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Response to SSRIs and role of the hormonal therapy in post-menopausal depression

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Abstract The aim of this study is to prospectively evaluate the antidepressant response to SSRIs in depressed post-menopausal women with or without hormonal therapy (HT), and to analyze the possible influence of basal serum levels of gonadotropins and sexual hormones on the antidepressant response. 170 post-menopausal women with a depressive episode (DSM-IV criteria) – 47 on HT and 123 not on HT – started the treatment with an SSRI. Depressive symptoms were assessed at baseline and 7 weeks thereafter by raters blind to treatment regimen. Response rates were 63.2% in the group without HT and 83.7% in the HT group ($p=0.013$). An inverse correlation emerged between the basal levels of LH and the improvement in HRSD scores ($p=0.001$) in the group without HT. In conclusion, HT appeared to improve the antidepressant response to SSRIs. Furthermore, in post-menopausal women, LH basal levels may be taken into account as possible predictor of response.

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1. Introduction

Major depression has an increased prevalence in women in comparison with men (Weissman et al., 1996). This increased prevalence is especially observed from puberty to the end of reproductive age (Weissman and Olfson, 1995; Weissman et al., 1996). Variations in hormonal levels in women have been associated to an increased depressive symptomatology, as happens in premenstrual depressive disorder, in puerperal

depression and in perimenopausal depression (Schmidt et al., 2004; Freeman et al., 2004); these hormone-responsive mood disorders often occurs in the same vulnerable women (Freeman et al., 2004; Studd and Panay, 2004). Moreover, in surgical menopause an increase in depressive symptomatology can be observed as well (Sherwin and Gelfand, 1985). During perimenopause (Freeman et al., 2004; Harlow et al., 2003) and the postpartum period a higher incidence of first onset of mood disturbances is common. Furthermore, abrupt interruption of estrogens replacement therapy in women with recurrent major depression can induce the rapid onset of a depressive episode (Stewart et al., 2004).

In post-menopause instead, it has not been documented a higher risk to develop depression (McKinlay et al., 1987; Avis et al., 1994). However, the lower levels of estrogens that characterize menopause could negatively affect the response

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to antidepressants, in particular to selective serotonin reuptake inhibitors (SSRIs) (Thase et al., 2005; Pinto-Meza et al., 2006), considering the well documented interaction between estrogens and the serotonergic system (Bethua et al., 2002; McEwen, 2002). The greatest reduction of estrogen levels is especially observed during the late menopausal transition and the first year post-menopause (Santoro et al., 1996; Archer, 1999; Schmidt et al., 2004). During perimenopause estrogens alone are effective in relieving depression in some women (Schmidt et al., 2000; Soares et al., 2001), but they are ineffective in most post-menopausal women (Morrison et al., 2004). Few studies evaluated the influence of hormonal therapy (HT) on the response to antidepressants in menopausal women obtaining ambiguous results (Schneider et al., 1997, 2001; Amsterdam et al., 1999; Thase et al., 2005). Moreover, there is a lack of studies with a considerable sample size, a prospective design and a complete basal assessment of relevant hormonal levels.

The aim of our study is to prospectively evaluate the antidepressant response to SSRIs in depressed post-menopausal women with or without HT. In this evaluation we also analyzed the influence of basal serum levels of gonadotropins (LH, FSH) and sexual hormones (estrogens, progestogens) on the antidepressant response.

2. Methods and materials

2.1. Sample

We screened 200 female patients aged ≥ 40 consecutively admitted to our Research Center for Mood Disorders (San Raffaele Hospital, Milan, Italy) for a Major Depressive Episode (due to Major Depressive Disorder or Bipolar Disorder) according to DSM-IV criteria.

Patients were required to have at least 12 consecutive months of amenorrhea (Sherman, 2005) and additionally, a serum FSH level of at least 30 IU/L (consider that the measure of FSH levels is not a single reliable hormonal marker of menopausal status [Burger et al., 1999]), and an LH level of more than 5 IU/L (Wilson et al., 1998). We excluded patients with bilateral oophorectomy or menopause induced by pathological conditions, chemotherapy, behaviors such as extreme exercise or anorexia nervosa and somatic or neurological illnesses impairing psychiatric evaluation. We also excluded patients with any concomitant axis I diagnosis or a history of drug or alcohol abuse according to DSM-VI criteria, following a best estimate procedure (Leckman et al., 1982). Patients underwent physical examination, laboratory analysis and electrocardiogram. They had to have a 21 item Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1967) score ≥ 18 .

One-hundred and seventy patients entered the study (134 unipolars; 36 bipolars), 47 women were on HT and 123 were not. After the procedure has been fully explained, informed written consent was obtained. The study was approved by the Ethical Committee of our Hospital and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines.

2.2. Clinical and laboratory assessment

Mood assessment was performed using the 21 items HRSD and the Clinical Global Impression Severity (CGI-S) (Guy, 1976), administered at baseline and weekly thereafter for 7 weeks. Response was defined as a $\geq 50\%$ decrease in the HRSD total score from baseline and remission was defined as a HRSD total score ≤ 8 . The assessment was performed by two trained psychiatrists with a good inter-rater reliability (Intraclass Correlation Coefficient on HRSD=0.95) blind to

Table 1 Sociodemographic and clinical variables at baseline

	HRT group	No HRT group	<i>p</i>
Age, y	54.5(5.0)	61.3(7.4)	<0.0001
Education, y	8.9(2.4)	7.8(4.0)	ns
Age at psychopathological onset, y	38.2(10.7)	42.2(14.2)	ns
No. of depressive episodes	3.3(2.2)	3.5(3.4)	ns
No. of manic episodes	2.0(1.2)	2.7(3.4)	ns
Episode duration, wk	13.8(13.5)	20.8(22.2)	ns
Age at menopause onset	49.5(2.8)	48.0(4.3)	ns
Body Mass Index	24.3 (2.1)	24.7 (1.7)	ns
FSH, mU/mL	38.8(32.5)	72.1(34.1)	<0.0001
LH, mU/mL	25.3(27.6)	33.3(14.8)	0.0927
Estradiol, pg/mL	56.1(87.5)	24.0(20.8)	0.0168
Progesterone, ng/mL	1.74(4.5)	0.54(0.5)	0.0684
HRSD score	27.0(4.1)	27.7(4.7)	ns
CGI-S score	5.06(0.78)	5.08(0.81)	ns

the treatment regimen. Patients were asked to report side effects daily on a diary.

Serum levels of FSH, LH, estrogens and progestogens were determined between 7 and 8 a.m. the day before starting the antidepressant treatment.

Hormone determinations were carried out with the ECLIA procedure (electrochemiluminescence immunoassay) using a commercial kit (Elecsys, Roche).

2.3. Drug treatments

Use of psychoactive drugs was not permitted (except for mood stabilizers in bipolar patients and lorazepam up to 2 mg/day for insomnia) during the 2 weeks before the beginning of the trial (4 weeks for fluoxetine). During the first week before baseline both groups observed a single blind placebo lead-in in order to exclude placebo responders (subjects with $\geq 20\%$ improvement on the HAM-D). Patients had not to take HT for at least 12 weeks before the onset of the current depressive episode. 95 patients were administered fluvoxamine (200.6 \pm 49.7 mg/day), 28 patients started taking sertraline (150 \pm 51.7 mg/day), 26 took citalopram (30 \pm 12.8 mg/day), 14 took paroxetine (30 \pm 11.7 mg/day), and 7 took fluoxetine (31.8 \pm 8.7 mg/day) (data in parenthesis refer to the mean dose at the end of the study \pm standard deviations). Among bipolar patients, in addition to SSRIs, 21 were taking lithium, 7 carbamazepine, 3 valproate and 3 lithium+carbamazepine.

Concerning the kind of HT used, 66% of women were taking conjugated estrogens (mean dose[*sd*] 0.611[0.021]mg) plus medroxyprogesterone (10–12 days per month; 5[0.71] mg) and 34% were taking estrogens alone 0.689 [0.037]mg). No other psychoactive medication was allowed except for lorazepam up to 2 mg as hypnotic.

2.4. Statistical analysis

Independent sample *t*-tests and Pearson χ^2 tests were used to investigate differences among the two groups for demographic and baseline clinical variables. Changes in HRSD scores over time were analyzed with a repeated-measures analysis of variance with presence/absence of HT as between-subjects factor. An "intent-to-treat" analysis was carried out for all patients who had a baseline

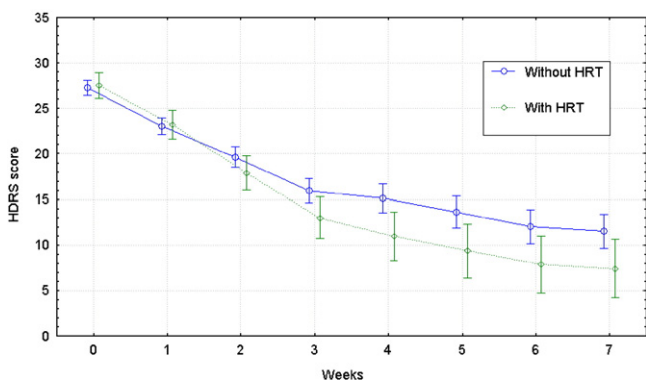


Figure 1 HRSD score reduction over time in the two groups with or without HT (Completers data; age included as a covariate).

assessment and at least 1 assessment after randomization, with the last observation carried forward (LOCF) on the HRSD. Analysis of covariance (ANCOVA) was used when including clinical and demographic features in the model. All *p* values were two-tailed and statistical significance was set at 5% level (*p* < .05).

Simple linear regression models were used to analyze the relation between baseline hormonal levels and response (defined as the difference between the values on the first and last HRSD scale). Multiple regression models were used to study the influence of clinical and demographic variables on this relation. As we study the influence of the levels of 4 hormones on response, we use the Bonferroni correction of significance level: correlations with *p* < 0.0125 (i.e. 0.05/4) were considered significant.

Computerized analyses were performed with a commercially available statistical package (Statsoft Inc, 2000).

3. Results

One-hundred seventy of the 200 screened patients entered the study and 30 were excluded (21 according to the above mentioned exclusion criteria and 9 as placebo responders during the 1 week-run-in period).

Baseline clinical and demographic variables of the groups with or without HT did not differ except for age and, as expected, for FSH and estrogens (see Table 1). Moreover, as expected, the frequency of hysterectomies was higher in the HT group (26% vs. 4.9%). The SSRI treatment was well tolerated and 157/170 patients completed the 7-weeks period of observation. Eight patients dropped out for unpleasant side effects from mild to moderate (5 in fluvoxamine treatment, 1 in

Table 3 Correlations between baseline hormonal levels and changes in HRSD scores at the end of the trial

	HRT group		No HRT group			
	<i>p</i>	<i>r</i>	No	<i>p</i>	<i>r</i>	No
FSH, mU/mL	0.828	0.0423	29	0.952	-0.009	48
LH, mU/mL	0.957	0.0103	30	0.001	-0.4428	50
Estradiol, pg/mL	0.874	0.0303	30	0.973	0.0051	46
Progesterone, ng/mL	0.806	0.0487	28	0.576	-0.0837	47

sertraline, 1 in paroxetine and 1 in citalopram), 4 because they did not come to the planned visit, 1 for change of residence.

3.1. Clinical outcome

The group taking HT showed a better response to SSRI treatment at the overall repeated measures ANOVA (*F*(7,1141)=4.5548; *p*=0.00005, completers data).

Analyzing the response for each week of treatment the two groups were significantly different from the third week in the ITT analysis and from the second in the completers analysis (Data shown as ITT [Completers]; Week 1: *p*=0.770 [*p*=0.770] Week 2: *p*=0.060 [*p*=0.047] Week 3: *p*=0.020 [*p*=0.012] Week 4: *p*=0.005 [*p*=0.002] Week 5 *p*=0.010 [*p*=0.006] Week 6: *p*=0.019 [*p*=0.019] Week 7: *p*=0.023 [*p*=0.024]; see Fig. 1). Age was included as covariate since it was different between the groups (see Table 1).

The time course of CGI reduction was very similar to that of HRSD, with a difference between the groups that emerged from the third week and remained stable up to the end of the observation period (*F*(7, 1141)=4.1706; *p*=0.00015, repeated measures ANOVA for completers). There were no significant differences in response between the two groups with estrogens alone or estrogens plus progestogens. There were no significant differences in response among different antidepressants, nor between unipolar and bipolar patients.

The rates of responders and remitters were also different between the groups at the end of the study. Remission rates were 52.63% (60/114) in the group not taking HT and 79.07% (34/43) in the HT group ($\chi^2=9.08$; *df*=1; *p*=0.002).

Response rates were 63.16% (72/114) in the group not taking HT and 83.72% (36/43) in the HT group (Table 2) ($\chi^2=6.149$; *df*=1; *p*=0.013).

Table 2 HRSD scores: observed means and 95% confidence intervals for each week in the two treatment groups

Weeks	Without HT			With HT		
	Mean	-95.00%	+95.00%	Mean	-95.00%	+95.00%
Baseline	27.57	26.75	28.39	26.95	25.63	28.28
1	23.25	22.34	24.15	22.39	20.93	23.85
2	19.70	18.61	20.80	17.30	15.54	19.06
3	16.24	14.94	17.54	12.34	10.21	14.46
4	15.60	14.08	17.12	10.18	7.71	12.65
5	14.11	12.41	15.80	8.46	5.69	11.23
6	12.30	10.50	14.11	7.13	4.20	10.07
7	11.81	9.98	13.65	6.69	3.71	9.67

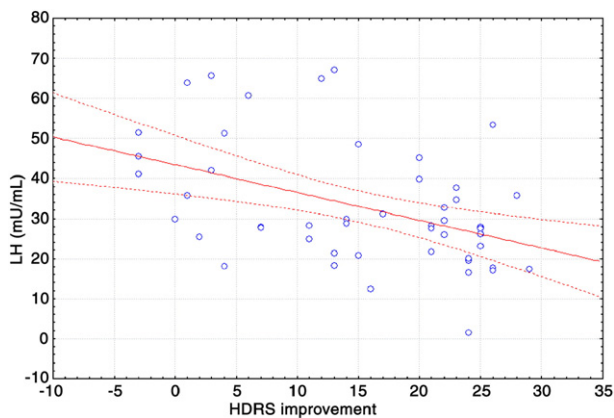


Figure 2 Correlations between baseline luteinizing hormone levels and changes in HRSD scores at the end of the trial.

3.2. Role of hormonal status

There was no significant correlation between the basal levels of FSH, estrogens and progestogens and the antidepressant response to SSRIs.

However, an inverse correlation emerged between the basal levels of LH and the improvement in HRSD scores ($N=80$ $r=-0.24$; $p=0.033$), but it did not survive to the Bonferroni correction. However, analyzing this correlation separately for the two groups (see Table 3), we found a significance in the group without HT ($N=50$ $r=-0.44$; $p=0.001$, see Fig. 2), but not in the group taking HT ($N=30$; $r=-0.010$; $p=0.957$). These correlations remained unchanged when age or years from menopause onset were included in the model.

Estrogens levels in the group without HT were inversely correlated with age ($N=80$; $r=-0.31$; $p=0.006$).

4. Discussion

In our study we found that HT significantly affects the antidepressant response to SSRIs in post-menopausal women: women taking HT showed a significantly better response to antidepressants compared to the ones without HT. This effect appeared within 2–3 weeks of treatment and remained significant until the end of the trial.

It is known that estrogens exert numerous and important effects on the central nervous system and, in particular, facilitatory effects on the serotonergic system (Betha et al., 2002; McEwen, 2002). This evidence provides a theoretical explanation about the mechanism through which the action of antidepressant drugs, and especially SSRIs, can be increased by the concomitant assumption of estrogens.

The role of HT and antidepressant treatment in peri- and post-menopausal women has been investigated in studies with different experimental designs.

The retrospective, 4 arms study by Schneider et al. (1997), found fluoxetine to be superior to placebo in the group of patients taking HT ($N=72$), but not in those without it ($N=286$), and also a significant interaction between HT status and treatment effect on HRSD improvement. In a subsequent study of Schneider et al. (2001), a clear difference between the response rates in women with or

without HT emerged only in the younger group of women (60–64 years old).

It has been suggested that estrogens alone are effective in treating depression in perimenopausal women (Schmidt et al., 2000; Soares et al., 2001), but not in those that are 5–10 years post-menopausal (Morrison et al., 2004). In our study also the patients on HT with a longer post-menopausal status were more responsive than those without it; on this base our findings should be attributed to a specific effect of the augmentation of estrogens on serotonergic antidepressants' action rather than to a psychotropic effect of estradiol. However, Amsterdam et al. (1999) did not find any significant difference in the response to 20 mg/day fluoxetine in women with or without HT, although the considered sample showed a relatively young age (52.2 ± 5.3 ; 51.4 ± 5.5 respectively).

Thase et al. (2005) conducted a pooled analysis of eight randomized controlled trials of depressed patients which underwent therapies with SSRI, venlafaxine or placebo. Among women they found a significant interaction reflecting poorer SSRI response in the older age group (≥ 50) versus the younger one (<50), a difference that disappeared in women taking HT. However, Soares et al. (2003a,b) reported about 2 studies in which they evaluated citalopram as adjunctive treatment to HT and citalopram alone (13 and 22 patients, respectively) in peri- and post-menopausal women. The response rates of the two studies were similar.

The 7-week period of observation of our study does not permit to completely understand if the advantage of the HT group derives from a shortening of the onset of action of SSRI by HT or by an ultimate greater efficacy of this combination. Both the hypothesis would be in accord with the antagonism of estrogens on 5HT_{1A} receptors; e.g. this mechanism has been postulated to be involved in the accelerating and augmenting properties of pindolol (Perez et al., 1997; Zanardi et al., 1997). Longer trials are needed to better elucidate this point.

A second and unexpected result deals with the predictive value of basal levels of LH on the antidepressant response; particularly, we found an inverse correlation between the levels of the gonadotropin and the clinical improvement, as measured on the HRSD. This effect appears as a trend in the whole sample, but is selectively significant in the patients not taking HT.

Therefore, patients with low LH basal levels show a better response to antidepressants, and this is also in agreement with the evidence that patients on HT have a superior response: in this group, in fact, we registered lower LH values, presumably dependent on the HT itself. It is not easy to argue if LH levels may have a causal role in the antidepressant response or if this observation is just an epiphenomenon. However, it is interesting to observe that 5-HT and tryptophan levels, are usually inversely correlated to LH levels (Vitale and Chiochio, 1993; Carretti et al., 2005). On this basis, we can hypothesize that in women who were not on HT, low LH levels could indicate a greater activity of the serotonergic system. Such a condition may represent a favourable substrate for SSRIs action, since the reuptake inhibition could determine stronger effects in presence of high 5-HT concentrations.

It can also be considered that in some patients low LH levels might be due to spontaneous secretion of estrogenic poussè, which may decrease LH secretion and increase the effect of therapy; however no correlation was found between estrogens and response.

Another possible hypothesis originates from the evidence that the hypothalamus–pituitary–ovarian-axis (HPO) activity is inhibited by the hypothalamus–pituitary–adrenal-axis (HPA), particularly by the action of corticotropin releasing hormone (CRH) and cortisol on the release of gonadotropin releasing hormone (GnRH), LH and FSH (Young and Korszun, 2002; Vadakkadath Meethal and Atwood, 2005; Carrasco and Van de Kar, 2003; Kalantaridou et al., 2004; Swaab et al., 2005). Thus, the lower LH basal levels observed in responders are possibly correlated to a hyperactivity of the HPA axis present before the treatment. Since the effectiveness of antidepressants, especially when it manifests itself through a sustained response, is mediated by a reduction of the HPA activity (Holsboer and Barden, 1996; Holsboer, 2000; Zobel et al., 2001) and such an effect could occur more likely in those subjects starting with higher basal activity levels.

Some studies have also showed lower plasma LH levels in post-menopausal depressed women (Altman et al., 1975; Amsterdam et al., 1983; Brambilla et al., 1990); women with this hormonal profile may constitute a subtype of patients with a favourable response to antidepressants.

A limit of our study includes the lack of a specific assessment for perimenopausal symptoms (i.e. hot flashes, night sweats, vaginal dryness).

However this is not a critical limitation because some studies actually evidenced that vasomotor symptoms like hot flashes and night sweats are not correlated with mood (Soares and Cohen, 2001; Morgan et al., 2005) and our patients are post-menopausal women only. Even if progestogens have been reported to cause irritability and fatigue (Klaiber et al., 1996; Soares et al., 2003a,b), in line with the findings of Odmark et al. (2004), we did not find any difference in response among patients taking estrogens alone or in combination with progestogens.

In summary, in post-menopausal women, LH basal levels may be taken into account as possible predictors of response. Moreover, in our sample HT significantly improved the response to SSRI antidepressants. Although the current indications for HT, given the associated risk factors (Grady et al., 2002; Hulley et al., 2002; Rossouw et al., 2002), are confined to its use at the lowest possible dose for the shortest period of time to manage menopause related symptoms, it may be useful to consider their favourable effects on the antidepressant response.

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