women with no/mild depressive symptoms (adjusted odds ratio (aOR) 1.67, 95% CI 1.04–2.68), and to report them as severe (aOR 1.63, 95%CI 0.95–2.83). A higher symptom burden was observed despite the fact that 20% of women with moderate/severe depressive symptoms (vs. 4.6% no/mild depressive symptoms) were using an SSRI or SNRI, medications known to improve vasomotor symptoms. The percentage of women with menopausal symptoms, and the percentage with severe vasomotor symptoms were linearly associated with the depressive symptom score.

Conclusions—Depressive symptoms “amplified” the menopausal experience, or alternatively, severe vasomotor symptoms worsened depressive symptoms.

Keywords

hot flashes; night sweats; vaginal dryness; dyspareunia and depressive symptoms

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INTRODUCTION

Women are at a two-fold greater risk for developing depression as compared to men.^{1,2} Six recent longitudinal studies have documented an increased risk of depressive symptoms during the menopausal transition.^{3,4–8} Two of these were prospective cohort studies^{5,9} and on the basis of these two studies it can be estimated that 26–33% of women will develop a first episode of depression during the menopausal transition, especially when concurrent with negative life experiences.

Some studies have supported an association between hot flashes and depression^{7,8;10;11} while others have not.^{3,9} However, to our knowledge, prior studies have not examined whether the severity of depressive symptoms is associated with severity of menopausal symptoms. Across a wide range of chronic medical illnesses, patients with comorbid depression and/or anxiety have reported more symptoms and more functional impairment than patients with medical illness alone even when controlling for severity of illness.¹² For example, among patients with diabetes and among patients with inflammatory bowel disease, those with anxiety and depression had significantly more disease-related symptoms and functional impairment than did patients with no psychiatric illness after adjustment for severity of inflammatory bowel disease¹³ or diabetes,¹⁴ respectively.

We performed a large cross-sectional population-based study of midlife women. Our objective was to assess whether menopausal symptoms were more common and/or more severe among women with self-reported depressive symptoms. We hypothesized that there would be a significant association between depressive symptoms and menopausal symptom burden.

METHODS

Study Design and Setting

The primary purpose of the QUEST study¹⁵ was to gather information related to HT discontinuation. It was a computer-assisted telephone survey that included demographic data, HT attitudes, detailed experiences with HT discontinuation, and factors that might affect the ability to discontinue HT including decisional conflict, symptom severity, symptom distress, as well as depressive symptoms. The study was conducted at Group Health (GH) and Harvard Pilgrim Health Care (HPHC). Group Health is an integrated health plan in Washington State, with approximately 530,000 enrollees, including more than 88,000 women aged 50–80 years. Harvard Pilgrim Health Care is one of the largest HMOs in New England, with more than 900,000 members. The Institutional Review Boards at Group Health and Harvard Pilgrim Health Care approved the study.

Data collection and study sample

We surveyed a random sample of 2,090 women ages 45 to 70 who were enrolled from January 1, 2005, to May 31, 2006, at Group Health (staff model only), N=1090, or at Harvard Pilgrim Health Care, N= 1000. Women had to have filled at least 2 prescriptions for HT in some 6-month period between January 1, 2005, and May 31, 2006, and the second prescription had to be within 90 days of the “run-out” date of the first prescription. The sample was stratified by site and was divided between women who were still using HT (N=1,040) and those who had discontinued HT (N=1,050), according to the automated pharmacy data profile, on May 31, 2006. “Users” were defined as women with at least 2 fills in 2003 and at least 1 fill for HT in the 180 days prior to the reference date and nonusers as women who did not have at least 2 fills in 2003 or a fill for HT in the 180 days prior to the reference date. In addition, we randomly sampled 200 women who had discontinued HT use prior to January 1, 2005, and 240 women

who had never used HT (divided nearly equally between the two sites), resulting in a total sample size of 2,530 women.

For this analysis, women currently taking HT were excluded because HT affects both vasomotor symptoms and possibly depression. Women taking selective serotonin reuptake inhibitors (SSRIs) or selective norepinephrine reuptake inhibitors (SNRIs) were included in order to make our findings relevant and generalizable to all women with depressive symptoms.

Measures

We assessed depressive symptoms using the Patient Health Questionnaire (PHQ-8),¹⁶ an instrument that provides both a dichotomous indicator of major depression and a continuous severity score. As a severity measure the PHQ-8 score ranges from 0 to 24 because each of the eight items can be scored from 0 (not at all) to 3 (nearly every day). Severity categories are defined as 0–4, no depression; 5–9, mild; 10–14, moderate; 15–19, moderately severe; 20–24, severe. A PHQ score of 10 or greater has a sensitivity for major depression of 88%, a specificity of 88% and a positive likelihood ratio of 7.1.¹⁷ For this study, women with PHQ-8 scores ≥ 10 (moderate to severe depressive symptoms) were defined as “depressed.” Women with PHQ-8 score <10 (mild or no depressive symptoms) were classified as “not depressed,” consistent with other studies.¹⁸

Menopausal symptoms were assessed using questions from the Wiklund Menopause Symptom Checklist.¹⁹ Women were asked whether, within the past 4 weeks, did they have “hot flashes/sudden flushes of warmth”, “night or day sweats/cold sweats”, or “pain with sexual activity or vaginal dryness”. If they experienced the symptom, they were asked, “Was the symptom mild, moderate or severe?” Other symptoms on the Checklist common to menopause, difficulty concentrating/memory loss, depressive symptoms/feeling sad or blue, trouble sleeping or waking early, irritability, anxiety, headaches, and body aches and pains were also assessed, but were not included in the analysis as these are all associated with depression. Thus, the presence or absence of 2 symptoms was assessed, 1) vasomotor symptoms (hot flashes and/or night sweats) and 2) vaginal pain/dryness. If present, the severity of these symptoms was assessed. Menopausal symptom burden was determined by the presence and severity of these 2 menopausal symptoms.

Potential confounding variables included age, smoking, body mass index (kg/m^2), hysterectomy status, and current use of SSRIs or SNRIs. All information was obtained by self-report at the time of the interview with the exception of age and current use of antidepressants and gabapentin. Automated medical record data was used to assess use of SSRIs, SNRIs, other antidepressants and gabapentin. This data was available at the GH site only ($n=588$). Some types of SSRIs and SNRIs as well as gabapentin have been shown to diminish vasomotor symptoms.²⁰

Statistical Analysis

We compared characteristics of women with moderate/severe depressive symptoms to women with mild/no depressive symptoms using chi-square tests for binary outcomes (percentages) and t-tests for means. Logistic regression models were used to determine the relative strengths of the associations between each menopausal symptom (any vasomotor symptoms (hot flashes or night sweats), moderate to severe vasomotor symptoms, any vaginal symptoms (dryness or pain), and moderate to severe vaginal symptoms) and the presence of moderate/severe depressive symptoms. We adjusted for variables that influenced the risk estimates associated with depressive symptoms by more than 10%, specifically, age and BMI (other significant associations did not alter findings when added to the model). We then determined the association of no depressive symptoms, mild depressive symptoms and at least moderate/

severe depressive symptoms to the percentage of women with: any vasomotor symptoms (hot flashes or night sweats), moderate to severe vasomotor symptoms, any vaginal symptoms (dryness or pain), and moderate to severe vaginal symptoms using chi square analyses. All analyses were performed using SAS V9.0.

RESULTS

Of the 2,530 potentially eligible women, 202 (8%) were ineligible: 114 were no longer in the health plan, 33 were premenopausal, 26 were physically/mentally unable to complete the telephone interview, 21 had a language barrier, 3 had died and 5 were ineligible for other reasons. Of the 2,328 eligible women, 1,358 completed the survey, resulting in an overall response rate of 58.3%. Of 1,358 women surveyed, 8 had unknown menopausal status or were premenopausal and 580 women were taking HT at the time of the survey. These women were excluded from the analysis. The percentage of women with moderate/severe depressive symptoms taking HT was not different than the overall percentage of women with no/mild depressive symptoms taking HT (44% versus 43%). Of the remaining 770 women (588 GH, 212 HPHC), 98 (12.7%) were identified with moderate to severe depressive symptoms and 672 (87.3%) were identified as having either mild or no depressive symptoms.

The characteristics of the women are shown in Table 1. Women with moderate/severe depressive symptoms were more likely to be younger, have had a hysterectomy, have a greater mean BMI, have a high school education or less and to not report good/excellent health. They were more likely to be using an antidepressant (43% vs. 20%), to feel anxious at least 50% of the time and to have a history of a panic attack. A higher proportion of women at Group Health than at Harvard Pilgrim Health Care had moderate/severe depressive symptoms.

After adjusting for age and BMI, women with moderate/severe depressive symptoms were almost twice as likely to report recent vasomotor symptoms (hot flashes and or night sweats) than women with no/mild depressive symptoms (aOR 1.67, 95% CI 1.04–2.68), and were more likely to report them as severe (aOR 1.63, 95% CI 0.95–2.83) (Table 2). The addition of other covariates to the model did not alter the findings appreciably. This higher frequency and severity of vasomotor symptoms was observed, despite the fact that 20% of women with moderate/severe depressive symptoms were using an SSRI or SNRI that may diminish vasomotor symptoms at the time of the survey (vs. 4.6% of women with no/mild depressive symptoms). The presence or severity of vaginal symptoms, were not significantly associated with moderate/severe depressive symptoms. In order to assess the effect of anxiety on these associations, we excluded from the analysis women who reported feeling anxious at least 50% of the time, but these findings persisted (data not shown).

The percentage of women with vasomotor symptoms as well as the percentage of women with severe vasomotor symptoms increased as the depression score category increased (none, mild, moderate/severe depressive symptoms) (Figure 1). In general, the percentage of women with vaginal symptoms as well as the percentage of women with severe vaginal symptoms also increased as the depression score category increased, but this relationship was not as strong as that observed for vasomotor symptoms.

DISCUSSION

We found a significant association between depressive symptoms and menopausal symptom burden (presence of hot flashes and night sweats). We hypothesized that depressive symptoms “amplified” the menopausal experience and this study suggests this indeed may be so (although alternatively one could argue that severe vasomotor symptoms worsen depressive symptoms).

Prior studies have supported an association of the presence of hot flashes with the presence of depression^{7;8;10;10;11} while others have not.^{3,9} To our knowledge, no prior studies examined whether the severity of depressive symptoms is associated with severity of menopausal symptoms. Of note, however, is a study by Freeman and colleagues suggesting that preexisting anxiety increases the risk of vasomotor symptoms. In this study, current depression was no longer significant when modeled with a history of anxiety.²¹ Not surprisingly, we also found that depressive symptoms were associated with a history of anxiety and panic attacks, but our numbers were too small to examine the effect of anxiety alone on menopausal symptom burden. When women who reported feeling anxious at least 50% of the time were removed from our analyses, our findings did not change.

Epidemiologic studies among community respondents have found that anxiety and depression are associated with high rates of both medical symptom reporting and health care seeking.^{22–26} The association of depression and anxiety with symptom burden holds across both somatic symptoms not specific to one bodily system²⁷ as well as to symptoms of chronic medical illnesses such as diabetes, congestive heart failure and osteoarthritis.²⁸

Several mechanisms have been proposed to explain the relationship between medical symptoms and depression, which is likely to be bidirectional. Depression may lead to heightened symptom awareness through the physiological consequences of poor adherence to self-care regimens (diet, exercise)²⁹ or increased muscle tension, autonomic nervous system and pituitary axis dysregulation.¹² The burden of physical symptoms and resulting functional impairment are also likely to provoke or worsen episodes of depression. Somatic and psychological distress may be co-equal and essential components of anxiety and depressive disorders.³⁰

Symptom experiences depend on perception, evaluation and response to symptoms based on personal and sociocultural milieu.³¹ While somatization disorder is relatively rare, the tendency for somatization exists across a continuum.^{32;33} How persons feel about their health is linked to their tendency to somatize.³⁴

Somatosensory, or symptom, amplification can be thought of as the tendency to experience somatic sensations as unusually intense, noxious and disturbing, or interpreted as indicative of medical illness requiring treatment.^{35–36;37} Amplification is associated with reporting of more bodily symptoms, increased pain sensitivity, introspectiveness,³⁷ dysthymic disorder, major depression, and with the decision to seek care for common physical symptoms.^{27;32} Symptom amplification among women with depression may result in more bothersome vasomotor symptoms compared to non-depressed women.

Our study has limitations. First, in order to make our findings generalizable, we included women taking SSRIs. Multiple studies have demonstrated benefit of the use of SSRIs for treatment of vasomotor symptoms.²⁰ As expected, the number of women taking SSRIs in our study was greater among women with moderate/severe depressive symptoms than in women with no/mild depressive symptoms, but any confounding by SSRIs should have driven our odds ratios toward the null. Three small randomized trials have examined the effect of HT on treating minor and major depression in peri-^{38–39} and postmenopausal women.⁴⁰ Two studies evaluating perimenopausal women showed benefit with HT^{38;39} and one study that evaluated only postmenopausal women did not.⁴⁰ Second, we did not assess the impact of HT on depressive and vasomotor symptoms as use of HT was one of our exclusion criteria. Third, our study was cross-sectional and we cannot conclude direction of causality. All information was self-reported and we asked about symptoms in the “prior 4 weeks”. Many of the symptoms of depression as assessed by the PHQ are also symptoms with the menopausal transition (trouble sleeping, concentrating). However, when severity of vasomotor symptoms alone was analyzed

by severity of depressive symptoms, there was a clear association of increasing severity of vasomotor symptoms with increasing severity of depressive symptoms.

Our findings have potential relevant implications for clinical care. Recognition and concurrent treatment for depression in midlife may reduce patients' menopausal symptom burden, and decrease medical testing and costs. Our study did not address whether women with depressive symptoms might achieve additional benefit from the use of HT. There were women in our study with moderate/severe symptoms already taking antidepressants. There are three possible explanations of this observation: 1) their antidepressant therapy was suboptimal, 2) they might have benefited from HT, or 3) even in the face of optimal management of depressive and vasomotor symptoms, these women's symptoms would remain refractory to therapy. Future studies to assess whether women with adequate therapy of depressive symptoms derive additional benefit from the use of HT are needed.

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Figure 1. The percentage of women with symptoms and severe symptoms by depressive symptom score category (none, mild, moderate/severe)

On the x axis are 3 categories of depressive symptoms defined by PHQ9 score: none = 0–4; mild = 5–9; moderate to severe = 10 or greater. On the y axis are the percentages of women within each category with a symptom present (vasomotor or vaginal dryness/pain) and if the symptom is present, the percentage of women that have severe symptoms.

Table 1

Characteristics of Midlife Women, Moderate/Severe Depressive Symptoms Versus No/Mild Depressive Symptoms

	Moderate/severe depressive symptoms N=98	No/mild depressive symptoms N=672	P value
	N(%)	N(%)	
Age (mean, years) (SD)	55.3 +/-6.0	57.5 +/- 5.9	0.0005
Caucasian	83(85)	604(90)	0.09
Perimenopausal	17(17)	89(13)	0.27
Hysterectomy *	20(25)	125(23)	0.59
Body Mass Index (mean, kg/m2) (SD)	30.4 +/- 7.2	27.4 +/- 5.7	0.0001
Education above High School	74(76)	571(85)	0.02
Current Smoker	14(14)	61(9)	0.11
Health Good/Excellent	32(32)	461(69)	<0.0001
Anxious > 50% of time	26(38)	25(6)	<0.0001
History of panic attack	17(25)	28(7)	<0.0001
Former HT use *	72(76)	526(79)	0.50
Former (prior 12 mo) but not current antidepressant use **	10(16)	45(13)	0.51
Current antidepressant use **	27(43)	71(20)	<0.0001
Current SSRI/SNRI use **	20(32)	31(9)	0.002
Site			
Group Health	68(15)	387(85)	0.03
Harvard	30(10)	285(90)	

* Numbers may not sum to total due to missing.

** Data available from GH site only, N=414 (63 depressed, 351 not depressed).

Table 2

Presence of menopausal symptoms among women with moderate to severe depressive symptoms as compared to women with no or mild depressive symptoms

	Mod/ severe depressive symptoms N=98	No/mild depressive symptoms N=672	Unadjusted OR (95%CI)	Adjusted * OR (95% CI)*
VMS	69%	56%	1.82(1.15–2.87)	1.67(1.04–2.68)
Severe VMS	53%	40%	1.72(1.01–2.91)	1.63 (0.95–2.83)
Vaginal dryness/pain	31%	28%	1.15(0.72–1.85)	1.17(0.72–1.90)
Severe vaginal dryness/pain	34%	24%	1.65(0.71–3.82)	1.57(0.64–3.85)

* Adjusted for age, BMI

VMS = vasomotor symptoms