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Depressive symptoms during the menopausal transition:

The Study of Women's Health Across the Nation (SWAN)

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Abstract

Background—The influence of menopausal status on depressive symptoms is unclear in diverse ethnic groups. This study examined the longitudinal relationship between changes in menopausal status and the risk of clinically relevant depressive symptoms and whether the relationship differed according to initial depressive symptom level.

Methods—3302 African American, Chinese, Hispanic, Japanese, and White women, aged 42-52 years at entry into the Study of Women's Health Across the Nation (SWAN), a community-based, multisite longitudinal observational study, were evaluated annually from 1995 through 2002. Random effects multiple logistic regression analyses were used to determine the relationship between menopausal status and prevalence of low and high depressive symptom scores (CES-D <16 or ≥ 16) over 5 years

Results—At baseline, 23% of the sample had elevated CES-D scores. A woman was more likely to report CES-D ≥ 16 when she was early peri-, late peri-, postmenopausal or currently/ formerly using hormone therapy (HT), relative to when she was premenopausal (OR range 1.30 to 1.71). Effects were somewhat stronger for women with low CES-D scores at baseline. Health and psychosocial factors increased the odds of having a high CES-D and in some cases, were more important than menopausal status.

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Limitations—We used a measure of current depressive symptoms rather than a diagnosis of clinical depression. Thus, we can only make conclusions about symptoms current at annual assessments.

Conclusion—Most midlife women do not experience high depressive symptoms. Those that do are more likely to experience high depressive symptom levels when perimenopausal or postmenopausal than when premenopausal, independent of factors such as difficulty paying for basics, negative attitudes, poor perceived health, and stressful events.

Keywords

Depressive symptoms; menopause; longitudinal; CES-D

1. Background

Controversy exists over whether the menopausal transition is a risk factor for the development of depression. Clinical and epidemiological studies of menopausal status and depressive symptoms (Avis et al., 1994;Bosworth et al., 2001;Bromberger et al., 2001;Freeman et al., 2004;Matthews et al., 1990;Schmidt et al., 2004;Woods and Mitchell, 1997) have been limited by small samples, short follow-up, limited analytic approaches, or samples of primarily white women. The impact of the perimenopause on depressive symptoms is an important quality of life and health care issue (Avis et al., 2003).

Women may vary in their vulnerability to increased depressive symptoms during the menopausal transition. One theory posits that depression or elevated depressive symptom levels prior to the transition may increase vulnerability to the potential effects of the transition (Avis et al., 1994). Varying results of studies could be attributed to different proportions of women with initial high levels of depressive symptoms in the study samples. In contrast, the Penn Ovarian Aging Study (POA), found that premenopausal women with CES-D scores <16 at study entry who subsequently had CES-D scores ≥ 16 were more likely to have begun the menopausal transition than to have remained premenopausal (Freeman et al, 2006). Thus, one might hypothesize that the effects of the menopausal transition would be more pronounced in women with initially low levels of depressive symptoms because they have a greater potential to experience an increase in these. .

We tested two hypotheses:(1) longitudinal change in menopausal status across time is associated with an increased risk of elevated depressive symptoms, independent of relevant demographic, psychosocial, behavioral, and health factors; and (2) the association between change in menopausal status and increased depressive symptoms differs according to depressive symptom level prior to the menopausal transition, independent of relevant covariates. These hypotheses were addressed using a unique cohort with five years of annual follow-ups from SWAN, a multiethnic study of 3302 women as they approached and underwent the menopausal transition.

2. Methods

2.1. Sample

We used data from the baseline evaluation and five subsequent annual assessments in SWAN. Study design has been described previously (Sowers et al., 2000). Briefly, a screening survey conducted between November 1995 and October 1997 assessed eligibility for SWAN. Community-based samples of women were selected at seven sites across the United States using a variety of recruitment strategies and sampling frames.

Each site recruited white women and women from one specified minority group (African Americans in Pittsburgh, Boston, the Detroit area, and Chicago; Japanese in Los Angeles;

Chinese in the Oakland region; and Hispanic in Newark). Eligibility included aged 42-52 years, an intact uterus, at least one menstrual period and no use of reproductive hormones in the previous 3 months, and self-identification with one of the site's designated race/ethnic groups. Of the 16,065 women screened, 3302 were enrolled in the longitudinal cohort. Participants did not differ statistically by age, marital status, parity or menopausal status from those eligible women who did not enroll. Women with a high school education or less and those who reported that it was hard or very hard to pay for basics were less likely to participate. Study retention rate at the end of the fifth follow-up visit was 79%, at which time nearly a quarter of participants were postmenopausal.

After excluding women with incomplete baseline data, the analytic sample to address the first hypothesis was 3193 women. The analytic sample for the second hypothesis was 2885 women after excluding a further 308 women with only baseline data (n=252) or missing covariate data (n=15). The 41 women who reported surgical menopause (bilateral oophorectomy or hysterectomy) or pregnancy at a follow-up visit were censored from that visit forward leaving 2885 women at visit 5.

2.2. Procedures

SWAN participants were assessed at baseline and annually with a common protocol. All study forms and materials were translated and back-translated into Spanish, Japanese, and Cantonese. Bilingual staff administered the protocol, as appropriate. All protocols were approved by the institutional review board at each site and signed written informed consent was obtained from all participants at each visit.

2.3. Measures

Depressive symptoms—Depressive symptoms were assessed annually with the Center for Epidemiologic Studies Depression (CES-D) Scale, a 20-item measure that asks about the frequency of being bothered by depressive symptoms during the previous week on a 4-point scale of 0 (rarely) to 3 (most or all of the time) (Radloff,1977). A score of 16 or above is commonly used to identify potential clinical depression (Boyd et al.,1982) and was used to indicate clinically relevant depressive symptoms in this study. The CES-D has been shown to be valid and reliable in diverse ethnic populations (Guarnaccia et al., 1989;Jones-Webb and Snowden, 1993;Ying, 1988).

Baseline measures—A standard set of baseline s*ociodemographic variables* included ethnicity, age, education attainment, and level of difficulty paying for basics,. Primary *race/ethnicity* was self-identified. *Parity* (live births) was coded as any/none. *Attitudes toward aging/menopause* were assessed using a seven-item scale (Sommer et al, 1999).

Annual measures—The following time-varying covariates were obtained at every visit: *Menopausal status classification* was based on menstrual bleeding patterns in the previous 12 months and was categorized as:1) premenopausal=menses in the past 3 months with no change in regularity; 2) early perimenopausal=menses in the past three months with change in regularity; 3) late perimenopausal=no menses within the past 3 months, but some menstrual bleeding within the past 12 months; 4) postmenopausal=no menses within the past 12 months; 5) hormone therapy=currently using hormone therapy or hormone use at a previous follow-up visit. The classifications are, with the exception of 'hormone therapy,' similar to those recommended by the World Health Organization (WHO Scientific Group, 1996) and the STRAW conference (Soules et al., 2001). All women were pre- or early perimenopausal at baseline.

Body mass index *(BMI, kg/m^2)* was based on measurements of height and weight using a standard protocol. *Perceived Health* was measured with a single question with five response categories (excellent to poor) extracted from the SF-36 (Ware and Sherbourne, 1992). Reports of hot flashes or night sweats on at least 6 days in the previous two weeks were used as an indicator of vasomotor symptoms. Current and past year use of *hormone therapy* and p*sychotropic medication* were reported and current use was verified by examination of medication containers in the clinic by the interviewers or the labels were read by participants over the telephone. Current smoking was assessed.

Psychosocial variables included *social support*, 4 items from the Medical Outcomes Study Social Support Survey (Sherbourne and Stewart, 1991) and *stressful life events* based on a checklist of 18 life events rated according to how stressful they were. *Number of very stressful events* since the last study visit was categorized as 0, 1 or 2 or more.

2.4 Data Analyses

Random effects logistic regression models were used to examine whether the menopausal transition was associated with increased reporting of depressive symptoms independent of other confounders. The inclusion of a (woman-specific) random intercept induces correlation between all observations from a given woman and enables us to ascribe a 'woman-specific' interpretation to model parameters. Random effects logistic regression models are relatively robust to missing data and make use of all available data across all visits. Thus, we included the entire sample and not just the women who were premenopausal at study entry.

To test our first hypothesis, we modeled the odds of having a CES-D score ≥ 16 at any given assessment as a function of the participant's menopausal status (and other covariates) at that assessment (baseline and the first five annual visits). To address our second hypothesis, we included baseline CES-D score (< 16 or ≥ 16) as an independent predictor and modeled CES-D score at annual visits 1 through 5 as the outcome. We included an interaction term between baseline CES-D score and menopausal status at each visit to determine if the effect of status on follow up depressive symptoms differed for those who reported high depressive symptoms at baseline versus those who did not.

Baseline age, race/ethnicity, site and years since baseline were included in all models and baseline menopause status was forced into the analysis for hypothesis two. We selected potential confounders and covariates based on the literature and a priori hypotheses. Those that were significant ($p < 0.05$) were retained, thus creating the most parsimonious model. The final models also included baseline attitudes toward menopause and time-varying covariates - menopausal status, perceived health, vasomotor symptoms, medication use, social support, very stressful life events, and smoking (for the first hypothesis). Analyses were run using SAS (Version 8, SAS Institute, Inc., Cary, NC) and STATA (Version 7, STATA Corporation, College Station, TX).

3. RESULTS

At baseline, 23% of the sample scored ≥ 16 on the CES-D. Baseline characteristics varied significantly between women with a CES-D score ≥ 16 and those with a score < 16 at baseline (Table 1). By the fifth annual follow-up, approximately 25% of the women were postmenopausal. Transition rates were similar among those with and without elevated depressive symptoms at baseline.

The odds of having a CES-D score ≥ 16 was significantly higher when a woman was early peri-, late peri-, postmenopausal or using HT (OR ranged from 1.30 to 1.71), relative to when she was premenopausal, after controlling for other covariates (Table 2). A woman also had

significantly higher odds of high CES-D scores when she was late peri-compared to when she was early perimenopausal. Other factors were also related to the odds of having a high CES-D, some of which had stronger associations with depressive symptoms than did menopausal status (Table 2).

The multivariate analyses addressing the second hypothesis showed a marginally significant interaction (P=.06) between baseline CES-D score and menopausal status. A woman with a CES-D ≤ 16 at baseline had a significantly higher odds of having a CES-D score ≥ 16 when she was late perimenopausal (OR=1.73, 95%CI=1.14, 1.77), postmenopausal (1.63, 95% CI=1.06, 2.51), or if she was a HT user (1.64, 95%CI=1.12, 2.39), compared to when she was premenopausal. Among those with baseline CES-D ≥ 16, a woman had the highest odds of a high CES-D when she was late perimenopausal (OR=1.50, 95%CI=.83, 2.71) but this was not significantly different from when she was premenopausal.

4. Discussion

Our data support the hypothesis that change in menopausal status across time is associated with an increased risk of high depressive symptoms, independent of relevant demographic, psychosocial, behavioral, and health factors. Overall, the risk for high depressive symptoms increased with the start of the menopausal transition and remained elevated through the early postmenopause. The odds were also increased among current and former HT users.

The results that women with low CES-D at baseline may be particularly affected by the change in status are consistent with findings from two recent studies of women with low depressive symptoms at baseline (Freeman et al, 2006;Cohen et al, 2006). The current study has extended their findings by including five different ethnic groups and adjusting for the multiple relevant risk factors for depression, such as stressful events and inadequate social support, and examining the influence of the postmenopause on risk for high depressive symptoms.

This is the first longitudinal study of menopause to include five different ethnic groups. Compared with white women, Chinese women had half the risk of depressive symptoms whereas the other racial/ethnic groups did not differ significantly from white women. In the POA study (Freeman et al, 2006). African American women had nearly twice the odds of high depressive symptoms as Whites, but there was no adjustment for indicators of socioeconomic status. In earlier cross-sectional analyses of SWAN, we found that adjusting for education and financial strain attenuated the significantly higher odds of CES-D score ≥ 16 in African American compared to White women (Bromberger et al., 2004).

Other factors contributed to high depressive symptom scores over five years including frequent vasomotor symptoms, low social support, and very stressful life events, the latter being the strongest predictor of high depressive symptom scores. This is consistent with numerous other studies demonstrating that social, psychological, and health factors have as great, or greater, impact on depressive symptom levels than has the menopausal transition (Bromberger and Matthews, 1996;Greene and Cooke, 1980).

Limitations in this study should be considered. Because we used a measure of current depressive symptoms rather than a diagnosis of clinical depression, we can only make conclusions about symptoms current at annual assessments. The binary CES-D score may have limited the opportunity to observe increases in symptoms in those who started with a high CES-D score at baseline. However, post hoc testing (not shown) showed ample fluctuation in depressive symptoms across visits.

Unique strengths of the present study include a large multiethnic cohort of women prior to or early in the transition with five years of follow-up data; consideration of multiple risk factors,

particularly life stressors; and statistical techniques that permitted comparisons of depressive symptom scores over time within and between women. Our data suggest that health care providers need to be aware of and sensitive to the potential vulnerability of women to elevated depressive symptoms during and after the menopausal transition. Depressive symptoms that emerge during the menopausal transition may develop into more serious clinical depressions (Judd et al., 1996).

The importance of the menopausal transition to mood and depressive symptoms has been debated for a long time. The current study provides important new information suggesting that depressive symptoms during the menopausal transition may not be due to vasomotor symptoms or even life stress alone and that more work is needed to disentangle the interrelationships among depressive symptoms, stress, bleeding patterns, and hormone dynamics during the transition.

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Table 1

Selected Baseline Characteristics by Baseline CES-D Score

Baseline Characteristics (%)	CES-D < 16 (n=2217)	CES-D ≥ 16 (n=668)	p-value
Age (years), mean ± SD	46.5 ± 2.7	46.0 ± 2.6	< 0.0001
Menopausal Status			< 0.0001
Premenopausal	56.0	46.0	
Early Perimenopausal	44.0	54.0	
Ethnicity			< 0.0001
African American	26.8	30.8	
White	48.5	45.8	
Chinese	9.3	4.9	
Hispanic	5.2	12.6	
Japanese	10.3	5.8	
Education			< 0.0001
≤ High School Degree	20.4	32.3	
Some College	31.6	35.2	
≥ College Degree	48.1	32.5	
Paying for Basics			< 0.0001
Not Very Hard	67.7	42.2	
Somewhat Hard	26.4	41.2	
Very Hard	5.9	16.6	
Attitude toward Aging & Menopause			< 0.0001
Neutral/Negative	16.6	31.1	
Slightly/Somewhat Positive	31.4	35.2	
Highly Positive	52.1	33.7	

Table 2

Random Effects Logistic Regression Model of Odds of High Depressive symptoms (CES-D ≥ 16)*

Covariates	p-value	Odds Ratio	95% C.I.
Status (compared to Premenopausal)	0.005		
Early Perimenopausal		1.30	1.09, 1.55
Late Perimenopausal		1.71	1.27, 2.30
Post Menopausal		1.57	1.15, 2.15
Hormone Therapy Users		1.43	1.10, 1.85
Late Perimenopausal compared to Early Perimenopausal **		1.32	1.02, 1.69
Ethnicity (compared to White)	0.008		
African American		1.06	0.84, 1.33
Chinese		0.51	0.33, 0.79
Hispanic		1.39	0.84, 2.30
Japanese		1.42	0.93, 2.17
Years since Baseline	<0.0001	0.88	0.84, 0.91
Baseline Paying for Basics (compared to Not Hard)	<0.0001		
Somewhat Hard		1.67	1.38, 2.01
Very Hard		2.13	1.59, 2.86
Hot Flashes / Night Sweats	<0.0001	1.77	1.51, 2.07
Attitudes (compared to Highly Positive)	<0.0001		
Slightly/Somewhat Positive		1.56	1.28, 1.89
Neutral/Negative		2.96	2.37, 3.70
Psychotropic Medication	<0.0001	1.82	1.52, 2.19
Social Support	<0.0001	0.83	0.81, 0.84
Very Stressful Life Events (compared to None)	<0.0001		
One		2.47	2.12, 2.89
Two or More		4.46	3.85, 5.16

* Also in model were site (p=0.19), baseline age (p=.006), overall health (p<0.0001) and smoker (p<0.0001).

** Postmenopausal compared to late perimenopausal, and to hormone therapy users were nonsignificant