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Original article

Effectiveness of antidepressant treatments in pre-menopausal versus post-menopausal women: A pilot study on differential effects of sex hormones on antidepressant effects

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Abstract

The incidence or recurrence of major depression is greatly increased in women during the transition to and after menopause and hormonal changes occurring during these periods are thought to play an important role in depressive recurrence. It has been also suggested that a chronic hypoestrogenic state may reduce the response to antidepressant drugs, but whether or not, and the extent to which hormonal changes related to menopause influence the response to antidepressant drugs, is yet to be determined. Thirty-nine female patients ($n = 17$ in pre-menopause; $n = 22$ in post-menopause) with major depressive disorder (MDD) based on DSM-IV criteria, who were not on hormonal replacement therapy, participated in the study in order to prospectively evaluate the effect of menopausal status and its hormonal correlates on the effectiveness of antidepressant treatment for 6 weeks. The Hamilton Depression Rating Scale-17 item (HAMD), the Montgomery–Åsberg Depression Rating Scale (MADRS) and the Clinical Global Impression Severity scale (CGI-S) were administered at baseline, week 1, week 3, and week 6. The CGI-I scale was also assessed at weeks 1, 3, and 6. After controlling for age, age at onset, baseline symptom severity, antidepressant dosage and hormonal levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH) and estradiol (E2), post-menopausal women showed a poor response to antidepressants over 6 weeks of treatment, compared to the response of pre-menopausal women. Old age and high levels of FSH were also associated with the efficacy of antidepressants in post-menopausal women. In conclusion, sex hormones are known to interact with serotonergic, noradrenergic and dopaminergic systems. Despite methodological limitations, our study suggests that menopausal status and old age are predictors of a poor response to antidepressant treatment. Furthermore, the FSH may interfere with the mechanism of action of the antidepressant agents. Hence, larger, randomized and controlled trials are warranted to expand our understanding of this area.

Keywords: Depression; Menopause; Antidepressant; Mood disorders

1. Introduction

It is well known that the prevalence of major depressive disorder (MDD) is twice as high in women than it is in men; this gender gap begins in adolescence and continues to midlife [1], with a further increased incidence of MDD in women during peri-menopause and menopause [2–4].

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Menopause is the natural permanent cessation of menstruation, resulting from the loss of ovarian follicular development [5]. The transition to menopause is characterized by significant hormonal changes. During peri-menopause and in the post-menopausal period, there is a great reduction in the secretion of estradiol, the major estrogens in humans. Other changes involve the levels of follicle-stimulating hormone (FSH, that stimulates the growth of immature ovarian follicles), inhibin (a peptide that inhibits the synthesis and secretion of FSH), activin (a peptide that enhances FSH synthesis and secretion), follistatin (a gonadal protein that inhibits FSH release), luteinizing hormone (LHthat triggers ovulation), progesterone (a hormone necessary for gestation), gonadotropin-releasing hormone (responsible for the release of FSH and LH from the anterior pituitary) and androgens [6].

It has been suggested that such hormonal changes during the immediate pre-menopausal years are responsible for affective instability, depressive symptoms and the onset/recurrence of MDD [2,7]. There is in fact evidence that serotonergic neurons in the brain are sensitive to the presence or absence of the ovarian hormones, estrogens and progesterone. In fact, the presence of endogenous and exogenous estrogens modulates the serotonergic, noradrenergic and dopaminergic neurotransmission [8–11], induces new dendritic spine formation and regulates neurotropic factors [12].

In addition, a chronic hypoestrogenic state may reduce the response to selective serotonin reuptake inhibitors (SSRIs) [13–15] and there is evidence that hormonal replacement therapy (HRT) improves the effect of SSRIs in post-menopausal depressed patients as well [16–19]. However, whether or not, and the extent to which, hormonal changes related to menopause influence the response to antidepressant drugs, is yet to be determined. Papers previously published on this issue, focused on the potential benefit of hormonal replacement therapy (HRT) combined with antidepressants or alone in the treatment of peri-menopausal and post-menopausal depressive women (for a recent review see [20]). In the present study, we aimed to investigate for the first time the response to antidepressant treatment in post-menopausal women not receiving concurrent HRT, to evaluate the effect of menopausal status, and its hormonal correlates, on effectiveness of antidepressants.

2. Subjects and methods

2.1. Design

A prospective, 6-week, open-label naturalistic study for comparison of antidepressant response in pre-menopausal versus post-menopausal women with MDD.

2.2. Subjects

The subjects consisted of 39 Korean female patients who were diagnosed as MDD, according to the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) criteria [21]. All patients were recruited following an advertisement at the Depression Clinical Research Unit of Kangnam St. Mary's Hospital, which is a teaching hospital located in Seoul, South Korea. Post-menopause was defined as amenorrhea for more than 12 months [2], while pre-menopausal women were defined by the absence of significant vasomotor symptoms or menstrual irregularity; if irregular cycles were reported, we included women younger than 37 years [2]. Exclusion criteria were: serious suicide risk, hormonal treatment, pregnancy, lactation, participation in another study in the previous 30 days, psychotherapy initiated in the last 6 months, substance use disorder in the last 6 months, any other current occurrence or past history of axis I disorders other than MDD such as psychotic disorders and bipolar disorders, axis II disorders, significant medical conditions such as malignancy, hysterectomy or oophorectomy. The study was strictly reviewed and approved by the Institutional Review Board at Kangnam St. Mary's Hospital and all subjects provided written informed consent after all study procedures were explained to them prior to participating in the study.

2.3. Psychiatric diagnosis

Following entry into the study, the axis I diagnosis was evaluated by consensus between the two board-certified psychiatrists (CUP, TSK) according to the DSM-IV criteria, using a structured clinical interview for DSM-IV Axis I Disorders-Clinical Version [22].

2.4. Medications

Currently available antidepressants (e.g., selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, noradrenergic and specific serotonin antidepressants and tricyclic antidepressants, etc.) were recommended to be dosed using a flexible titration strategy within approved dosage guidelines based on each manufacturer's package inserts, with consideration of an individual's clinical response and tolerability. No other psychotropic medications were permitted during the study with the exception of hypnotics for insomnia and benzodiazepoines for anxiety. Over-the-counter (OTC) medications (e.g., acetaminophen, etc.) were only allowed on an as-needed basis.

2.5. Assessments

At baseline, all patients were evaluated for depressive severity by the Hamilton Depression Rating Scale-17 item (HAMD) [23] and the Montgomery–Åsberg Depression Rating Scale (MADRS) [24]; the Clinical Global Impression Severity scale (CGI-S) [25] was also administered. All women were prospectively followed for 6 weeks during antidepressant treatment and evaluated by the HAMD, the MADRS, the CGI-S and the Clinical Global Impression Scale-Improvement (CGI-I) [25] at weeks 1, 3 and 6.

Non-fasting blood samples for hormone assays were collected at the intake. Levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH) and estradiol (E2) were tested. Assays of hormonal levels were conducted by

immunoradiometric method using commercially available kits (FSH, BioSourceFSH-IRMA Kit; LH, Biosourse LHsp-IRMA Kit; E2, Biosourse E2-RIA-CT Kit, Biosourse Europe SA, Nivelles, Belgium).

2.6. Statistical analysis

Clinical and demographic features in pre-menopausal and post-menopausal women were analyzed by the chi-square test and the Student's *T*-test. The association between menopausal status and response to antidepressant treatment was analyzed by the analysis of covariance for repeated measures, including the following as covariates: baseline depressive severity, age, treatment dosages, hormonal levels of LH, E2 and FSH, and other potential confounders. Furthermore, a regression analysis was performed to analyze the impact of each factor on final depressive severity (week 6).

Since different antidepressant drugs require different dosages, we uniformed doses according to the Antidepressant Treatment History Form [26] and for each woman we calculated the citalopram equivalent dose received during the 6 weeks of follow-up.

With a standard level of significance ($\alpha = 0.05$), in our sample we had a post-hoc sufficient power (0.80) to detect only large effect sizes ($d = 0.82$), corresponding to a difference between pre-menopausal and post-menopausal women of 4.95 points on both the final HAMD and MADRS scores, of 0.7 points on the CGI-S scores and of 0.6 on the CGI-I scores (explained variance range: 14.2–14.5%). Because of the small sample size we had a low statistical power (a priori 0.46), thus smaller influences exerted by the menopausal status on recovery from depression with antidepressant treatment may have been largely missed.

3. Results

3.1. Subjects

Seventeen patients were pre-menopausal (44%) and 22 patients were post-menopausal (56%). Pre-menopausal women had a mean age of 36 ± 5 years, with a mean age at the onset of depression of 34 ± 7 years. Post-menopausal women were significantly older (on average 61 ± 6 years; $T = 10.9$, $P < 0.0001$), and also significantly older at the onset of their depressive disorder (55 ± 10 years; $T = 6.6$, $P < 0.0001$). Other detailed demographics and clinical features of the pre-menopausal and post-menopausal women are described in Table 1.

Post-menopausal women were not different from pre-menopausal women for age at menarche and marital status. Pre-menopausal women were less likely to have had children, but this was probably due to their younger age. Pre-menopausal and post-menopausal mothers were, however, not different for the age at their first partum and, overall, the women were not different for the number of past spontaneous or induced abortions. The two groups were not different for the presence of medical conditions or family history of psychiatric disorders.

3.2. Age at onset

As mentioned in the sample description, post-menopausal women were significantly older at the time of their first illness episode. However, age at onset was not correlated with depressive severity at any stage of the follow-up (data not shown, all *P*-values >0.05).

3.3. Hormonal levels

As expected, post-menopausal women were markedly different from pre-menopausal women for levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH) and estradiol (E), with increased levels of FSH and LH and decreased levels of E2 in post-menopausal women.

In the overall sample, levels of LH and E2 were not correlated with depressive severity at any stage of the follow-up (data not shown, all *P*-values >0.05), while levels of FSH were found to be significantly associated with severity of depression at weeks 3 and 6 (HAMD week 3, $R = 0.34$, $P = 0.04$; week 6, $R = 0.50$, $P = 0.002$; MADRS week 6, $R = 0.50$, $P = 0.002$).

Analyzing the pre- and post-menopausal women separately (Table 2), FSH levels were not associated with depressive severity in pre-menopausal women, while LH levels were associated with baseline severity, and week 3 severity and improvement in this group (at the MADRS and CGI-I). Furthermore, E2 levels were associated with depressive severity and improvement at week 3 in pre-menopausal women (at the HAMD, MADRS and CGI-I), as well as with improvement at week 1 at the CGI-I in post-menopausal women.

3.4. Medications

Prescribed antidepressants were as follows: mirtazapine ($n = 14$, 36%), paroxetine ($n = 13$, 33%), citalopram ($n = 4$, 10%), venlafaxine ($n = 2$, 5%) and combined treatment, consisting of mirtazapine plus other antidepressant, specifically citalopram ($n = 1$), paroxetine ($n = 2$), sertraline ($n = 2$), venlafaxine ($n = 1$). Patients were prospectively followed for 6 weeks. Post-menopausal women were more likely to be treated with more than one antidepressant drug, specifically mirtazapine plus other antidepressants. Though dosages (citalopram equivalents) were slightly higher in post-menopausal women, the difference was not statistically significant at any stage of the follow-up. Only a marginal trend ($P = 0.08$) could be observed at the end of the trial (week 6). The overall mean dosage was not different between pre-menopausal and post-menopausal women.

Patients were also administered with anti-anxiety drugs, such as lorazepam ($n = 28$, 72%), alprazolam ($n = 9$, 23%) and clonazepam ($n = 2$, 5%). Anti-anxiety treatment type was not significantly different in the two groups of women, nor were the dosages at any time of the assessment, except a small trend for a higher likelihood of pre-menopausal women to receive lorazepam and slightly higher doses. Nevertheless, this difference may be linked to the older age of

Table 1
Demographics and clinical parameters of pre-menopausal and post-menopausal women

	Pre-menopausal women ($n = 17$)	Menopausal women ($n = 22$)	Statistical details	
Mean age	36.3 (±5.1)	61.9 (±8.6)	$T = 10.9$	$P < 0.0001$
Mean age at menarche	15.5 (±1.4)	15.5 (±1.4)	$T = 0.2$	$P = 0.87$
No. single	4 (23.5)	3 (13.6)	$\chi^2 = 0.63$	$P = 0.42$
No. married	13 (76.5)	19 (86.4)		
Women having had children	11 (68.8)	22 (100)	$\chi^2 = 9.7$	$P = 0.002$
Women not having had children	5 (31.3)	0		
Women with a history of abortion (spontaneous or induced)	9 (56.3)	8 (36.4)	$\chi^2 = 1.50$	$P = 0.22$
Women without a history of abortion (spontaneous or induced)	7 (43.7)	14 (63.6)		
Mean age at first partum	23.6 (±4.3)	24.3 (±4.9)	$T = 0.3$	$P = 0.75$
Women with comorbid medical conditions	3 (17.6)	9 (40.9)	$\chi^2 = 2.53$	$P = 0.11$
Women without comorbid medical conditions	14 (82.4)	13 (59.1)		
Women with a family history for psychiatric disease	3 (17.6)	1 (4.5)	$\chi^2 = 1.81$	$P = 0.18$
Women without a family history for psychiatric disease	14 (82.4)	21 (95.5)		
Age at onset of depressive disorder	34.2 (±7.0)	54.7 (±10.1)	$T = 6.6$	$P < 0.0001$
Previous depressive episodes	0.6 (±0.9)	1.2 (±1.4)	$T = 1.3$	$P = 0.22$
FSH levels (IU/L)	4.6 (±2.2)	62.6 (±27.8)	$T = 8.6$	$P < 0.0001$
LH levels (IU/L)	4.9 (±3.2)	16.7 (±8.4)	$T = 5.5$	$P < 0.0001$
E2 levels (pg/mL)	153.6 (±108.0)	40.4 (±25.5)	$T = -4.8$	$P < 0.0001$
Administered with mirtazapine	8 (47.1)	6 (26.1)	$\chi^2 = 11.86$	$P = 0.018$
Administered with paroxetine	6 (35.3)	7 (30.4)		
Administered with citalopram	3 (17.6)	1 (4.3)		
Administered with venlafaxine	0	2 (8.7)		
Administered with sertraline	0	1 (4.3)		
Administered with mirtazapine + other AD[a]	0	6 (26.1)		
Need to change antidepressant during the trial	2 (12.5)	4 (18.2)	$\chi^2 = 0.23$	$P = 0.63$
No need to change antidepressant during the trial	14 (87.5)	18 (81.8)		
Citalopram eq. dose (week 1) (mg/day)	28.7 (±7.3)	33.2 (±11.3)	$T = -1.38$	$P = 0.18$
Citalopram eq. dose (mg/day) (week 3) (mg/day)	34.4 (±8.1)	38.6 (±12.5)	$T = -1.19$	$P = 0.24$
Citalopram eq. dose (mg/day) (week 6) (mg/day)	32.0 (±5.6)	39.1 (±14.4)	$T = -1.80$	$P = 0.08$
Mean citalopram eq. dose (mg/day)	32.0 (±4.8)	37.0 (±10.6)	$T = -1.7$	$P = 0.10$
Administered with lorazepam	9 (53.3)	19 (86.4)	$\chi^2 = 5.1$	$P = 0.08$
Administered with alprazolam	6 (37.5)	3 (13.6)		
Administered with clonazepam	1 (6.3)	0		
Anti-anxiety drug dosages (week 1) (mg/day)	2.7 (±0.5)	2.3 (±0.6)	$T = 1.09$	$P = 0.29$
Anti-anxiety drug dosages (week 3) (mg/day)	2.7 (±0.4)	2.0 (±0.8)	$T = 2.0$	$P = 0.06$
Anti-anxiety drug dosages (week 6) (mg/day)	2.2 (±0.9)	1.6 (±0.6)	$T = 1.8$	$P = 0.08$

Data represent mean ± SD or %. FSH, follicle stimulating hormone; LH, luteinizing hormone; E2, estradiol.
[a] See subjects' description for details.

post-menopausal women (in fact it is not recommended to prescribe benzodiazepines at high doses for elderly people).

In the overall sample, baseline and final dosages of drugs (citalopram equivalents) were related to the baseline severity at the time of HAMD (week 1: $R = 0.81$, $P = 0.014$; week 6: $R = 0.77$, $P = 0.025$), signifying that more severe patients received higher doses of treatment throughout the 6 weeks of treatment. Dosages at week 3 were related to the severity in the same week (week 3 HAMD: $R = 0.74$, $P = 0.034$; week 3 MADRS: $R = 0.74$, $P = 0.034$; week 3 CGI-S: $R = 0.73$, $P = 0.038$), indicating that doses were augmented according to the current depression severity.

3.5. Menopause and response to antidepressant treatment

As shown in Table 3, in simple univariate analyses pre-menopausal and post-menopausal women were not different at any time of the assessment, for any index of outcome.

Nevertheless, given the mentioned differences observed between pre- and post-menopausal women as pertained age, age at onset and levels of LH, FSH and E2, we controlled for these variables; furthermore, even if not significantly different in the two groups, we controlled also for baseline depressive severity and antidepressant dosage.

By performing the analysis of covariance for repeated measures, including the mentioned variables as covariates, we detected a significant effect of the menopausal status on severity of depression (HAMD scores) ($F = 10.8$, d.f. = 1,24, $P = 0.004$), as well as a significant effect on the course of improvement (menopausal status × time: $F = 3.6$, d.f. = 2,56, $P = 0.034$) (Fig. 1). Performing a regression analysis on final the HAMD scores (week 6) and including all factors, significant effects were observed for menopausal status, age and FSH levels (Table 4). Antidepressant type and benzodiazepine treatment did not affect result.

A similar effect of menopausal status, though less significant, was observed when analyzing MADRS scores (effect of

Table 2
Correlation (R) between hormonal levels and depressive severity and improvement at baseline, weeks 1, 3 and 6

	Pre-menopausal women ($n = 17$)			Post-menopausal women ($n = 22$)		
	FSH	LH	E2	FSH	LH	E2
HAMD						
Baseline	−0.50	−0.28	0.05	0.13	0.05	0.26
Week 1	−0.08	0.30	−0.08	0.31	0.14	0.02
Week 3	0.10	0.44	**0.59**	−0.01	0.13	0.38
Week 6	0.28	**0.48**	−0.17	0.23	0.01	−0.11
MADRS						
Baseline	0.21	**0.63**	0.39	0.39	−0.06	−0.17
Week 1	−0.09	0.48	0.03	**0.53**	0.01	−0.29
Week 3	0.10	**0.60**	**0.55**	**0.45**	0.09	−0.26
Week 6	0.21	0.37	−0.01	**0.46**	0.02	−0.09
CGI-S						
Baseline	−0.50	0.15	0.40	**0.55**	0.07	−0.27
Week 1	−0.12	0.17	−0.01	0.13	−0.09	−0.08
Week 3	0.28	0.50	0.31	0.03	−0.08	0.25
Week 6	0.19	0.26	0.16	0.33	0.01	0.05
CGI-I						
Week 1	0.12	0.14	−0.26	−0.12	0.11	0.49
Week 3	0.23	**0.64**	**0.57**	0.27	−0.09	0.05
Week 6	−0.25	0.39	0.24	0.09	0.25	0.37

FSH, follicle-stimulating hormone; LH luteinizing hormone; E, estradiol; HAMD, Hamilton Depression Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; CGI-S, Clinical Global Impression Scale-severity; CGI-I, Clinical Global Impression Scale-improvement. T3 levels were not available in pre-menopause women. Significant correlations with an alpha level of 0.05 are shown in bold type.

Table 3
Clinical rating scale scores at baseline and weeks 1, 3 and 6 in pre-menopausal and post-menopausal women

	For non-menopausal women ($n = 16$)	For post-menopausal women ($n = 22$)	T (d.f. = 36)	P
HAMD				
Baseline	27.6 (±5.6)	27.9 (±4.7)	−0.21	0.84
Week 1	21.6 (±5.4)	20.9 (±4.7)	0.43	0.67
Week 3	13.1 (±7.1)	15.9 (±7.0)	−1.20	0.24
Week 6	9.0 (±4.1)	12.6 (±7.9)	−1.63	0.11
MADRS				
Baseline	33.1 (±5.8)	31.1 (±5.3)	1.10	0.28
Week 1	24.7 (±8.1)	23.6 (±6.6)	0.44	0.66
Week 3	18.3 (±6.9)	18.1 (±7.5)	0.07	0.95
Week 6	11.9 (±4.3)	15.5 (±7.8)	−1.66	0.11
CGI-S				
Baseline	4.9 (±0.4)	4.8 (±0.8)	0.54	0.59
Week 1	4.0 (±0.5)	4.0 (±0.9)	0.18	0.86
Week 3	3.3 (±0.6)	3.1 (±1.0)	0.41	0.68
Week 6	2.4 (±0.6)	2.7 (±1.1)	−1.06	0.30
CGI-I				
Week 1	2.8 (±1.3)	2.8 (±1.2)	−0.06	0.96
Week 3	2.1 (±1.1)	1.9 (±0.8)	0.51	0.62
Week 6	1.6 (±0.7)	1.8 (±0.8)	−0.66	0.51

Data represent mean ± SD. HAMD, Hamilton Depression Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; CGI-S, Clinical Global Impression Scale-severity; CGI-I, Clinical Global Impression Scale-improvement.

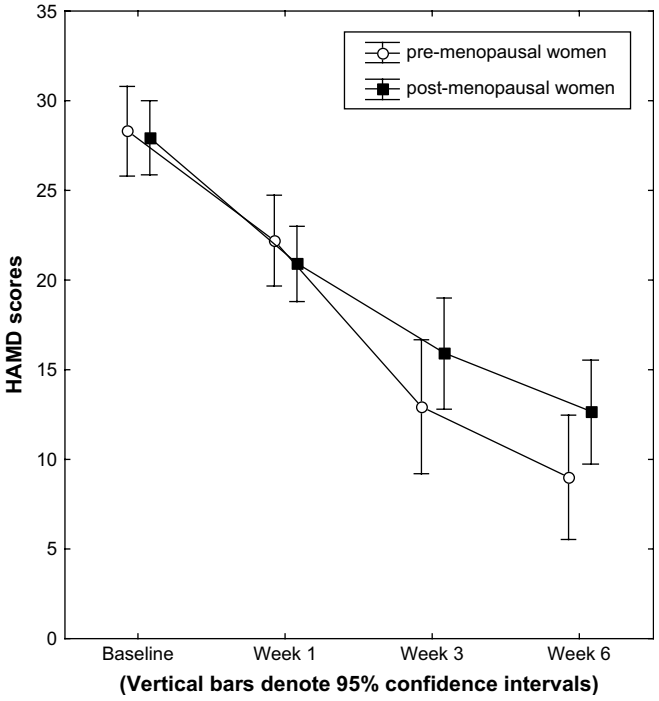

Fig. 1. Decrease of depressive severity during treatment in pre-menopausal and post-menopausal women. HAMD, Hamilton Depression Rating Scale.

menopausal status: $F = 3.7$, d.f. = 1,24, $P = 0.065$; menopausal status × time: $F = 4.1$, d.f. = 2,56, $P = 0.021$). The regression analysis was also significant ($F = 4.01$, d.f. = 8,21 $P = 0.005$), confirming that significant effects were exerted by the menopausal status ($\beta = -0.79$, $P = 0.031$), age ($\beta = 1.03$, $P = 0.015$) and FSH levels ($\beta = 0.76$, $P = 0.023$).

Finally, analyzing CGI-S and CGI-I scores, we were not able to detect a significant effect of the menopausal status in the analysis of covariance through time (CGI-S: effect of menopausal status, $P = 0.24$; menopausal status × time, $P = 0.17$; CGI-I: effect of menopausal status, $P = 0.54$; menopausal status × time, $P = 0.17$), as well as in the regression analysis (the model was not significant for both CGI-S ($P = 0.45$) and CGI-I ($P = 0.54$) scores), possibly due to its more limited sensitivity to changes.

Table 4
Regression analysis on depressive severity at week 6

	β	T	P
Menopausal status	−0.82	−2.47	**0.022**
Age (years)	0.85	2.30	**0.032**
Age at onset (years)	−0.30	−0.98	0.34
Baseline depressive severity (HAMD scores)	−0.05	−0.32	0.76
Mean dose (citalopram equivalents)	0.34	1.92	0.07
FSH levels	0.74	2.27	**0.034**
LH levels	−0.19	−0.79	0.44
E2 levels	−0.11	−0.48	0.64

Overall significance of the model ($F = 3.60$, d.f. = 8,21, $P = 0.009$). HAMD, Hamilton Depression Rating Scale.

4. Discussion

The aim of the present work was to analyze the impact of menopausal status and its hormonal correlates on the response to various antidepressant treatments. To do that, we compared the outcome of pre-menopausal and post-menopausal women, taking into account a number of demographic, clinical and hormonal descriptors. To avoid the interference of hormonal stabilization exerted by hormonal replacement therapies (HRTs), we excluded post-menopausal women taking such adjunctive therapies from our analyses.

Two major findings of interest were obtained: first, the menopausal status had a significant effect on response to antidepressants, slowing down the recovery from depressive symptoms; second, high levels of follicle-stimulating hormone (FSH) predicted a poor response to antidepressants, particularly in post-menopausal women.

Consistent data do exist regarding the association between menopausal hormonal changes and depression. Levels of estradiol (E2) have been reported to be lowered in both pre- and peri-menopausal depressed women [3,4,27,28]; increased levels of FSH have been also reported in post-menopausal depression [3,27,29–31], as well as increased luteinizing hormone (LH) levels [3,27,31]. In our sample, baseline depressive scores were associated with LH levels, but only in pre-menopausal women, while in post-menopausal women, only FSH was correlated with baseline global severity (CGI-S). No associations were observed between E2 and basal depression in both pre- and post-menopausal women.

The main aim of our work was to investigate the effect of hormonal changes occurring with menopause and response to antidepressant treatment. Few data are available regarding this matter. There is evidence that HRTs improve the effect of SSRIs in post-menopausal depressed patients [16–19], but little is known about the interplay between hormonal changes and antidepressant efficacy.

Data emerging from our study support a role of FSH in the response to antidepressant treatment. This data is in line with two previous published works: in 2003, Daly et al. reported that FSH levels decrease concurrently with the improvement of depressive symptoms in peri-menopausal women not treated with antidepressants [32]; in 2006, Shahine et al. described increased FSH levels in a woman of reproductive age treated with SSRIs for major depression [33]. Recently, Harvey et al. reported less exacerbation of symptoms within the first 2 weeks of treatment in post-menopausal women, probably because of less fluctuation in hormonal levels [34]. Our sample was too small to test this hypothesis, nevertheless only two women showed a worsening symptomatology at week 1, and both were pre-menopausal, in line with Harvey et al. [34]. Nevertheless, both women showed decreased severity at weeks 3 and 6.

Since we found that basal FSH levels predict response to treatment, we can hypothesize an interaction between FSH and the targets of the antidepressant drugs. This interaction may be mediated by the modulation of neurotransmitters, such as acetylcholine, norepinephrine, dopamine, serotonin, melatonin, and glutamic acid, which have been shown to exert an important control on the release of FSH in the anterior pituitary gland [35,36].

Recently, Zanardi at al. reported a positive correlation between levels of LH and response to antidepressant treatment in patients without HRT [19]. We could not observe the same association in our post-menopausal sample, however, an association was detected in pre-menopausal women between basal LH levels and baseline and week 3 depression severity scores.

Finally, though clinical studies have documented that estrogen treatment often ameliorates mood disturbances and depressive symptoms occurring during menopause, we did not observe an effect of basal estradiol levels on response to antidepressant treatment. We only observed higher levels associated with a more severe symptomatology at week 3 in pre-menopausal women and with a poor improvement after 1 week of treatment in post-menopausal women. The small intra-group variation compared to the large variation in pre- and post-menopausal status could explain this finding.

Other data that emerged from our study was a negative effect of age on response to antidepressant treatment, which was independent of hormonal levels and menopausal status; the result is in line with previous reports [37–42].

To summarize, our data support a poorer response to antidepressant treatment in post-menopausal women compared to pre-menopausal women. Other predictors of a poor outcome are high FSH levels and old age.

Nevertheless, some limitations characterize the present work. First, the small sample size strongly reduced the statistical power of our analyses and we were able to significantly detect only large effects exerted by clinical and hormonal indicators. Furthermore, to improve the possibility of noticing some difference, and given the preliminary nature of our analyses, we did not apply a Bonferroni correction, but this could have led to false positives, thus our result should be taken with caution. Second, data on presence and severity of menopause-related symptoms (pain, vasomotor symptoms, sexual dysfunction, etc.) were not collected. This is a critical point, because such symptoms may interfere with the assessment of depressive symptoms. However, in such a case post-menopausal women should have presented with more severe symptomatology since the baseline, but this was not observed in our post-menopausal women. Even if it is not possible to exclude that menopause-related symptoms may affect recovery with treatment, our women were in menopause from a mean of 12.5 ± 8.5 years, thus it is likely that peri-menopausal symptoms were absent in most of the cases. Nevertheless, since there is a lack of information in the literature in this field, specifically comparing pre- and post-menopausal women not treated with adjunctive hormonal therapies, further research, using bigger samples, and taking into account menopause-related symptoms, is thus needed.

Third, our pre- and post-menopausal samples had some specific characteristics, which can limit the generalization of the results. Our post-menopausal sample was characterized by an old onset age, ranging from 35 to 74 years, with a median

of 54 and a mode of 58. Even if the old age of these women did impair the assessment of previous episodes that occurred at a younger age, the sample is characterized by a late-onset depressive disorder and it is possible that the majority of post-menopausal women in our sample did not experience depressive episodes before menopause. We tried to control for this possible confounding effect by including the age of onset in the analyses and we found age at onset affecting neither depressive severity nor treatment outcome. Furthermore, MDD single episode was not an exclusion criterion in our study and our pre-menopausal sample had a high rate of women in their first depressive episode (approximately 50%). Thus, the specific composition of our pre- and post-menopausal samples limits their representativeness and result may not be reliable for earlier onset or recurrent post-menopausal MDD. Finally, patients were treated with different antidepressants and benzodiazepines. Nevertheless, the type of treatments was not related with depressive scores during the follow-up and did not affect the association between post-menopausal status and poor response to treatment. Finally, since different drugs require different dosages, we made them uniform as explained in Section 2 and we included the mean dose given to each woman in the analyses. However, the influence of different treatments at different dosages cannot be totally excluded and studies on larger and more homogenous samples are needed.

To conclude, the present paper suggests that post-menopausal women gain less benefit from antidepressant treatments compared to pre-menopausal women, and old age independently predicts a poorer outcome in line with previous evidence. Furthermore, a high basal level of FSH hormone significantly predicted the response to antidepressant treatments in post-menopausal women; this data could be of interest in order to develop augmentation drugs favoring the efficacy of antidepressants in post-menopausal women suffering from depression.

References

[1] Kessler RC, McGonagle KA, Swartz M, Blazer DG, Nelson CB. Sex and depression in the national comorbidity survey. I: lifetime prevalence, chronicity and recurrence. J Affect Disord 1993;29(2-3):85–96.

[2] McKinlay SM, Brambilla DJ, Posner JG. The normal menopause transition. Maturitas 1992;14(2):103–15.

[3] Harlow BL, Wise LA, Otto MW, Soares CN, Cohen LS. Depression and its influence on reproductive endocrine and menstrual cycle markers associated with perimenopause: the Harvard study of moods and cycles. Arch Gen Psychiatry 2003;60(1):29–36.

[4] Freeman EW, Sammel MD, Liu L, Gracia CR, Nelson DB, Hollander L. Hormones and menopausal status as predictors of depression in women in transition to menopause. Arch Gen Psychiatry 2004; 61(1):62–70.

[5] Utian WH. The international menopause society menopause-related terminology definitions. Climacteric 1999;2(4):284–6.

[6] Siefer D, Kennard E. Menopause: endocrinology and management. Totowa (NJ): Humana Press; 1999.

[7] Hay AG, Bancroft J, Johnstone EC. Affective symptoms in women attending a menopause clinic. Br J Psychiatry 1994;164(4):513–6.

[8] Halbreich U, Kahn LS. Role of estrogen in the aetiology and treatment of mood disorders. CNS Drugs 2001;15(10):797–817.

[9] Bethea CL, Lu NZ, Gundlah C, Streicher JM. Diverse actions of ovarian steroids in the serotonin neural system. Front Neuroendocrinol 2002; 23(1):41–100.

[10] Kugaya A, Epperson CN, Zoghbi S, van Dyck CH, Hou Y, Fujita M, et al. Increase in prefrontal cortex serotonin 2A receptors following estrogen treatment in postmenopausal women. Am J Psychiatry 2003;160(8): 1522–4.

[11] Garlow S, Musselman D, Nemeroff C. The neurochemistry of mood disorders: clinical studies. In: Charney D, Nestler E, Bunney B, editors. Neurobiology of mental illness. New york, NY: Oxford University Press; 1999. p. 348–64.

[12] Bryant DN, Sheldahl LC, Marriott LK, Shapiro RA, Dorsa DM. Multiple pathways transmit neuroprotective effects of gonadal steroids. Endocrine 2006;29(2):199–207.

[13] Thase ME, Entsuah R, Cantillon M, Kornstein SG. Relative antidepressant efficacy of venlafaxine and SSRIs: sex–age interactions. J Womens Health (Larchmt) 2005;14(7):609–16.

[14] Pinto-Meza A, Usall J, Serrano-Blanco A, Suarez D, Haro JM. Gender differences in response to antidepressant treatment prescribed in primary care. Does menopause make a difference? J Affect Disord 2006;93(1-3):53–60.

[15] Spinelli MG. Neuroendocrine effects on mood. Rev Endocr Metab Disord 2005;6(2):109–15.

[16] Schneider LS, Small GW, Hamilton SH, Bystritsky A, Nemeroff CB, Meyers BS. Estrogen replacement and response to fluoxetine in a multicenter geriatric depression trial. Fluoxetine collaborative study group. Am J Geriatr Psychiatry 1997;5(2):97–106.

[17] Westlund Tam L, Parry BL. Does estrogen enhance the antidepressant effects of fluoxetine? J Affect Disord 2003;77(1):87–92.

[18] Liu P, He FF, Bai WP, Yu Q, Shi W, Wu YY, et al. Menopausal depression: comparison of hormone replacement therapy and hormone replacement therapy plus fluoxetine. Chin Med J (Engl) 2004;117(2):189–94.

[19] Zanardi R, Rossini D, Magri L, Malaguti A, Colombo C, Smeraldi E. Response to SSRIs and role of the hormonal therapy in post-menopausal depression. Eur Neuropsychopharmacol 2007;17(6-7):400–5.

[20] Cohen LS, Soares CN, Joffe H. Diagnosis and management of mood disorders during the menopausal transition. Am J Med 2005;118(Suppl 12B):93–7.

[21] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington DC: American Psychiatric Association; 1994.

[22] First MB, Spitzer RL, Gibbon M, Williams JB. Structured clinical interview for DSM-IV axis I disorders – patient edition (SCID-I/P, Version 2.0). New York: Biometrics Research Department, New York State Psychiatric Institute; 1995.

[23] Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62.

[24] Montgomery S, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382–9.

[25] Guy W. ECDEU assessment manual for psychopharmacology: revised. Rockville, MD; 1976.

[26] Sackeim HA, Prudic J, Devanand DP, Decina P, Kerr B, Malitz S. The impact of medication resistance and continuation pharmacotherapy on relapse following response to electroconvulsive therapy in major depression. J Clin Psychopharmacol 1990;10(2):96–104.

[27] Abe T, Suzuki M, Wada Y, Yamaya Y, Moritsuka T. Clinical and endocrinological features of statistical clusters of women with climacteric symptoms. Tohoku J Exp Med 1985;146(1):59–68.

[28] Young EA, Midgley AR, Carlson NE, Brown MB. Alteration in the hypothalamic–pituitary–ovarian axis in depressed women. Arch Gen Psychiatry 2000;57(12):1157–62.

[29] Huerta R, Mena A, Malacara JM, Diaz de Leon J. Symptoms at perimenopausal period: its association with attitudes toward sexuality, life-style, family function, and FSH levels. Psychoneuroendocrinology 1995;20(2): 135–48.

[30] Rajewska J, Rybakowski JK. Depression in premenopausal women: gonadal hormones and serotonergic system assessed by D-fenfluramine challenge test. Prog Neuropsychopharmacol Biol Psychiatry 2003; 27(4):705–9.

[31] 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(4):375–82.
[32] Daly RC, Danaceau MA, Rubinow DR, Schmidt PJ. Concordant restoration of ovarian function and mood in perimenopausal depression. Am J Psychiatry 2003;160(10):1842–6.
[33] Shahine LK, Lathi RB. Night sweats and elevated follicle-stimulating hormone levels while taking selective serotonin reuptake inhibitors. Obstet Gynecol 2006;108(3 Pt 2):741–2.
[34] 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(6):951–8.
[35] Barraclough CA, Wise PM. The role of catecholamines in the regulation of pituitary luteinizing hormone and follicle-stimulating hormone secretion. Endocr Rev 1982;3(1):91–119.
[36] McCann SM, Kimura M, Walczewska A, Karanth S, Rettori V, Yu WH. Hypothalamic control of FSH and LH by FSH-RF, LHRH, cytokines, leptin and nitric oxide. Neuroimmunomodulation 1998;5(3-4):193–202.
[37] Georgotas A, McCue RE, Cooper TB. A placebo-controlled comparison of nortriptyline and phenelzine in maintenance therapy of elderly depressed patients. Arch Gen Psychiatry 1989;46(9):783–6.
[38] Lebowitz BD, Pearson JL, Schneider LS, Reynolds 3rd CF, Alexopoulos GS, Bruce ML, et al. Diagnosis and treatment of depression in late life. Consensus statement update. JAMA 1997;278(14):1186–90.
[39] Grigoriadis S, Kennedy SH, Bagby RM. A comparison of antidepressant response in younger and older women. J Clin Psychopharmacol 2003; 23(4):405–7.
[40] Zanardi R, Cusin C, Rossini D, De Ronchi D, Serretti A. Comparison of response to fluvoxamine in nondemented elderly compared to younger patients affected by major depression. J Clin Psychopharmacol 2003; 23(6):535–9.
[41] Fischer LR, Wei F, Solberg LI, Rush WA, Heinrich RL. Treatment of elderly and other adult patients for depression in primary care. J Am Geriatr Soc 2003;51(11):1554–62.
[42] Mandelli L, Serretti A, Zanardi R, Rossini D, De Ronchi D, Tarricone I, et al. Antidepressant response in the elderly. Psychiatry Res 2007;152: 37–44.