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The Influence of Menopausal Status and Postmenopausal Use of Hormone Therapy on Presentation of Major Depression in Women

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Abstract

Objective: The purpose of this study was to determine whether there are differences in depression characteristics among premenopausal, perimenopausal, and postmenopausal women with major depressive disorder. This study also evaluated these differences between postmenopausal women with major depressive disorder who are taking and not taking hormone therapy.

Methods: Analyses conducted with data from the Sequenced Treatment Alternatives to Relieve Depression study focused on female outpatients with non-psychotic major depressive disorder seeking treatment in 41 primary or psychiatric care settings across the United States. Baseline demographic and clinical characteristics were compared among women not taking hormone therapy who were premenopausal (N=950), perimenopausal (N=380), or postmenopausal (N=562). These

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comparisons were also made between postmenopausal women (n=768) taking (N=171) or not taking (N=562) hormone therapy.

Results: After adjusting for sociodemographic and clinical baseline differences, premenopausal women were more likely to present with irritability than either peri- or postmenopausal women, and were more likely to have decreased appetite and less likely to have early morning insomnia than perimenopausal women. Postmenopausal women were more likely to have suicidal ideation and poorer physical functioning than either of the other groups, and were more likely to have sympathetic arousal and gastrointestinal symptoms than premenopausal women. After adjusting for baseline differences, postmenopausal women taking hormone therapy had better physical functioning, fewer melancholic features, less sympathetic arousal, and more lack of involvement in activities than women not taking hormone therapy.

Conclusions: Menopausal status and postmenopausal use of hormone therapy may influence the clinical presentation of major depressive episodes in women.

Keywords

menopause; hormone therapy; depression; major depressive disorder

INTRODUCTION

The sex difference in prevalence of major depressive disorder (MDD) is well established, with rates about twice as high in women than in men.¹⁻³ A number of studies have also demonstrated differences in the clinical presentation of MDD in women versus men, including presenting symptoms, course of illness features, comorbidity, and functional impairment.⁴⁻⁸ Moreover, sex differences in treatment response, both to antidepressants and psychotherapy, have been reported in some but not all studies.^{4,9-16}

Reproductive hormonal factors are likely to contribute to the sex differences in depression, which begin around the time of puberty and persist through midlife.^{2,17} Some women appear to be particularly susceptible to developing depression during times of hormonal fluctuation, including the premenstrual phase of the menstrual cycle, the postpartum period, and the perimenopause.¹⁸⁻²⁰ Fluctuations in estrogen and progesterone are known to affect neurotransmitters involved in depression, including both serotonin and norepinephrine.^{21,22} In addition, some studies have suggested that menopausal status may influence antidepressant treatment response, particularly with tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs).^{9,11,12,14,15,23}

Despite the clear influences of hormonal factors on depression in some women, to the best of our knowledge, no study has examined whether the clinical presentation of depression in women differs according to their menopausal status. Further, no study has assessed the possible effects of hormone therapy on the characteristics of depression in postmenopausal women. A recent report²⁴ did find that hormonal contraceptives may affect depression severity and symptom profile in premenopausal women. Moreover, several studies have found that estrogen is efficacious in treating perimenopausal depression.²⁵⁻²⁷ Others have suggested that hormonal therapy may enhance antidepressant treatment response in postmenopausal women who are treated with SSRIs.^{15,28-30} Hence, postmenopausal women with depression who are taking hormone therapy may present differently than those who are not.

The purpose of this report was to determine whether the presentation of depression in women differs according to menopausal status or the presence/absence of hormone therapy. To determine the former, we compared baseline sociodemographic and clinical characteristics among premenopausal, perimenopausal, and postmenopausal women with MDD who were

not taking hormone therapy. To determine the latter, we evaluated differences in depression characteristics in postmenopausal women who were and were not taking hormone therapy.

METHODS

The current study used data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study,³¹⁻³² a National Institute of Mental Health (NIMH)-supported study that provided an opportunity to examine differences in the presentation of depression as a function of menopausal status in women seeking treatment for a major depressive episode. The goal of STAR*D was to define prospectively which of several treatments are most effective for participants with non-psychotic MDD and who report an unsatisfactory clinical outcome to an initial, and if necessary, subsequent treatment(s). The study protocol was developed according to the principles of the Declaration of Helsinki. All risks, benefits, and adverse events associated with STAR*D were explained to participants, who provided written informed consent prior to study participation. The population and methods of STAR*D are described in detail elsewhere.³¹⁻³²

Study Population

STAR*D enrolled 4041 participants from July 2001 through April 2004. To achieve the goal of recruiting a broadly representative group of participants with MDD, STAR*D enrolled patients from 18 primary and 23 psychiatric care clinical sites across the United States that serve either the public or private sectors. Advertising for participants was not permitted as it tends to enroll a less representative study sample.³³ Every effort was made to recruit a broad spectrum of participants representing all racial groups and both sexes.

Inclusion/Exclusion Criteria

The inclusion criteria were broad so as to acquire a sample representative of individuals with MDD who would receive medication or psychotherapy in everyday practice. Eligible participants were outpatients aged 18–75 with non-psychotic MDD who scored ≥ 14 on the 17-Item Hamilton Rating Scale for Depression^{34,35} (HRSD₁₇) and for whom antidepressant treatment was deemed appropriate by the treating clinician. Participants with suicidal ideation were eligible, as long as outpatient treatment was deemed clinically safe. Participants with most general medical conditions (GMCs) were eligible; however, persons with medical contraindications that precluded randomization to treatments used in the first two steps of the study were excluded.

Participants with a lifetime history of schizophrenia, schizoaffective or bipolar disorder, or MDD with psychotic features were excluded, as were those with a primary diagnosis of anorexia nervosa, bulimia, or obsessive-compulsive disorder because these primary psychiatric conditions required a different initial treatment.³⁶ Participants with currently active and clinically significant substance abuse were eligible, as long as in-patient care was not required clinically at study entry. Those with active substance dependence who required detoxification were not eligible for reasons of medical safety. Participants with severe, unstable concurrent psychiatric conditions likely to require hospitalization within six months of study entry were also ineligible.

Participants were excluded if they had an established, well-documented history of non-response or clear intolerability in the current major depressive episode to one or more of the protocol treatments delivered at an adequate dose. Participants taking concomitant anxiolytics or sedative hypnotics could enter the study as long as their clinician determined that the antidepressant treatments in the protocol were appropriate and safe. Participants were excluded if they were currently receiving a targeted psychotherapy aimed at their depression; they could

participate if they had not responded to such psychotherapy and subsequently terminated it prior to study enrollment, or if they were receiving counseling or therapy for other problems. Participants who were breastfeeding, pregnant or intended to become pregnant within nine months of enrollment were also excluded.

Assessments

Clinical Research Coordinators (CRCs) at each of 14 Regional Centers were trained and certified in implementing the treatment protocol and in data collection methods. After obtaining written informed consent at the screening/baseline visit, participants were evaluated by the CRC. Sociodemographic and clinical information was collected, as was prior course of illness, current and past substance abuse, prior suicide attempts, current GMCs, and prior history of treatment in the current major depressive episode. The CRC completed the HRSD₁₇ (at baseline to establish inclusion/exclusion criteria) and the Quick Inventory of Depressive Symptomatology—Clinician-rated³⁷⁻³⁸ (QIDS-C₁₆). Current GMCs were assessed using the Cumulative Illness Rating Scale³⁹⁻⁴¹ (CIRS), and the presence or absence of 11 Axis I psychiatric disorders was assessed using the Psychiatric Diagnostic Screening Questionnaire (PDSQ).⁴²⁻⁴³ A Research Outcomes Assessor called participants for a telephone interview within 72 hours of the baseline visit to complete the HRSD₁₇ and the 30-item Inventory of Depressive Symptomatology—Clinician-rated (IDS-C₃₀).^{38,44} Also within 72 hours of enrollment, a telephonic Interactive Voice Response (IVR) system was used to collect the 16-item Quick Inventory of Depressive Symptomatology—Self-Rated^{37,38} (QIDS-SR₁₆) for assessment of depression severity, and the following measures of quality of life and functioning: the 12-item Short-Form Health Survey⁴⁵ (SF-12), the 16-item Quality of Life Enjoyment and Satisfaction Questionnaire⁴⁶ (Q-LES-Q), and the five-item Work and Social Adjustment Scale⁴⁷ (WSAS).

Group Assignment / Definition of Menopausal Status

Menopausal status was determined based on both current age and the participant's response to the following question: "Is the patient postmenopausal or post-hysterectomy, or male?" A woman was classified as premenopausal if she was younger than 40 years of age. Of those classified as premenopausal, 49 (4.74 %) answered "yes" to the above question (indicating that they were postmenopausal or post-hysterectomy). These women were still included in the premenopausal group due to the very low prevalence (1-2%) of naturally occurring menopause in women under 40 years old. Those in this age group who were post-hysterectomy but still had ovaries were likely to still be premenopausal, and those who also had both ovaries removed were likely to be taking menopausal hormone therapy and would thus be excluded from the analyses. Women who were at least 40 years old and who reported not being postmenopausal or post-hysterectomy were classified as perimenopausal. Finally, women who were at least 40 years old and reported being postmenopausal or post-hysterectomy were operationally defined as postmenopausal. A small number of these women may have had a hysterectomy without ovariectomy and were still cycling. Women who had either experienced natural menopause or had undergone a hysterectomy were included in the study, with the exception of those women on hormone therapy.

Of the 4041 participants enrolled, 62.7% were women (N=2532). Because administration of hormonal therapies such as hormonal contraceptives and menopausal hormone therapy could affect the presentation of depressive and menopausal symptoms, women taking these medications (N=636 women; 71 progesterone, 147 estrogen, 302 combination, 116 unknown/other) were excluded from the analyses comparing premenopausal, perimenopausal, and postmenopausal women. Of the remaining 1896 women, four were excluded due to missing information about age or menopausal status. Thus, the analyses regarding menopausal status were conducted with a sample of 1890 women. Of these, 950 (50.1%) were classified as

premenopausal, 380 (20.0%) were classified as perimenopausal, and 562 (29.6%) were classified as postmenopausal (Figure 1a).

Regarding the comparison with postmenopausal women by hormone therapy status, of the total number of eligible women enrolled in STAR*D (N=2532), 768 were postmenopausal. Of these, 35 (4.5%) could not be classified into either group. Thus the analyses regarding hormone therapy status were conducted with a sample of 737 postmenopausal women. Of these, 171 (22.3%) were taking hormone therapy and 562 (73.2%) were not taking hormone therapy (Figure 1b).

Statistical Analyses

Descriptive statistics are presented as percentages for categorical variables and as means and standard deviations for continuous variables. Chi-square tests and both parametric and nonparametric analysis of variance methods were used to compare the distribution of discrete and continuous, respectively, sociodemographic and clinical characteristics across menopausal status. After adjusting for baseline sociodemographic and clinical characteristics that differed across menopausal status, regression models (linear for continuous measures and logistic regression for binary measures) were used to assess the independent effect of menopausal status on symptom severity, depressive features, functioning, quality of life, and presence of psychiatric comorbidities and the significance level from a likelihood ratio test is presented. If significant differences were identified after adjustment, post-hoc comparisons were made using a Bonferroni correction.

Chi-square tests and both parametric and nonparametric analysis of variance methods were similarly used to compare the distribution of discrete sociodemographic and clinical characteristics across those women taking and not taking hormone therapy. After adjusting for baseline sociodemographic and clinical characteristics that differed across menopausal status, regression models (linear for continuous measures and logistic regression for binary measures) were used to assess the independent effect of hormone therapy on symptom severity, depressive features, quality of life, functioning, presence of depressive symptoms and presence of psychiatric comorbidities, with menopausal status entered into the model as a two-level design variable. A p-value < .05 indicated a significant difference in all analyses except for the post-hoc analyses, for which a p-value of < .0167 indicated a significant difference.

RESULTS

Sociodemographic and Baseline Characteristics

Table 1 shows the sociodemographic and baseline clinical characteristics of the study sample by menopausal status. Most of the postmenopausal women were seen in primary care settings, while the majority of the premenopausal and perimenopausal women were seen in psychiatric care settings. The average ages of premenopausal, perimenopausal and postmenopausal women were 29.4±5.9 years, 45.0±4.0 years and 54.6±7.9 years, respectively.

Several characteristics of depression history differentiated the three menopausal status groups. Specifically, premenopausal and perimenopausal women were more likely to have a positive family history of depression (Pre: 58%, Peri: 63%, Post: 51%, $p=.0008$) and were approximately twice as likely to report a past suicide attempt than postmenopausal women (Pre: 23%, Peri: 20%, Post: 12%, $p<.0001$). Premenopausal women had the youngest age of onset of their first depressive episode and postmenopausal women had the oldest age of onset (Pre: 19.0 (87.9), Peri: 26.6 (13.4), Post: 35.1 (17.8), $p<.0001$). Postmenopausal women were most likely to present with a chronic depressive episode (Pre: 21%, Peri: 26%, Post: 37%, $p<.0001$), had the longest duration of depressive illness (Pre: 10.5 (8.0), Peri: 18.4 (13.2), Post:

19.6 (16.3), $p < .0001$), and had the greatest medical comorbidity based on the CIRS (Pre: 2.2 (1.9), Peri: 3.1 (2.1), Post: 3.9 (2.4), $p < .0001$).

Depression Severity, Subtype, and Level of Functioning

With regard to symptom severity (Table 2), no differences were found among the menopausal status groups in total scores on either the HRSD₁₇ (Pre: 2.06 (6.5), Peri: 20.1 (6.5), Post: 20.4 (6.7), $p = .4763$) or the IDS-C₃₀ (Pre: 37.4 (11.3), Peri: 36.0 (11.6), Post: 36.6 (12.1), $p = .1311$). Total scores on the QIDS-SR₁₆ differed slightly but significantly as a function of menopausal status, with premenopausal women demonstrating the highest mean score of the three groups (Pre: 16.4 (4.2), Peri: 15.5 (4.4), Post: 15.8 (4.3), $p = .0008$). Postmenopausal women were the most likely to present with anxious features (Pre: 48%, Peri: 44%, Post: 55%, $p = .0057$). The differences found in QIDS-SR₁₆ scores and anxious features were no longer statistically significant after adjustment for differences in baseline sociodemographic and clinical characteristics. Postmenopausal women showed higher mental (Pre: 24.7 (8.2), Peri: 26.0 (8.7), Post: 28.8 (9.2), $p < .0001$) and lower physical (Pre: 52.0 (10.3), Peri: 49.9 (11.9), Post: 43.4 (11.9), $p < .0001$) functioning on the SF-12, though after adjustment, only the difference in SF-12 physical functioning remained significant ($p < .0001$), with the postmenopausal group showing significantly lower physical functioning than both the premenopausal and perimenopausal groups (post-hoc comparisons $p < .0010$ for both pairwise comparisons).

Profile of Depressive Symptoms

Table 3 shows individual depressive symptoms measured by the IDS-C₃₀ compared on the basis of menopausal status. After adjustment for baseline differences, only early morning insomnia (OR_{Peri vs. Pre} = 1.79 (1.34, 2.36), OR_{Post vs. Pre} = 1.36 (1.02, 1.82), $p = .0003$), irritability (OR_{Peri vs. Pre} = 0.55 (0.38, 0.79), OR_{Post vs. Pre} = 0.43 (0.38, 0.79), $p < .0001$), decreased appetite (OR_{Peri vs. Pre} = 0.77 (0.59, 1.02), OR_{Post vs. Pre} = 0.64 (0.48, 0.85), $p = .0081$), suicidal ideation (OR_{Peri vs. Pre} = 1.16 (0.88, 1.54), OR_{Post vs. Pre} = 1.54 (1.16, 2.06), $p = .0074$), sympathetic arousal (OR_{Peri vs. Pre} = 1.39 (1.02, 1.90), OR_{Post vs. Pre} = 1.59 (1.14, 2.22), $p = .0144$), and gastrointestinal symptoms (OR_{Peri vs. Pre} = 1.31 (0.99, 1.73), OR_{Post vs. Pre} = 1.47 (1.10, 1.96), $p = .0244$) showed significant differences between groups. Post-hoc tests were performed for these symptoms to determine the significant differences between individual groups. Perimenopausal women were less likely to have irritability and were more likely to have early morning insomnia than premenopausal women. Postmenopausal women were more likely to have suicidal ideation, sympathetic arousal and gastrointestinal symptoms than premenopausal women, and less likely to have a decreased appetite and have irritability. Perimenopausal women were less likely to have suicidal ideation than postmenopausal women.

Psychiatric Comorbidity

Table 4 provides rates of psychiatric comorbidity as a function of menopausal status. Premenopausal women were more likely to have a comorbid diagnosis of obsessive compulsive disorder (Pre: 17%, Peri: 12%, Post: 12%, $p = .0116$), social phobia (Pre: 38%, Peri: 27%, Post: 24%, $p < .0001$), drug abuse (Pre: 8%, Peri: 5%, Post: 3%, $p = .0020$), bulimia (Pre: 19%, Peri: 13%, Post: 13%, $p = .0012$), and generalized anxiety (Pre: 28%, Peri: 24%, Post: 22%, $p = .0335$) than the other groups. After adjustment, none of these differences in psychiatric comorbidity remained significant.

Comparison of Postmenopausal Women Taking Versus Not Taking Hormone Therapy

Baseline sociodemographic and clinical characteristics of postmenopausal women by hormone therapy status are presented in Table 5. Women taking hormone therapy were significantly less likely to be Hispanic (Non-hormone: 20%, Hormone: 10%, $p = .0031$); more likely to be Caucasian (Non-hormone: White: 71%, Black 23%, Other 6%; Hormone: White 83%, Black

15%, Other 2%, $p = .0031$), married (Non-hormone: 35%, Hormone: 47%, $p = .0066$) and have private insurance (Non-hormone: 48%, Hormone: 61%, $p = .0110$), and had more years of education (Non-hormone: 12.3 (3.9), Hormone: 13.2 (3.4), $p = .0025$). Women taking hormone therapy were also more likely to have recurrent depression (Non-hormone: 69%, Hormone: 83%, $p = .0006$) and had, on average (SD), greater medical comorbidity on the CIRS (Non-hormone: 3.9 (2.4), Hormone: 4.5 (2.4), $p = .0016$).

We found no significant differences between the two groups with regard to the severity of depression HRSD₁₇ (Non-hormone: 20.4 (6.7), Hormone: 20.0 (6.9), $p = .5230$) or the presence of atypical (Non-hormone: 17%, Hormone: 14%, $p = .3998$); however, after adjustment for baseline sociodemographic and clinical differences, those taking hormone therapy were less likely to have melancholic features (OR=0.53 (.30, .93), $p = .0289$). Women taking hormone therapy had better physical functioning on the SF-12 (Non-hormone: 43.4 (11.9), Hormone: 45.7 (12.2), $p = .0379$), which remained significant, ($\beta = -2.72$ (-4.72, -0.73), $p = .007$) after adjustment for baseline sociodemographic and clinical differences (Table 6). Symptom profiles were similar between the two groups, except that even after adjustment for baseline sociodemographic and clinical differences, women taking hormone therapy were significantly more likely to endorse lack of involvement in activities (OR=2.02 (1.09, 3.75), $p = .0266$) and less likely to endorse sympathetic arousal (OR=0.62 (0.40, 0.97), $p = .0359$) (Table 7). With regard to psychiatric comorbidities on the PDSQ (Table 8), women taking hormone therapy were significantly less likely to report agoraphobia (Non-hormone: 14%, Hormone: 8%, $p = .0400$), although this difference was no longer significant after adjustment.

DISCUSSION

To the best of our knowledge, this is the first study to examine the influence of menopausal status on the presentation of MDD in women, and the first to examine the effect of hormone therapy on the characteristics of major depression in postmenopausal women.

Our finding that postmenopausal women have more general medical comorbidity, an older age of onset, and less likelihood of family history of depression or past suicide attempt suggests that their depression may be related more to general medical comorbidity, hormonal factors, and/or aging than to a lifelong depressive disorder. After adjustment for baseline differences, we found several differences in symptom profiles among pre-, peri- and postmenopausal women. Our finding of more irritability in premenopausal women may reflect the influence of the menstrual cycle on the presentation of depression, since many women experience premenstrual worsening of depression or other premenstrual mood changes, of which irritability is the most common.⁴⁸ It was surprising that postmenopausal women reported more suicidal ideation, particularly given the similarity of their severity of illness to the other groups and their less frequent history of suicide attempt. One could speculate that this increased suicidal ideation is related to their greater likelihood of being widowed or divorced, which may reflect a lack of social support, and their lower level of resources given their lower income and less private insurance. To examine whether marital status explained the finding, we compared mean score of the suicidal ideation item from the QIDS-SR16 across marital status groups and found no statistically significant difference in the scores. Our finding of a greater likelihood of sympathetic arousal, gastrointestinal symptoms and lower physical functioning in postmenopausal women, characteristics which were present even after adjustment for differences in general medical comorbidity, may be a reflection of age, as these symptoms were also noted to increase with age in a study by Husain et al.,⁴⁹ who conducted a recent analysis of age-related characteristics of depression that also used the STAR*D population for its study sample. However, an independent effect of hormones is suggested by the fact that postmenopausal women in the study taking hormone therapy had a lower rate of sympathetic arousal and higher physical functioning; this is also consistent with findings in premenopausal

women taking versus not taking hormonal contraceptives in another report from the STAR*D study.²⁴

Previous reports suggest that women commonly present with atypical depressive features, such as hypersomnia and hyperphagia.^{4,5,7,50} Interestingly, we found no difference in the presence of atypical or melancholic features of depression by menopausal status, with about 20% of women in each group showing each of these subtypes. While hypersomnia was more common in premenopausal women than in the other two groups, the difference was no longer significant after adjustment. We did find that early morning insomnia was less common and decreased appetite was more common in premenopausal women; however, it is important to note that in all three of the menopausal status groups, midnocturnal awakening was the most common sleep disturbance and decreased appetite was more common than increased appetite. It is also notable that anxious depression was the most common subtype among all three groups and was seen most frequently in postmenopausal women, although the difference by menopausal status was no longer significant after adjustment.

In addition to differences in the presentation of depression by menopausal status, we also found that depression in postmenopausal women may be influenced by whether or not concomitant hormone therapy is being taken. The women in our study who were taking hormone therapy were more likely to be Caucasian, non-Hispanic, or married, with more years of education and private insurance. The higher educational level in women taking hormone therapy is consistent with the literature⁵⁰ prior to the publication of the Women's Health Initiative results,⁵¹ which is when our study was initiated. Women taking hormone therapy were also more likely to have a recurrent course of depression and greater general medical comorbidity. The greater general medical comorbidity in women taking hormone therapy likely results in increased contact with health care providers and therefore increased opportunities for hormone therapy to be prescribed.

Comparing symptom profiles after adjustment for baseline differences, women on hormone therapy reported better physical functioning, fewer melancholic features, less sympathetic arousal, and more lack of involvement in activities compared to women not on hormone therapy. The better physical functioning, less melancholia, and less sympathetic arousal (i.e., less anxiety) are consistent with the beneficial effects on sleep, energy, mood, and quality of life that have been described with hormone therapy.⁵² However, the similar overall severity of depression in those taking and not taking hormone therapy is consistent with literature showing that estrogen is not a treatment for major depression in postmenopausal women,⁵³ although it also suggests that hormone therapy does not worsen depressive symptoms.

There are several limitations to this study. The sample was restricted to outpatients with nonpsychotic MDD and may not be generalizable to all depressed women. It was not a random sample of depressed patients as seen in epidemiologic studies; however, we did use broad inclusion criteria, recruited patients from primary and psychiatric care sites across the United States, and had appropriate minority representation. Hence, our sample was probably representative of depressed patients seeking care in outpatient settings. Another limitation was the definition of menopausal status used, which was based on a combination of age and a question about menopausal status and hysterectomy status. More detailed questions about irregular or skipped menstrual cycles and timing of cessation of cycles would have enabled more exact classification of women as pre-, peri, or postmenopausal. In addition, we do not know the timing of the onset of depression in postmenopausal women in relation to their beginning or stopping hormone therapy, information that may have further clarified the effect of hormone therapy on depressive symptom presentation. It is also true that—at least to some extent—age and menopausal status covary and some of the differences identified may have more to do with age differences than reproductive hormonal status. Much of our data rely on

self-report and patient recall, which may be unreliable. Finally, the self-report PDSQ was used to diagnose comorbid Axis I psychiatric disorders though it is a screening tool.

In conclusion, the depressive episode presentation in women may be influenced by menopausal status as well as postmenopausal use of hormone therapy. The differences reported should be considered in the clinical evaluation and management of female patients with depression. Future analyses will examine the impact of menopausal status and hormone therapy on antidepressant treatment response.

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Menopause Paper Sample Size-Part a

*Menopausal status could not be determined for 4 of the women in the STARD population.

Total Sample Size Possible: N=1892

*Menopausal status could not be determined for 4 of the women in the STARD population.

Total Sample Size Possible: N=733

Figure 1.
Consort Chart

Table 1

Demographic and Baseline Characteristics by Menopausal Status

Characteristics	Premenopausal N=950 n(%)	Perimenopausal N=380 n(%)	Postmenopausal N=562 n(%)	Unadjusted p-value
Race				0.0013
White	656(69.0)	297(78.2)	401(71.3)	
Black or African-American	201(21.2)	61(16.0)	128(22.8)	
Other	93(9.8)	22(5.8)	33(5.9)	
Ethnicity-Hispanic				0.0047
Yes	149(15.7)	45(11.8)	111(19.7)	
No	800(84.3)	335(88.2)	451(80.3)	
Employment Status				<.0001
Employed	590(62.2)	228(60.0)	242(43.2)	
Unemployed	356(37.6)	151(39.7)	245(43.8)	
Retired	2(0.2)	1(0.3)	73(13.0)	
Marital Status				<.0001
Married	366(38.6)	175(45.7)	197(35.5)	
Never	390(41.1)	66(17.6)	64(11.4)	
Divorced	187(19.7)	131(34.8)	227(40.3)	
Widowed	6(0.6)	8(1.9)	72(12.9)	
Family History of Depression				0.0008
Yes	545(58.0)	236(62.6)	283(50.6)	
No	395(42.0)	141(37.4)	276(49.4)	
Attempted Suicide				<.0001
Yes	217(22.9)	75(19.7)	66(11.7)	
No	732(77.1)	305(80.3)	496(88.3)	
Setting				<.0001
Primary	326(34.3)	163(42.9)	326(58.0)	
Specialty	624(65.7)	217(57.1)	236(42.0)	
Insurance Status				0.0415
Private	460(50.5)	188(50.9)	260(47.8)	
Public	150(16.5)	53(14.4)	118(21.7)	

Characteristics	Premenopausal N=950 n(%)		Perimenopausal N=380 n(%)		Postmenopausal N=562 n(%)		Unadjusted p-value
None	301(33.0)		128(34.7)		166(30.5)		
Recurrent							0.0491
Yes	665(75.1)		258(73.7)		352(69.2)		
No	220(24.9)		91(26.3)		157(30.8)		
Chronic							<.0001
Yes	193(20.5)		95(25.5)		188(33.6)		
No	746(79.5)		278(74.5)		371(66.4)		

Characteristic	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	p-value
Education (Yrs of Schooling)	948	13.3(3.0)	378	13.7(3.2)	559	12.3(3.9)	<.0001
Age at onset of 1st MDE	935	19.0(7.9)	374	26.6(13.4)	557	35.1(17.8)	<.0001
Length of Illness (Yrs)	935	10.5(8.0)	374	18.4(13.2)	557	19.6(16.3)	<.0001
Monthly Income	815	2179.0(2530.4)	331	2623.9(3072.6)	473	2112.1 (3206.7)	0.0266
Number of General Medical Comorbidities	950	2.2(1.9)	380	3.1(2.1)	562	3.9(2.4)	<.0001

MDE: Major Depressive Episode, CIRS: Cumulative Illness Rating Scale

Table 2

Depression Characteristics by Menopausal Status

Characteristic	Premenopausal		Perimenopausal		Postmenopausal		Unadjusted p-value	Adjusted* p-value
	n	Mean(SD)	n	Mean(SD)	N	Mean(SD)		
HRSD ₁₇	866	20.6(6.5)	353	20.1(6.5)	517	20.4(6.7)	0.4763	0.7546
IDS-C ₃₀	861	37.4(11.3)	351	36.0(11.6)	518	36.6(12.1)	0.1311	0.7687
QIDS-SR ₁₆	947	16.4(4.2)	376	15.5(4.4)	558	15.8(4.3)	0.0008	0.2156
SF-12 (Mental)	852	24.7(8.2)	350	26.0(8.7)	528	28.8(9.2)	<.0001	0.0678
SF-12 (Physical)	852	52.0(10.3)	350	49.9(11.9)	528	43.4(11.9)	<.0001	<.0001**
WSAS	852	24.1(9.3)	350	24.2(9.0)	528	23.8(10.4)	0.8219	0.7680
Q-LES-Q	852	40.7(15.1)	350	41.2(15.3)	528	40.6(16.4)	0.8725	0.8659

	Premenopausal		Perimenopausal		Postmenopausal		Unadjusted p-value	Adjusted* OR
	n(%)		n(%)		n(%)			Peri vs. Pre
Atypical features							0.2757	1.00
Yes	179(20.5)		70(19.7)		89(17.0)			0.76
No	693(79.5)		285(80.3)		433(83.0)			0.2727
Anxious features							0.0057	0.83
Yes	421(48.3)		157(44.2)		285(54.8)			0.96
No	451(51.7)		198(55.8)		235(45.2)			0.4359
Melancholic features							0.0616	0.73
Yes	195(22.3)		61(17.1)		96(18.4)			0.75
No	678(77.7)		295(82.9)		425(81.6)			0.1267

* Analyses adjusted for race, ethnicity, family history of depression, attempted suicide, setting, chronicity, age at onset of 1st MDE, monthly total income and CIRS total score

** Post-hoc tests were performed where adjusted p-values were less than 0.05 and revealed a significant difference between the perimenopausal and postmenopausal groups (p < .0001) and the pre- and postmenopausal groups (p < .0001)

HRSD₁₇: 17-item Hamilton Rating Scale for Depression, IDS-C₃₀: 30-item Inventory of Depressive Symptomatology – Clinician-rated, QIDS-SR₁₆: 16-item Quick Inventory of Depressive Symptomatology – Self-Rated, SF-12: 12-item Short Form health survey, WSAS: Work and Social Adjustment Scale, Q-LES-Q: Quality of Life Enjoyment and Satisfaction Questionnaire, MDE: Major Depressive Episode, CIRS: Cumulative Illness Rating Scale

Table 3

Profile of Depressive Symptoms (IDS-C₃₀) by Menopausal Status

Depression Symptoms	Premenopausal N=950 n(%)	Perimenopausal N=380 n(%)	Postmenopausal N=562 n(%)	Unadjusted p-value	Adjusted OR*		Adjusted* p-value
					Peri vs. Pre	Post vs. Pre	
Sleep Onset Insomnia	621(71.22)	240(67.42)	363(69.54)	0.4079	0.97	1.02	0.9482
Mid-Nocturnal Insomnia	687(78.87)	306(85.96)	448(85.82)	0.0006	1.54	1.30	0.0744
Early Morning Insomnia / Hypersomnia	412(47.19) 226(25.89)	212(59.55) 79(22.19)	303(58.16) 95(18.20)	< .0001 0.0040	1.78 0.82	1.36 0.70	0.0003 0.1320
Mood-Sad	858(98.28)	342(96.07)	510(97.70)	0.0663	0.46	1.10	0.0657
Mood-Irritable ^{1,2}	770(88.20)	283(79.49)	390(74.71)	< .0001	0.55	0.43	< .0001
Mood-Anxious	724(82.83)	301(84.55)	430(82.38)	0.6887	1.24	1.02	0.4898
Reactivity of Mood	648(74.31)	261(73.52)	378(72.41)	0.7385	1.07	1.05	0.9117
Mood Variation	428(49.03)	140(39.33)	220(42.15)	0.0024	0.75	0.82	0.1089
Quality of Mood	659(75.49)	262(73.60)	402(77.16)	0.4799	0.93	1.25	0.2881
Appetite-Decreased ²	452(51.95)	158(44.38)	222(42.61)	0.0013	0.77	0.64	0.0081
Appetite-Increased	203(23.33)	81(22.75)	125(23.99)	0.9107	1.01	1.14	0.7181
Weight-Decrease	288(32.99)	110(30.99)	145(27.83)	0.1316	0.98	0.82	0.4195
Weight-Increase	221(25.32)	81(22.82)	135(25.91)	0.5544	0.84	0.99	0.5203
Concentration/Decision Making	798(91.41)	328(92.13)	467(89.46)	0.3269	1.16	0.78	0.3188
Outlook-Self	757(86.91)	284(79.78)	382(73.18)	< .0001	0.72	0.66	0.0663
Outlook-Future	680(78.16)	287(80.62)	401(76.82)	0.4056	1.40	1.27	0.1326
Suicidal Ideation ^{2,3}	407(46.62)	162(45.89)	258(49.43)	0.3996	1.16	1.54	0.0129
Involvement	782(89.58)	294(82.58)	432(82.76)	0.0002	0.63	0.70	0.0631
Energy/Fatigability	811(92.90)	318(89.33)	475(91.00)	0.1026	0.81	0.88	0.6880
Pleasure/Enjoyment	647(74.11)	253(71.07)	371(71.07)	0.3614	0.87	0.82	0.4210
Sexual Interest	586(67.12)	236(66.29)	316(60.54)	0.0375	1.07	0.78	0.1037
Psychomotor Slowing	543(62.20)	228(64.04)	349(66.86)	0.2179	1.07	1.07	0.8508
Psychomotor Agitation	558(63.99)	213(59.83)	300(57.47)	0.0451	0.87	0.78	0.2471
Somatic (pain) Complaints	690(79.04)	287(80.62)	425(81.42)	0.5369	0.99	0.79	0.3926
Sympathetic Arousal ²	574(65.83)	261(73.31)	414(79.31)	< .0001	1.39	1.59	0.0141

Depression Symptoms	Premenopausal N=950 n(%)	Perimenopausal N=380 n(%)	Postmenopausal N=562 n(%)	Adjusted OR*		
				Unadjusted p-value	Peri vs. Pre	Post vs. Pre
Panic/Phobic Symptoms	349(40.02)	122(34.37)	222(42.61)	0.0473	0.84	1.16
Gastrointestinal ²	351(40.21)	169(47.47)	276(52.87)	<.0001	1.31	1.47
Interpersonal Sensitivity	598(68.50)	221(62.08)	284(54.41)	<.0001	0.86	0.78
Leadren Paralysis/Physical Energy	370(42.38)	158(44.38)	270(51.72)	0.0028	1.20	1.33
						0.1261
						0.0224
						0.2415
						0.1310

* Analyses adjusted for race, ethnicity, family history of depression, attempted suicide, setting, chronicity, age at onset of 1st MDE, monthly total income and CIRS total score.

¹ Significant post-hoc comparison of perimenopausal vs. premenopausal

² Significant post-hoc comparison of postmenopausal vs. premenopausal

³ Significant post-hoc comparison of perimenopausal vs. postmenopausal

IDS-C30: 30-item Inventory of Depressive Symptomatology. MDE: Major Depressive Disorder, CIRS: Cumulative Illness Rating Scale

Table 4

Psychiatric Comorbidities (PDSQ) by Menopausal Status

Psychiatric Comorbidity	Premenopausal n(%)	Perimenopausal n(%)	Postmenopausal n(%)	Unadjusted p-value	Adjusted OR [*]		Adjusted [*] p-value
					Peri vs. Pre	Post vs. Pre	
OCD				0.0161	0.820	0.626	0.1042
Absent	786(83.5)	329(87.7)	482(88.4)				
Present	155(16.5)	46(12.3)	63(11.6)				
Panic				0.1244	0.750	0.875	0.4283
Absent	804(85.3)	336(89.6)	472(86.6)				
Present	138(14.7)	39(10.4)	73(13.4)				
Social Phobia				<.0001	0.784	0.791	0.1886
Absent	586(62.4)	275(73.3)	416(76.3)				
Present	353(37.6)	100(26.7)	129(23.7)				
PTSD				0.1568	1.036	1.066	0.9383
Absent	740(78.5)	308(82.4)	444(81.8)				
Present	203(21.5)	66(17.6)	99(18.2)				
Agoraphobia				0.7479	1.376	1.116	0.3424
Absent	825(87.9)	328(87.7)	469(86.5)				
Present	114(12.1)	46(12.3)	73(13.5)				
Alcohol abuse				0.6266	1.207	1.434	0.3487
Absent	854(90.7)	342(91.4)	502(92.1)				
Present	88(9.3)	32(8.6)	43(7.9)				
Drug abuse				0.0020	0.755	0.672	0.4253
Absent	868(92.2)	354(94.6)	526(96.7)				
Present	73(7.8)	20(5.4)	18(3.3)				
Somatiform				0.2077	0.887	1.006	0.9498
Absent	912(96.9)	365(97.6)	520(95.6)				
Present	29(3.1)	9(2.4)	24(4.4)				
Hypochondriasis				0.6168	1.484	0.939	0.3156
Absent	893(94.8)	353(94.4)	510(93.6)				
Present	49(5.2)	21(5.6)	35(6.4)				

Psychiatric Comorbidity	Premenopausal n(%)	Perimenopausal n(%)	Postmenopausal n(%)	Unadjusted p-value	Adjusted OR*		Adjusted* p-value
					Peri vs. Pre	Post vs. Pre	
Bulimia				0.0012	0.701	0.802	0.1673
Absent	762(80.8)	326(86.9)	475(87.2)				
Present	181(19.2)	49(13.2)	70(12.8)				
Anxious				0.0355	0.826	0.709	0.1180
Absent	678(72.1)	284(75.9)	425(78.0)				
Present	262(27.9)	90(24.1)	120(22.0)				

* Analyses adjusted for race, ethnicity, family history of depression, attempted suicide, setting, chronicity, age at onset of 1st MDE, monthly total income and CIRS total score

PDSQ: Psychiatric Diagnostic Screening Questionnaire, OCD: Obsessive-Compulsive Disorder, PTSD: Post-Traumatic Stress Disorder, MDE: Major Depressive Episode, CIRS: Cumulative Illness Rating Scale

Table 5

Baseline Characteristics in Postmenopausal Women by Hormone Therapy Status

Characteristic	Non-Hormone n(%)	Hormone n(%)	Unadjusted p-value
Race			0.0052
White	401(71.35)	142(83.04)	
Black or African-American	128(22.78)	26(15.20)	
Other	33(5.87)	3(1.75)	
Ethnicity-Hispanic			0.0031
Yes	111(19.75)	17(9.94)	
No	451(80.25)	154(90.06)	
Employment Status			0.1073
Employed	242(43.21)	82(47.95)	
Unemployed	245(43.75)	60(35.09)	
Retired	73(13.04)	29(16.96)	
Marital Status			0.0066
Married	197(35.18)	81(47.37)	
Never	64(11.42)	11(6.43)	
Divorced	227(40.54)	67(39.18)	
Widowed	72(12.86)	12(7.02)	
Family History of Depression			0.0959
Yes	283(50.63)	99(57.89)	
No	276(49.37)	72(42.11)	
Attempted Suicide			0.6927
Yes	66(11.74)	22(12.87)	
No	496(88.26)	149(87.13)	
Setting			0.4021
Primary	326(58.01)	93(54.39)	
Specialty	236(41.99)	78(45.61)	
Medical Insurance			0.0110
Private	260(47.79)	103(60.95)	
Public	118(21.70)	26(15.38)	

Characteristic	Non-Hormone n(%)	Hormone n(%)	Unadjusted p-value
None	166(30.51)	40(23.67)	
Recurrent			0.0006
Yes	352(69.16)	133(83.13)	
No	157(30.84)	27(16.88)	
Chronic			0.8674
Yes	188(33.63)	56(32.94)	
No	371(66.37)	114(67.06)	

Characteristic	n	mean (SD)	n	mean (SD)	p-value
Age	562	54.6(7.9)	171	54.6(8.2)	0.9394
Education (Yrs of Schooling)	559	12.3(3.86)	171	13.2(3.4)	0.0025
Age at onset of 1st MDE	557	35.1(17.8)	169	32.5(16.7)	0.0849
Length of Illness	557	19.6(16.3)	169	22.3(16.2)	0.0592
Total Income	473	2112(3206.7)	158	2243(2106.8)	0.5571
Number of General Medical Comorbidities	562	3.9(2.4)	171	4.5(2.4)	0.0016

MDE: Major Depressive Episode, CIRS: Cumulative Illness Rating Scale

Table 6
Depression Characteristics in Postmenopausal Women by Hormone Therapy Status

Characteristics	Non-Hormone		Hormone		Unadjusted p-value	Adjusted* p-value
	n	Mean(SD)	n	Mean(SD)		
HRSD ₁₇	517	20.4(6.7)	167	20.0(6.9)	0.5230	0.5696
IDS-C ₃₀	518	36.6(12.1)	168	35.3(11.8)	0.2253	0.3709
QIDS-SR ₁₆	558	15.8(4.3)	171	15.3(4.3)	0.1587	0.2858
SF-12 (Mental)	528	28.8(9.2)	164	28.7(9.0)	0.8822	0.9635
SF-12 (Physical)	528	43.4(11.9)	164	45.7(12.2)	0.0379	0.0075
WSAS	528	23.8(10.4)	164	23.0(9.4)	0.3424	0.2607
Q-LES-Q	528	40.6(16.4)	164	43.3(15.9)	0.0710	0.0806

	Non-Hormone (ref) n(%)	Hormone n(%)	Unadjusted p-value	Adjusted* OR	Adjusted* p-value
Atypical			0.3998	0.83	0.4960
Yes	89(17.05)	24(14.29)			
No	433(82.95)	144(85.71)			
Anxious			0.0152	0.71	0.0896
Yes	285(54.8)	74(44.05)			
No	235(45.2)	94(55.95)			
Melancholic			0.1107	0.53	0.0265
Yes	96(18.4)	22(13.1)			
No	425(81.6)	146(86.9)			

* Models adjusted for race, ethnicity, marital status, medical insurance, years of schooling, CIRS total categories, and recurrent episodes

HRSD₁₇: 17-item Hamilton Rating Scale for Depression, IDS-C₃₀: 30-item Inventory of Depressive Symptomatology – Clinician-rated, QIDS-SR₁₆: 16-item Quick Inventory of Depressive Symptomatology – Self-Rated, SF-12: 12-item Short Form health survey, WSAS: Work and Social Adjustment Scale, Q-LES-Q: Quality of Life Enjoyment and Satisfaction Questionnaire, CIRS: Cumulative Illness Rating Scale

Table 7

Profile of Depressive Symptoms in Postmenopausal Women by Hormone Therapy Status

Depression Symptoms	Non-Hormone (ref) n(%)	Hormone n(%)	Unadjusted p-value	Adjusted* OR	Adjusted* p-value
Sleep Onset Insomnia	363(69.5)	110(65.5)	0.3238	0.94	0.7658
Mid-Nocturnal Insomnia	448(85.8)	152(90.5)	0.1194	1.55	0.1484
Early Morning Insomnia	303(58.2)	105(62.5)	0.3193	1.28	0.2215
Hypersomnia	95(18.2)	31(18.5)	0.9411	0.97	0.9074
Mood-Sad	510(97.7)	163(97.0)	0.6223	0.89	0.8441
Mood-Irritable	390(74.7)	122(72.6)	0.5896	0.93	0.7303
Mood-Anxious	430(82.4)	132(78.6)	0.2699	0.92	0.7364
Reactivity of Mood	378(72.4)	115(68.5)	0.3228	0.89	0.5951
Mood Variation	220(42.2)	67(39.9)	0.6045	0.92	0.6630
Quality of Mood	402(77.2)	122(72.6)	0.2305	0.71	0.1351
Appetite-Decreased	222(42.6)	58(34.5)	0.0635	0.72	0.1078
Appetite-Increased	125(24.0)	51(30.4)	0.1000	1.42	0.1052
Weight-Decrease	145(27.8)	43(25.6)	0.5716	0.88	0.5623
Weight-Increase	135(25.9)	47(28.0)	0.5977	1.13	0.5948
Concentration/Decision Making	467(89.5)	149(88.7)	0.7782	1.02	0.9456
Outlook-Self	382(73.2)	127(75.6)	0.5359	1.05	0.8209
Outlook-Future	401(76.8)	126(75.0)	0.6291	0.92	0.7116
Suicidal Ideation	258(49.4)	72(42.9)	0.1382	0.71	0.0878
Involvement	432(82.8)	153(91.1)	0.0091	2.02	0.0266
Energy/Fatigability	475(91.0)	156(92.9)	0.4531	1.31	0.4415
Pleasure/Enjoyment	371(71.1)	108(64.3)	0.0968	0.73	0.1239
Sexual Interest	316(60.5)	109(64.9)	0.3139	1.10	0.6498
Psychomotor Slowing	349(66.7)	111(66.1)	0.8507	1.13	0.5647
Psychomotor Agitation	300(57.5)	101(60.1)	0.5452	1.00	0.9853
Somatic (pain) Complaints	425(81.4)	133(79.2)	0.5188	0.92	0.7395
Sympathetic Arousal	414(79.3)	120(71.4)	0.0336	0.62	0.0359
Panic/Phobic Symptoms	222(42.6)	66(39.3)	0.4474	1.09	0.6542
Gastrointestinal	276(52.9)	92(54.8)	0.6696	1.09	0.6493

Depression Symptoms	Non-Hormone (ref) n(%)	Hormone n(%)	Unadjusted p-value	Adjusted* OR	Adjusted* p-value
Interpersonal Sensitivity	284(54.4)	92(54.8)	0.9358	1.05	0.7953
Leadren Paralysis/Physical Energy	270(51.7)	78(46.4)	0.2325	0.99	0.9768

* Models adjusted for race, ethnicity, marital status, medical insurance, years of schooling, CIRS total categories and recurrent episodes, CIRS: Cumulative Illness Rating Scale

Table 8
Psychiatric Co-Morbidities (PDSQ) in Postmenopausal Women by Hormone Therapy Status

Psychiatric Co-Morbidity	Non-Hormone (ref) n(%)	Hormone n(%)	Unadjusted p-value	Adjusted* OR	Adjusted p-value
OCD			0.8723	1.12	0.7097
Absent	482(88.4)	152(88.9)			
Present	63(11.6)	19(11.1)			
Panic			0.1626	0.63	0.1519
Absent	472(86.6)	155(90.6)			
Present	73(13.4)	16(9.4)			
Social Phobia			0.4041	1.01	0.9772
Absent	416(76.3)	135(79.4)			
Present	129(23.7)	35(20.6)			
PTSD			0.2153	0.80	0.3822
Absent	444(81.8)	146(85.9)			
Present	99(18.2)	24(14.1)			
Agoraphobia			0.0400	0.63	0.1625
Absent	469(86.5)	158(92.4)			
Present	73(13.5)	13(7.6)			
Alcohol abuse			0.1543	0.66	0.3089
Absent	502(92.1)	163(95.3)			
Present	43(7.9)	8(4.7)			
Drug abuse			0.2983	0.57	0.3888
Absent	526(96.7)	167(98.2)			
Present	18(3.3)	3(1.8)			
Somatoform			0.8586	1.39	0.5086
Absent	520(95.6)	164(95.9)			
Present	24(4.4)	7(4.1)			
Hypochondriasis			0.4024	1.33	0.5354
Absent	510(93.6)	163(95.3)			
Present	35(6.4)	8(4.7)			
Bulimia			0.6874	0.98	0.9384

Psychiatric Co-Morbidity	Non-Hormone (ref) n(%)	Hormone n(%)	Unadjusted p-value	Adjusted* OR	Adjusted p-value
Absent	475(87.2)	147(86.0)			
Present	70(12.8)	24(14.0)			
Anxious			0.1551	0.75	0.2513
Absent	425(78.0)	142(83.0)			
Present	120(22.0)	29(17.0)			

* Models adjusted for race, ethnicity, marital status, medical insurance, years of schooling, CIRS total categories and recurrent episodes.

PDSQ: Psychiatric Diagnostic Screening Questionnaire, OCD: Obsessive-Compulsive Disorder, PTSD: Post-Traumatic Stress Disorder, CIRS: Cumulative Illness Rating Scale