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Impact of Reproductive Status and Age on Response of Depressed Women to Cognitive Therapy

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Abstract

Objective: Previous research suggests that reproductive hormones are potential affective modulators in mood disorders and may influence response to antidepressant medications. To our knowledge, there are no data on relationships between hormonal status and response to psychotherapy for recurrent major depressive disorder (MDD).

Methods: At two sites, female outpatients ($n = 353$), aged 18–70, with recurrent MDD received 12–14 weeks of cognitive therapy (CT). Menopausal status and age were based on self-report. In the parent study, nonresponse to therapy was defined as persistence of a major depressive episode (MDE) as defined by the DSM-IV or a final Hamilton Rating Scale for Depression-17-Item ($HRSD_{17}$) score of ≥ 12 or both. More traditional definitions of response (at least a 50% reduction in pretreatment $HRSD_{17}$) and remission (a final $HRSD_{17} \leq 6$) were also examined.

Results: Controlling for pretreatment $HRSD_{17}$ scores, there were no significant differences found in the rates of response to CT or symptom status among premenopausal, perimenopausal, and postmenopausal women.

Conclusions: We found no support for the hypotheses that response to CT or the rates of change in depressive symptoms are moderated by reproductive status. The findings, however, are limited by the absence of early follicular phase serum sampling/analysis to estimate hormone levels and the reliance on self-report to establish menopausal status. These data motivate a full investigation of the effects of reproductive status on response to psychosocial interventions.

Introduction

Over 30 years ago, Weissman and Klerman[1] concluded that women had an increased prevalence of depression. Today, although no gender differences are found in the overall rates of mental illness, the risk of experiencing an episode of major depressive disorder (MDD) remains double for women over that for men, according to contemporary epidemiologic findings.[2,3] Reasons proposed for this disparity include epidemiologic measurement bias (i.e., sampling bias, definition of case, differences in incidence, and assessment bias), biologic sex differences, social norms, and psychologic vulnerabilities.[4]

Recent longitudinal studies also suggest that the menopausal transition, in particular, can be a period of increased mood lability as well as significantly increased risk for new-onset depression.[5–8] Perimenopausal depression is diagnosed when an onset of MDD in midlife can be associated with menstrual cycle irregularity or somatic symptoms of the menopausal transition, a process of diagnosis that is based on the overall clinical picture.[9] The World Health Organization (WHO) defines perimenopause as a period characterized by hormonal variability, change in menses pattern, often accompanied by somatic and mood symptoms, typically beginning between 2 and 8 years before menopause and extending up to 1 year after the final menses.[10] Menopause is considered achieved after 12 months of amenorrhea (not due to another cause). In the United States, the median ages for this transition are 47.5 for perimenopause and 51 for completed menopause, with the average

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time between regular cycles and amenorrhea lasting approximately 8 years.[11]

Fluctuating hormones as a moderator of treatment

Included within studies of perimenopausal depression are investigations of the impact of hormonal milieu on treatment response. Because differential gender responses to antidepressant medications are reported in the literature,[12,13] several investigators have also examined whether reproductive status itself influences responsiveness to antidepressant medication, with most using age cutoffs as proxies for postmenopausal identification (age thresholds varying from 45 to 56).[12,14–17] Findings are mixed, with some study teams reporting differential response rates to classes of antidepressants between premenopausal and postmenopausal women.[12,14,18,19] Specifically, Harvey et al.[19] found in a clinical trial comparing imipramine with sertraline that premenopausal women experienced depressive symptom deterioration at a greater proportion of their visits than did postmenopausal women (8.6% vs. 4.5%, $p < 0.01$) or men (5.9%, $p < 0.01$). Conversely, another study team reported that younger women and men (< 50 years of age) and older men (> 50 years of age) had significantly higher remission rates (36%, 36%, and 35%, respectively) during treatment than did older women (28%, Wald chi-square = 4.2, df 1, $p < 0.04$).[14] However, others have failed to confirm such age-related differences in psychotropic treatment response.[15,17]

In studies of psychotherapy, gender has not been a consistent predictor of outcome, although most study designs are limited by differential dropout rates, small sample sizes, or small numbers of male participants.[20,21] To our knowledge, there have been no investigations of potential influences of reproductive status on women's response to psychotherapy. Given the cited research suggesting differential rates of symptomatic worsening and remission across reproductive groups of women receiving pharmacotherapy,[19] might perimenopausal processes moderate symptomatic response to psychotherapy?

Study aims

In view of this question surrounding potential associations between reproductive status and the response to psychotherapy for depression, data collected in a larger study (in which gender did not predict response) (Jarrett et al., unpublished observations) were analyzed for the purpose of comparing (1) response to cognitive therapy (CT) for depression in premenopausal, perimenopausal, and postmenopausal women and (2) rate of change in depressive symptoms over the course of 12–14 weeks of CT in the three groups of women.

Consistent with the biologic theories (hormonal instability/fluctuation and estrogen withdrawal) associating mood lability and depressive symptoms with women's reproductive events (i.e., puberty, pregnancy, postpartum, and the perimenopause; Table 1), we hypothesize women who have completed menopause (no longer menstruating) will experience greater benefit (response and faster relief from depressive symptoms) from CT compared to premenopausal or perimenopausal women. Further, consistent with epidemiologic findings and similar hypotheses in pharmacologic studies,[6,19,22] we hypothesized that the rate of change in depressive symptoms for women who are perimenopausal would be slower than that of premenopausal or postmenopausal women.

Table 1. Lifetime Prevalence of Major Depressive Disorder Across Female Life Cycle

Age range	*Corresponding developmental reproductive transition*	*Prevalence rate*
12–17	Puberty/maturation	12.4%[23]
18–29	Maturation/childbearing	16.0%[24]
30–44	Childbearing/perimenopause	19.3%[24]
45–59	Menopausal transition/ postmenopause	20.1%[24]
60+	Postmenopause	10.7%[24]

Materials and Methods

The rationale and design of the Continuation Phase Cognitive Therapy Relapse Prevention (C-CT-RP) trial and the specific elements of the protocol and cognitive therapy have been detailed elsewhere.[25] The trial was registered at ClinicalTrials.gov (NCT00118404, NCT00183664, and NCT00218764). Data were collected at two sites: the Department of Psychiatry, Psychosocial Research and Depression Clinic at The University of Texas Southwestern Medical Center (Principal Investigator: Robin B. Jarrett, Ph.D.) and in the Mood Disorders Treatment Research Program at the Western Psychiatric Institute and Clinic of the University of Pittsburgh Medical Center (Principal Investigators: Michael E. Thase, M.D. and Edward Friedman, M.D.). Research was approved by the Institutional Review Boards at each site before initiation and was reviewed annually through completion of the study. A summary of the procedures affecting the sample analyzed follows (Fig. 1).

Participants

From January 2000 to July 2008, 523 outpatients (353 women, 67%) between the ages of 18 and 70 years, diagnosed with recurrent MDD, were recruited from community settings using institutionally approved materials. Written informed consent was obtained at study screening and again at enrollment. Diagnosis of recurrent MDD was established according to the criteria in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. Text Revision (DSM-IV-TR).[26] Only data from women are included in this discussion.

Inclusion/exclusion criteria

Consenting outpatients were included when they (1) remitted between depressive episodes, had at least one prior episode with complete interepisode recovery, or had antecedent dysthymic disorder, and (2) scored ≥14 on the Hamilton Rating Score for Depression, 17-item ($HRSD_{17}$) at the initial and second interviews. Individuals were excluded if they (1) reported severe or poorly controlled concurrent medical disorders that may cause depression or require medication that could cause depressive symptoms, (2) suffered comorbid DSM-IV illnesses, such as bipolar disorder, active alcohol or substance dependence, primary obsessive compulsive disorder, or eating disorders, (3) could not

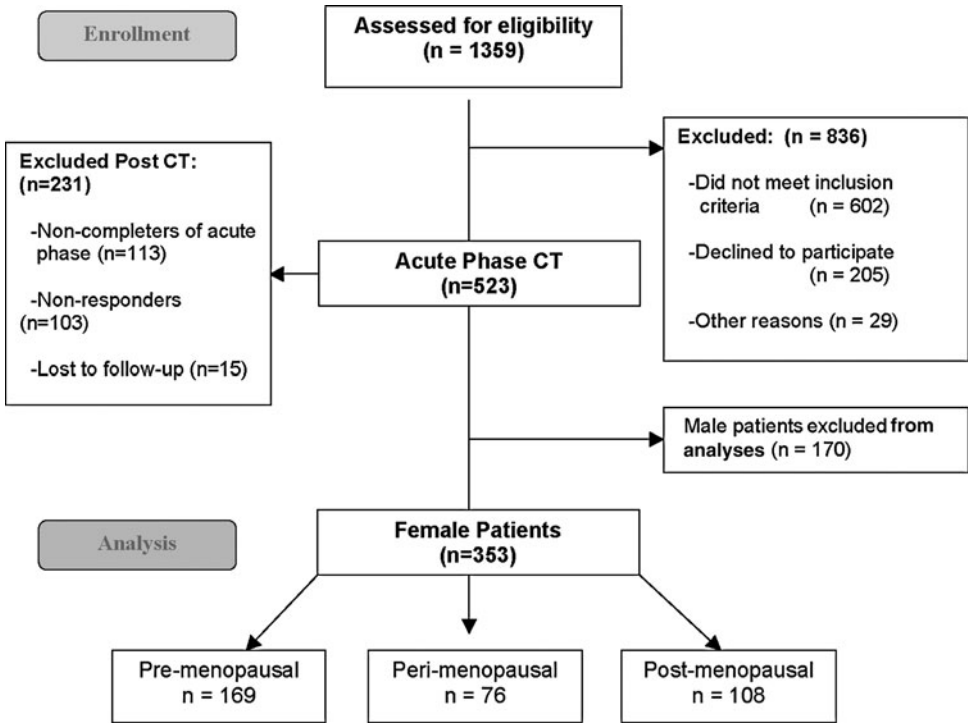

FIG. 1. The Consort 2010 flow diagram for division by strata. CT, cognitive therapy.

complete English language questionnaires, (4) were active suicide risks, (5) had previously not responded to a trial of at least 8 weeks of CT conducted by a certified therapist, (6) had previously not responded to at least 6 weeks of 40 mg of fluoxetine, (7) were pregnant or planned to become pregnant during the first 11 months after intake, or (8) did not provide informed consent. All excluded individuals were referred for nonprotocol treatment (e.g., hospitalization, pharmacotherapy, psychotherapy). If indicated after a review of medical history, a physical examination and appropriate laboratory tests were obtained to ensure that patients were diagnostically eligible. Patients who were taking psychotropic medication agreed to be withdrawn from the medication for at least 1 week before study entry.

Defining reproductive status

The investigator-developed demographic measure used in the study prompted the patient to record the presence or absence of hysterectomy, date of last menstrual period, and reproductive status. Women who self-reported the completion of menopause were considered postmenopausal ($n = 59$), and women who reported hysterectomy were defined as surgically menopausal ($n = 47$).[27] For the rest of the sample, reproductive status was inferred by age or the presence of a menstrual cycle in the previous year, with women > 18 years of age but < 42 classified as premenopausal ($n = 169$) and those between 42 and 51.5 considered perimenopausal ($n = 74$).[22] Two women older than 51.5 who did not complete the menopausal item but did not endorse menstruation in the previous year were designated as postmenopausal ($n = 2$), and 2 women older than 51.5 years but reporting menstruation in the last year were transferred to the perimenopausal group. Thus, the sample included 169 premenopausal, 76 perimenopausal, and 108 postmenopausal women. We believe this strategy provides a more accurate classification than relying on age alone and is consistent with strategies used by others.[28]

Procedures

The parent study contained four phases: (1) initial evaluation, (2) 16–20 individual sessions of acute phase CT, (3) 8 months of continuation phase treatment or follow-up only, and (4) 2 additional years of follow-up free of protocol treatment. We report findings from only the first two phases, using outcomes from the first blinded evaluation at the end of acute phase CT.

Acute phase CT

Acute phase CT consisted of 16–20 individual psychotherapy sessions, occurring over a maximum of 14 weeks and conducted according to the Beck treatment manual.[29] Sessions 1–8 were held twice weekly. Patients who experienced at least a 40% reduction in $HRSD_{17}$ scores by session 8 (early responders) began weekly sessions; patients who did not experience a 40% reduction (late responders) continued biweekly sessions for 4 additional weeks. Sixteen experienced therapists (11 male and 5 female) trained in CT conducted the treatment, meeting nearly weekly for supervision sessions at each site. Sessions were videotaped, randomly selected, and rated for adherence and competence according to the Cognitive Therapy Scale (CTS) by therapy supervisors and their teams.[30] No pharmacotherapy was provided during acute phase CT.

Measures

Patient background. Each patient completed an investigator-designed form to report demographics (e.g., age,

gender, ethnicity, marital status), use of medications, drugs, and alcohol; medical history; and reproductive status.

Structured Clinical Interview for DSM-IV (SCID).[31] The SCID is a clinician-administered, semistructured interview widely used in North American research to facilitate diagnosis of a range of psychiatric diagnoses according to the DSM-IV.[32] With the exception of dysthymic disorder, the reliability has been reported to be good to excellent (kappa ranging from 0.60 to 0.86) in diagnostic categories contained in the anxiety and mood disorder modules.[33] The screening, mood disorders, and mood differential modules were used to establish or rule out a diagnosis of MDD in participants.

Hamilton Rating Scale for Depression (HRSD). The $HRSD_{17}$[34] is a clinician rating scale designed to assess the severity of depressive symptoms in patients already diagnosed with MDD; higher scores reflect greater symptom severity. The clinician rates each of the 17 items on either a 3-point or 5-point scale, and the total score is determined by summing the item scores. Scores ≥ 24 indicate severe depression (typical of inpatients), scores ≤ 17 suggest mild symptoms (more typical of outpatients), and scores ≤ 6 indicate an absence of depressive symptoms (i.e., remission). With highly trained raters, the $HRSD_{17}$ has been found to have an excellent interrater reliability ($r = 0.85$).[35] There are few data on the internal consistency of the measure, but Schwab et al.[36] found that individual items correlated with a total score of 0.45–0.78. Regarding validity, Knesevich et al.[37] found $HRSD_{17}$ change scores to be correlated 0.68 with global change scores, and numerous studies have shown significant differences in the $HRSD_{17}$ scores of normal controls and patients with depression, supporting its criterion validity. The measure has also shown good convergent validity with other clinical self-report depression measures (r = approximately 0.83 and 0.70, respectively).[35] The current report makes use of 19 assessments, and the median alpha internal consistency is 0.784 (range 0.504–0.852).

Blinded clinical evaluations

A clinical evaluator masked to patient risk and treatment assignment collected symptom severity measures and assessed diagnostic status of the patients. All videotaped blinded evaluations were administered within approximately 7 days of their last acute treatment session, at the time the patient exited the protocol, or at any other time when a relapse or recurrence was suspected.

Outcome definitions

In the parent study, patients were judged to have not responded to acute phase CT if they (1) still met DSM-IV criteria for a major depressive episode (MDE) or (2) had a final $HRSD_{17}$ score of >12, or (3) both. In this report, patients are also classified as responders if they achieved at least a 50% reduction in pretreatment $HRSD_{17}$ scores at study exit and as remitters if they had a final $HRSD_{17} \leq 6$ at study exit.[38]

Statistical analyses

All analyses were generated using SAS software, version 9.2. The study statistician (A.M.) performed a power analysis on the protocol response data for the logistic regression model, with menopausal status as the independent variable (regressor) of interest and using the $HRSD_{17}$ score as a covariate. Based on this *post-hoc* power analysis and a sample size of 353 subjects, we are able to detect any odds ratio (OR) $\geq$ 1.43.

Results

Demographics

Race/ethnicity, marital and employment status, and years of education of the 353 female participants as reported at the diagnostic evaluation are all reported in Table 2, as are illness descriptors. The mean $HRSD_{17}$ score at final pretreatment evaluation was 20.7 (4.0), with no significant difference among the three reproductive status groups, although there were significant pretreatment demographic and clinical differences among the groups. Demographically, Caucasian women (78.5%, 277 of 353) and women engaged in full-time employment (42.0%, 147 of 353) were overrepresented in the sample (chi-square = 34.3, $p < 0.0001$ and chi-square = 48.7, $p < 0.0001$, respectively). Of clinical relevance, perimenopausal and postmenopausal women reported older age at onset of depression (chi-square = 62.0^{F}, $p < 0.0001$), longer duration of the current episode (chi-square = 11.3, $p < 0.004$), and longer duration of illness (chi-square = 101.5^{F}, $p < 0.0001$).

Number of CT sessions attended

Seventy-seven of the 353 (21.81%) women did not complete the acute phase CT (attending $<$ 14 of 16 sessions if considered an early responder or $<$ 18 of 20 sessions if a late responder). The noncompleters had an average of 5.78 (standard deviation [SD] = 5.32, median = 5) sessions of acute phase therapy. Among the 276 completers, 130 (47.10%) were early responders, with an average of 15.99 (SD = 0.44, median = 16) sessions of acute phase CT. One hundred forty-six of the 276 (52.89%) acute phase CT completers were late responders and attended an average of 19.97 sessions (SD = 0.22, median = 20; Table 3). The significant differences between those women who completed the acute phase CT (78.19%, 276 of 353) and those who did not were the same as the demographic pretreatment differences, namely, Caucasian women represented 65.44% (231 of 276) of the completers (chi-square = 12.94, $p < 0.0001$), and women employed full-time represented 35.14% (123 of 274) of the completers (chi-square = 15.84, $p < 0.0147$).

Response to CT

Hypothesis 1. Do more postmenopausal women respond to CT than do premenopausal or perimenopausal women? Based on hormonal theories, we hypothesized that a higher proportion of postmenopausal (natural or surgical) women would respond or have reduced depressive symptoms after CT compared to premenopausal and perimenopausal women. The results did not allow us to reject the null hypothesis that the groups differed.

In the group of premenopausal women, 37.3% (63 of 169) were classified as nonresponders, using the protocol definition, compared to 40.8% (31 of 76) in the perimenopausal group and 37.0% (40 of 108) in the postmenopausal group. Using logistic regression analysis, with the pretreatment $HRSD_{17}$ score included in the model as a covariate and

Table 2. Pretreatment Demographic, Clinical, and Cognitive Characteristics of Women at Different Menopausal Status

Domain	*Characteristic*	*Total* n = *353*	*Premenopausal* n = *169*[a]	*Perimenopausal* n = *76*[b]	*Postmenopausal* n = *108*[c]	*Test statistic, p value*
Demographic	Race, *n* (%)					Chi-square = 34.3[e] $p < 0.0001$
	White	277 (78.5)	111 (65.7)	65 (85.5)	101 (93.5)	
	Black	41 (11.6)	30 (17.8)	7 (9.2)	4 (3.7)	
	Hispanic	22 (6.2)	17 (10.1)	2 (2.6)	3 (2.8)	
	Other	13 (3.7)	11 (6.5)	2 (2.6)	0 (0.0)	
	Age mean (SD)	41.7 (12.4)	30.8 (6.1)	46.5 (2.9)	55.3 (6.8)	F = 623.1[d] $p < 0.0001$
	Marital status, *n* (%)					Chi-square = 4.4 $p < 0.112$
	Single	197 (55.8)	103 (61.0)	42 (55.3)	52 (48.2)	
	Partnered	156 (44.2)	66 (39.0)	34 (44.7)	56 (51.8)	
	Education mean (SD)	14.9 (2.9)	14.8 (2.8)	15.4 (3.0)	14.7 (3.0)	F = 1.4 $p < 0.247$
	Employment, *n* (%)					
	Full-time	147 (42.0)	76 (45.2)	31 (41.9)	40 (37.0)	Chi-square = 48.7
	Part-time	49 (14.0)	22 (13.1)	8 (10.8)	19 (17.6)	$p < 0.0001$
	Homemaker/caregiver	30 (8.6)	11 (6.6)	8 (10.8)	11 (10.2)	
	Student	17 (4.9)	16 (9.5)	1 (1.4)	0 (0.0)	
	Retired	11 (3.1)	0 (0.0)	0 (0.0)	11 (10.2)	
	Other	16 (4.6)	4 (2.4)	6 (6.1)	6 (5.6)	
	Unemployed	80 (22.9)	39 (23.2)	20 (27.0)	21 (19.4)	
Severity and Clinical	$HRSD_{17}$ At final pretreatment follow-up	20.7 (4.0)	20.8 (4.1)	20.5 (3.7)	20.7 (4.2)	F = 0.1 $p < 0.931$
	Age at onset, mean (SD), years	20.8 (10.3)	16.1 (6.2)	24.4 (10.3)	25.5 (12.1)	Chi-square = 62.0[f]
	Median	18.0	16.0	24.0	23.0	$p < 0.0001$
	Length of current episode, mean (SD), months	22.9 (36.2)	16.1 (22.0)	30.6 (54.8)	28.2 (36.2)	Chi-square = 11.3[f]
	Median	9.0	7.0	10.0	14.0	$p < 0.004$
	Length of illness, mean (SD) years	20.4 (11.7)	14.2 (7.4)	21.6 (10.2)	29.3 (12.1)	Chi-square = 101.5[f]
	Median	19.0	14.0	22.0	29.5	$p < 0.0001$
	No. of episodes, median	4.0	4.0	3.0	4.0	Chi-square = 1.3[f] $p < 0.512$
	Comorbid DSM-IV diagnoses, *n* (%)					
	Current	167 (47.3)	85 (50.3)	37 (48.7)	45 (41.7)	Chi-square = 2.0 $p < 0.360$
	Lifetime	270 (76.5)	138 (81.7)	55 (72.4)	77 (71.3)	Chi-square = 4.8 $p < 0.089$
	Current double depression, *n* (%)	19 (5.4)	6 (3.6)	4 (5.3)	9 (8.3)	Chi-square = 3.0 $p < 0.227$
	Depressive subtype, *n* (%)					
	RDC endogenous, definite	133 (38.3)	62 (37.6)	36 (48.0)	35 (32.7)	Chi-square = 5.4 $p < 0.109$
	DSM-IV melancholia	130 (37.0)	70 (41.4)	30 (40.0)	30 (28.0)	Chi-square = 5.4 $p < 0.068$

[a] *n* reduced 165 RDC endogenous definite.
[b] *n* reduced to 75 for DSM-IV melancholia and RDC endogenous definite.
[c] *n* reduced to 107 for DSM-IV melancholia and RDC endogenous definite.
[d] F statistics are from one-way ANOVA analysis.
[e] Chi-square statistics for contingency tables.
[f] Chi-square statistics are from Kruskal-Wallis test for medians.
$HRSD_{17}$, 17-item Hamilton Rating Scale for Depression; SD, standard deviation; RDC, research diagnostic criteria.

reproductive status entered as an independent variable, there were no statistically significant differences in nonresponse rates (chi-square [*df*, 2] = 0.45, $p \leq 0.799$; for perimenopausal women, OR = 0.837, 95% confidence interval [CI] 0.48-1.47; for postmenopausal women, OR = 1.01, 95% CI 0.60-1.68).

Regarding the conventional definition of remission ($HRSD_{17} \leq 6$ at study exit), 32.5% (55 of 169) of premenopausal women in the study sample were classified as remitted compared to 26.3% (20 of 76) of perimenopausal and 27.8% (30 of 108) of postmenopausal women. Adjusted for

Table 3. Average Number of Acute Phase Sessions by Menopause Status for Completers and Noncompleters of Acute Phase Cognitive Therapy

Group of women	*Total*	*Premenopausal*[a]	*Perimenopausal*[b]	*Postmenopausal*[c]
Noncompleters, $n=77$*	5.8 (5.3)	3.9 (4.4)	7.7 (6.2)	8.3 (4.8)
Completers				
Early Responders, n 130	16.0 (0.4)	15.9 (0.3)	16.2 (0.8)	16.0 (0.2)
Late Responders, n=130	20.0 (0.2)	20.0 (0.1)	19.9 (0.2)	20.0 (0.3)

[a]Among the premenopausal women, 41 are noncompleters, 67 are early responders, and 61 are late responders.
[b]Among the perimenopausal women, 19 are noncompleters, 23 are early responders, and 34 are late responders.
[c]Among the postmenopausal women, 17 are noncompleters, 40 are early responders, and 51 are late responders.
*$p \leq 0.05$ comparing patients in the three groups;
$p \leq 0.05$ comparing patients in the premenopausal and perimenopausal groups;
$p \leq 0.05$ comparing patients in the premenopausal and postmenopausal groups;
$p \leq 0.05$ comparing patients in the perimenopausal and postmenopausal groups.

pretreatment $HRSD_{17}$, there was no statistically significant difference in the remission rate among the three groups (chi-square [*df*, 2]=0.92, $p=0.630$; for perimenopausal women, OR=1.366, 95% CI 0.51-3.70; for postmenopausal women, OR=1.879, 95% CI 0.51-6.92).

Similarly, 52.1% (88 of 169) of premenopausal women experienced at least 50% reduction in the pretreatment $HRSD_{17}$ compared to 50.0% (38 of 76) in the perimenopausal group, and 50.9% (55 of 108) in the postmenopausal group. Adjusted for pretreatment $HRSD_{17}$, there were no statistically significant differences between women reporting at least 50% reduction in pretreatment $HRSD_{17}$ (chi-square [*df*, 2]=0.14, $p=0.931$; for perimenopausal women, OR=0.860, 95% CI 0.39-1.89; for postmenopausal women, OR=0.864, 95% CI 0.31-2.38).

Hypothesis 2. Do premenopausal and perimenopausal women have a lower rate of change in depressive symptoms (as measured by the $HRSD_{17}$ at each acute phase visit) than postmenopausal women during their participation in acute phase CT? In view of the mood lability and increased depressive symptoms associated with the menstrual cycle as well as the menopausal transition,[39,40] we hypothesized that the slope of $HRSD_{17}$ scores for women who have completed menopause would be steeper than that of women reporting menstrual cycles.

Although the $HRSD_{17}$ scores decreased dramatically during the course of acute phase therapy ($F_{1,640}=576.07$, $p<0.001$), the slopes of $HRSD_{17}$ scores from the two groups did not differ significantly. Using a hierarchical linear model with all available $HRSD_{17}$ scores across CT as the dependent variable and reproductive status (age categories) and pretreatment $HRSD_{17}$ score as covariates, we estimated random intercepts as well as random slopes, measuring the rate of change over time within each woman, considering time a random effect. The $HRSD_{17}$ scores from the premenopausal; perimenopausal, and postmenopausal women were compared in terms of mean intercept (mean $HRSD_{17}$ at the beginning of the acute phase) and slope (rate of change over the course of acute phase). There were no statistically significant differences among premenopausal, perimenopausal, and postmenopausal women in terms of mean $HRSD_{17}$ levels at the beginning of the acute phase treatment ($F_{2,511}=0.05$, $p=0.951$). Additionally, there were no statistically significant differences found among premenopausal, perimenopausal, and postmenopausal women in terms of rate of decrease in $HRSD_{17}$ score during the acute phase therapy ($F_{2,638}=2.23$, $p=0.108$).

Discussion

Although depressive symptoms have long been linked with hormonal status in women, there was no evidence that reproductive status influenced outcomes in this large sample of women receiving CT for recurrent MDD. Of menstruating women (233 of 353) in the sample, 75% (176) reported experiencing cycle-related changes in mood lability (50.2%, 117 of 176, premenopausal; 25.3%, 59 of 176, perimenopausal; 0% postmenopausal). Of the 24.5% (57 of 233) who reported no cycle-related mood lability, 73.68% (42 of 57) were premenopausal, and 26.32% (15 of 57) were perimenopausal (0% postmenopausal). Given our inability to reject the null hypothesis in a population of women who dominantly report cycle-related mood changes, the findings provocatively suggest CT may have moderated the presumed association between depressive symptoms and women's hormonal fluctuations. Recent biologic work suggests that independent of pharmacologic interventions, psychotherapy may stimulate changes in cAMP response element-binding protein (CREB) phosphorylation and brain-derived neurotrophic factor (BDNF) plasma levels in the brain, both implicated in the biomarkers of depression and anxiety.[41] Other bodies of research posit cognitive behavioral therapy (CBT) may normalize amygdala and dorsolateral prefrontal cortical activity in individuals with depression; this is supported by functional imaging demonstrating brain changes.[42,43]

This is the first investigation of potential relationships between psychotherapy response and female reproductive status; however, there is a small body of literature reporting on potential relationships between antidepressant therapy and hormonal status. Consistent with our findings, Cassano et al.[15] did not find a differential symptomatic response to fluoxetine treatment in a sample of premenopausal, perimenopausal, and postmenopausal women diagnosed with MDD. In a study of men and women diagnosed with chronic MDD or MDD superimposed on dysthymia (double depression), however, premenopausal women deteriorated at a greater proportion of their visits than did postmenopausal women or men, leading the investigators to conclude that acute worsening of depression *was* associated with reproductive variables.[19] Other research teams have also reported interactions between age and selective serotonin reuptake inhibitor

(SSRI) response, with postmenopausal women demonstrating poorer response to medication.[14] Reproductive status has also been associated with differential responses to sertraline and imipramine, with women more likely to respond to sertraline and men more likely to respond to imipramine (Wald chi-square = 6.80, df = 1, $p = 0.009$).[12]

It is important to note that no gender differences in response to CT were found in the complete dataset including men (chi-square = 0.04, $p = 0.85$; Jarrett et al., unpublished observations). Indeed, a recent review reported that the evidence available fails to support differential response rates of men and women with unipolar depression to psychotherapy.[21] In the related field of pharmacologic response, studies investigating associations between gender and antidepressant medication responses are equivocal, with some groups demonstrating differential responses,[12,44] and others failing to find such distinctions.[16,45,46] However, authors consistently conclude that insufficient research has been conducted to fully address the questions surrounding potential hormonal mediators or moderators of treatment response.

Limitations

Inferring hormonal status solely by self-report or chronologic age limits confident interpretation of these results. Simply using age for hypothesizing perimenopausal status introduces age-related confounders that may mediate or moderate outcomes alongside reproductive status. In addition, information gathered about hormonal interventions was not complete, preventing identification of women currently on *any* form of hormonal therapy (item inquired about hormonal contraception only). It is notable, however, that none of the women we categorized as postmenopausal reported cycle-related changes, indicating that assignment was likely accurate. As investigators did not collect information about hormone replacement therapy (HRT), study findings may be confounded by unknown moderators or mediators related to such hormone augmentation. Further limitations to our conclusions include lack of a control group and selection of patients with recurrent depression or dysthymic disorder for study. Characteristics of this subset of depressed women may impact on treatment response in a manner not representative of the treatment response by women experiencing a first onset of depression.

Implications for future research

As far as we have found in the literature, this is the largest study of adult females receiving psychotherapy for recurrent MDD, a population strongly represented in primary care patient visits.[47] Future research could inform this inquiry further and add confidence by including biologic measures of follicular phase status, more extensive reproductive-related demographic descriptors (such as average length of menstrual cycle, number of cycles in the previous 12 months, previous or ongoing use of HRT), and inquiry surrounding known age-related confounders (e.g., caring for aged parents, quality of life, status/independence of children, employment status).

Conclusions

Despite decades of research suggesting depressive symptoms are linked to menopause as well as the general public belief that women are more symptomatic around menstruation, we found no parallel differences in depressive symptom response or rate of symptom change among menstruating, perimenopausal, or postmenopausal women during acute CT for recurrent depression. Future research advantaged by early follicular phase serum sampling/analysis to establish hormone levels could further inform hypotheses about the link between depressive symptoms and hormonal status as well as the potential benefits of CT to moderate such an association.

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Disclosure Statement

A.R.B. and A.M. report that no competing financial interests exist. During the past 2 years, M.E.T. has consulted with, served on advisory boards for, or received honoraria for talks from AstraZeneca, Bristol-Myers Squibb Company, Eli Lilly and Company, Forest Laboratories, GlaxoSmithKline, Janssen Pharmaceutica, Lundbeck, MedAvante, Inc., Neuronetics, Inc., Novartis, Otsuka, Pamlab, Pfizer Pharmaceuticals, Schering-Plough, Shionogi, Shire US Inc., Supernus Pharmaceuticals, Takeda, Transcept Pharmaceuticals, and Wyeth Pharmaceuticals, and he has received grant support from Eli Lilly and Company, Forest Laboratories, GlaxoSmithKline, Otsuka, and Sepracor, Inc., in addition to funding from the NIMH. He has equity holdings for MedAvante, Inc., and has received royalties from American Psychiatric Publishing, Inc. (APPI), Guilford Publications, Herald House, and W.W. Norton & Company, Inc. Two books currently promoted by the APPI specifically pertain to CT. His spouse is an employee of Embryon, Inc. (formerly Cardinal Health and Advogent), which does business with several pharmaceutical companies that market medications used to treat depression. R.B.J. is a paid consultant to the NIH, and her medical center collects the payments from the CT she personally provides to patients.

References

1. Weissman MM, Klerman GL. Sex differences and the epidemiology of depression. Arch Gen Psychiatry 1977;34:98–111.
2. Kessler RC, ed. The epidemiology of depression among women. New York: Cambridge University Press, 2006.
3. Kessler RC. Epidemiology of women and depression. J Affec Disord 2003;74:5–13.

4. Wilhelm K, Parker G, Geerligs L, Wedgwood L. Women and depression: A 30 year learning curve. Aust NZ J Psychiatry 2008;42:3–12.
5. Bromberger JT, Matthews KA, Schott LL, et al. Depressive symptoms during the menopausal transition: The Study of Women's Health Across the Nation (SWAN). J Affect Disord 2007;103:267–272.
6. Bromberger JT, Assmann SF, Avis NE, Schocken M, Kravitz HM, Cordal A. Persistent mood symptoms in a multiethnic community cohort of pre- and perimenopausal women. Am J Epidemiol 2003;158:347–356.
7. Cohen LS, Soares CN, Vitonis AF, Otto MW, Harlow BL. Risk for new onset of depression during the menopausal transition: The Harvard Study of Moods and Cycles. Arch Gen Psychiatry 2006;63:385–390.
8. Freeman EW, Sammel MD, Lin H, Nelson DB. Associations of hormones and menopausal status with depressed mood in women with no history of depression. Arch Gen Psychiatry 2006;63:375–382.
9. Schmidt PJ, Rubinow DR. Reproductive ageing, sex steroids and depression. J Br Menopause Soc 2006;12:178–185.
10. World Health Organization. Research on the menopause in the 1990's: Report of a WHO scientific group. Geneva: WHO, 1996.
11. Rasgon N, Shelton S, Halbreich U. Perimenopausal mental disorders: Epidemiology and phenomenology. CNS Spectr 2005;10:471–478.
12. Kornstein SG, Schatzberg AF, Thase ME, et al. Gender differences in treatment response to sertraline versus imipramine in chronic depression. Am J Psychiatry 2000;157:1445–1452.
13. Kornstein SG. Gender differences in depression: Implications for treatment. J Clin Psychiatry 1997;58 (Suppl 15):12–18.
14. Thase ME, Entsuah R, Cantillon M, Kornstein SG. Relative antidepressant efficacy of venlafaxine and SSRIs: Sex-age interactions. J Womens Health 2005;14:609–616.
15. Cassano P, Soares CN, Cusin C, Mascarini A, Cohen LS, Fava M. Antidepressant response and well-being in pre-, peri- and postmenopausal women with major depressive disorder treated with fluoxetine. Psychother Psychosom 2005;74:362–365.
16. Entsuah AR, Huang H, Thase ME. Response and remission rates in different subpopulations with major depressive disorder administered venlafaxine, selective serotonin reuptake inhibitors, or placebo. J Clin Psychiatry 2001;62:869–877.
17. Quitkin FM, Stewart JW, McGrath PJ, et al. Are there differences between women's and men's antidepressant responses? Am J Psychiatry 2002;159:1848–1854.
18. Dorsey CM, Lee KA, Scharf MB. Effect of zolpidem on sleep in women with perimenopausal and postmenopausal insomnia: A 4-week, randomized, multicenter, double-blind, placebo-controlled study. Clin Ther 2004;26:1578–1586.
19. Harvey AT, Silkey BS, Kornstein SG, Clary CM. Acute worsening of chronic depression during a double-blind, randomized clinical trial of antidepressant efficacy: Differences by sex and menopausal status. J Clin Psychiatry 2007;68:951–958.
20. Frank E, Thase ME, Spanier CA, Reynolds CF 3rd, Kupfer DJ. Gender-specific response to depression treatment. J Gend Specific Med 1999;2:40–44.
21. Parker G, Blanch B, Crawford J. Does gender influence response to differing psychotherapies by those with unipolar depression? J Affect Disord 2011;130:17–20.
22. Bromberger JT, Schott LL, Kravitz HM, et al. Longitudinal change in reproductive hormones and depressive symptoms across the menopausal transition: Results from the Study of Women's Health Across the Nation (SWAN). Arch Gen Psychiatry 2010;67:598–607.
23. National Institute of Mental Health. Major depressive disorder in children. Available at www.nimh.nih.gov/statistics/1MDD_CHILD.shtml Accessed August 28, 2012.
24. Medicine HSo. National Comorbidity Survey (NCS): NCS-R lifetime prevalence estimates, 2007. Available at www.hcp.med.harvard.edu/ncs/ftpdir/NCS-R_Lifetime_Prevalence_Estimates.pdf
25. Jarrett RB, Thase ME. Comparative efficacy and durability of continuation phase cognitive therapy for preventing recurrent depression: Design of a double-blinded, fluoxetine- and pill placebo-controlled, randomized trial with 2-year follow-up. Contemporary Clin Trials 2010;31:355–377.
26. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th ed. Text revision. Washington, DC: American Psychiatric Association, 2000.
27. Shifren JL, Avis NE. Surgical menopause: Effects on psychological well-being and sexuality. Menopause 2007;14:586–591.
28. Sowers MF, Crawford SL, Sternfeld B, Morganstein D, Gold EB, Greendale GA. SWAN: A multicenter, multiethnic, community-based cohort study of women and the menopause. In: Lobo R, Kelsey J, Marcus R, eds. Menopause: Biology and pathobiology. San Diego, CA: Academic Press, 2000:175–188.
29. Beck JS. Cognitive therapy: Basics and beyond. New York: Guilford Press, 1995.
30. Vallis T, Shaw BF, Dobson KD. The Cognitive Therapy Scale: Psychometric properties. J Consult Clin Psychol 1986;54:381–385.
31. First MB, Spitzer RL, et al. Structured clinical interview for DSM-IV axis 1 disorders: (Scid 1) Clinician Version. Arlington, VA: American Psychiatric Publishing, Inc., (1997).
32. Summerfeldt LJ, Antony MM. Structured and semistructured diagnostic interviews. New York: Guilford Press, 2002.
33. Brown TA, Di Nardo PA, Lehman CL, Campbell LA. Reliability of DSM-IV anxiety and mood disorders: Implications for the classification of emotional disorders. J Abnorm Psychol 2001;110:49–58.
34. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62.
35. Clark LA, Watson D. Tripartite model of anxiety and depression: Psychometric evidence and taxonomic implications. J Abnorm Psychol 1991;100:316–336.
36. Schwab JJ, Bialow MR, Holzer CE. A comparison of two rating scales for depression. J Clin Psychol 1967;23:94–96.
37. Knesevich JW, Biggs JT, Clayton PJ, Ziegler VE. Validity of Hamilton Rating Scale for Depression. Br J Psychiatry 1977;131:49–52.
38. Rush AJ, Kraemer HC, Sackeim HA, et al. Report by the ACNP Task Force on response and remission in major depressive disorder. Neuropsychopharmacology 2006;31:1841–1853.
39. Hendrick V, Altshuler LL, Burt VK. Course of psychiatric disorders across the menstrual cycle. Harvard Rev Psychiatry 1996;4:200–207.
40. Burt VK, Stein K. Epidemiology of depression throughout the female life cycle. J Clin Psychiatry 2002;63 (Suppl 7):9–15.
41. Koch JM, Hinze-Selch D, Stingele K, et al. Changes in CREB phosphorylation and BDNF plasma levels during psychotherapy of depression. Psychother Psychosom 2009;78:187–192.

42. Mayberg HS. Defining neurocircuits in depression: Strategies toward treatment selection based on neuroimaging phenotypes. Psychiatr Ann 2006;36:259–268.
43. DeRubeis RJ, Siegle GJ, Hollon SD. Cognitive therapy versus medication for depression: Treatment outcomes and neural mechanisms. Nat Rev Neurosci 2008;9:788–796.
44. Baca E, Garcia-Garcia M, Porras-Chavarino A. Gender differences in treatment response to sertraline versus imipramine in patients with nonmelancholic depressive disorders. Prog Neuro-Psychopharmacol Biol Psychiatry 2004;28: 57–65.
45. Kornstein SG, Wohlreich MM, Mallinckrodt CH, Watkin JG, Stewart DE. Duloxetine efficacy for major depressive disorder in male vs. female patients: Data from 7 randomized, double-blind, placebo-controlled trials. J Clin Psychiatry 2006;67:761–770.
46. Bigos KL, Pollock BG, Stankevich BA, Bies RR. Sex differences in the pharmacokinetics and pharmacodynamics of antidepressants: An updated review. Gend Med 2009;6:522–543.
47. Simon GE, Arterburn D, Rohde P, et al. Obesity, depression, and health services costs among middle-aged women. J Gen Intern Med 2011;26:1284–1290.

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