ORIGINAL ARTICLE

Do Estradiol levels influence on the cognitive function during antidepressant treatments in post-menopausal women with major depressive disorder? A comparison with pre-menopausal women

Chi-Un Pae [*1,2], Laura Mandelli [3], Changsu Han [2,4], Byung-Joo Ham [5], Prakash S. Masand [2], Ashwin A. Patkar [2], David C. Steffens [2], Diana De Ronchi [3], Alessandro Serretti [*3]

1. Department of Psychiatry, The Catholic University of Korea College of Medicine, Seoul, South Korea.
2. Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA;
3. Institute of Psychiatry, University of Bologna, Bologna, Italy.
4. Department of Psychiatry, College of Medicine, Korea University, Seoul, South Korea.
5. Department of Psychiatry, Hangang Sacred Heart Hospital, Hallym University Medical Center, Seoul, South Korea

Correspondence to: Chi-Un Pae, MD
Department of Psychiatry, The Catholic University of Korea College of Medicine
505 Banpo-Dong, Seocho-Gu, Seoul 137-701, Korea.
TEL.: +82-2-590-2780, FAX: +82-2-536-8744, (Seoul); E-MAIL: pae@catholic.ac.kr

Or to: Alessandro Serretti
Institute of Psychiatry, University of Bologna,
Viale Carlo Pepoli 5, 40123 Bologna, Italy.
TEL: +39 051 6584233 FAX: +39 051 521030; E-MAIL: alessandro.serretti@unibo.it

Submitted: 2008-03-24 Accepted: 2008-06-19 Published online: 2008-08-30

Key words: **major depressive disorder; cognitive function; menopause; estradiol; sex hormones**

Neuroendocrinol Lett 2008; **29**(4):500–506 **PMID:** 18766158 NEL290408A19

Abstract

OBJECTIVES: A hypo-estrogenic status, as that occurring with menopause, has been proposed to negatively affect cognitive function in post-menopause women. Nevertheless, little is known about the improvement of cognitive functions during antidepressant treatment in post-menopausal women with major depressive disorder (MDD) and its relation with hormonal changes. Hence, this study aimed to investigate the role of menopausal status including the level of sex hormones on cognitive function during antidepressant treatment.

DESIGN AND SETTINGS: Thirty-nine female patients (n=17 in pre-menopause; n=22 in post-menopause) with MDD based on DSM-IV criteria and who were not on hormonal replacement therapies participated in a prospective, 6-week, open-label naturalistic study. All patients were recruited in a university-based hospital. The Hamilton rating scale for Depression (HAMD), Montgomery-Åsberg Depression Rating Scale (MADRS) and the Cognitive Failure Questionnaire (CFQ) were administered at baseline, week 1, week 3, and week 6. Levels of follicle stimulating hormone (FSH), luteinizing hormone (LH) and estradiol (E2) were collected at baseline visit.

RESULTS: Cognitive functioning improved during antidepressant treatment in the overall sample (p=0.00001). In post-menopausal women, E2 levels were

strongly correlated with CFQ scores at each measurement. After controlling for depression severity, E2 levels maintained a significant association with the baseline CFQ scores (regression analysis: β=–0.55 p=0.010; correlation: R=–0.54). In addition, the reduction of CFQ scores during antidepressant treatment was significantly associated with E2 levels (p=0.021), independently from the improvement of depressive symptoms, which however had a strong effect (p=0.0003). Nevertheless, we failed to find any association of CFQ score with sex hormones in pre-menopausal women.

MAIN FINDINGS: In post-menopausal women, the CFQ scores were correlated with E2 levels and the reduction of CFQ score during antidepressant treatment was also dependent on E2 levels, even controlling for depressive symptoms severity.

CONCLUSION: The present study further supports a crucial role of E2 on the cognitive function in post-menopause women. Moreover, our results suggest that E2 may influence the improvement of cognitive function in post-menopause women with MDD, during treatment with antidepressants.

Abbreviations:

ANCOVA – analysis of covariance
CFQ – Cognitive Failure Questionnaire
CGI-S – Clinical global impression – Severity scale
DSM-IV – Diagnostic and Statistical Manual of Mental Disorders – 4th edition
E2 – estradiol
ERT – estrogen replacement therapy
HAMD – follicle stimulating hormone, FSH: Hamilton rating scale for Depression
LH – luteinizing hormone
MADRS – Montgomery-Åsberg Depression Rating Scale
MDD – major depressive disorder
OTC – Over-the-Counter
SSRIs – selective serotonin reuptake inhibitors

1. INTRODUCTION

Post-menopause is a critical period, in which neurotransmitters, neuropeptides and neurosteroids undergo important changes as a consequence of the gonadal hormone production reduction (Genazzani *et al*. 2005). In this period, the occurrence or recurrence of depression is high (Freeman *et al*., 2004; Harlow *et al*., 2003; McKinlay *et al*., 1992) and it has been suggested that hormonal changes are responsible for affective instability and depressive symptoms (Hay *et al*., 1994; McKinlay *et al*., 1992). Furthermore, menopause is associated with a deterioration in many central nervous system's activities, particularly those associated with hippocampal functions such as memory, attention, cognition and autonomic control (Badgio and Worden 2007). This cognitive impairment may be triggered by a reduction of the level of estrogens along with other aging-related processes. Indeed, over the past two decades, the results of preclinical and clinical researches have implicated a role of estrogens on modulating cognitive function. Estrogens affects the structure and function of areas of the brain important for learning and memory, particularly by modulating the structure and function of the hippocampus (see (Daniel 2006) for a review).

It has been suggested that a chronic hypo-estrogenic state, like that occurring with menopause, may reduce the response to antidepressants such as selective serotonin reuptake inhibitors (SSRIs) (Pinto-Meza *et al*., 2006; Spinelli, 2005; Thase *et al*., 2005; Zanardi *et al*., 2007).

Furthermore, depressive symptoms largely impact on cognitive functioning of patients with mood disorder (for a recent review see (Porter *et al*. 2007), but improvement can be observed in many cases with antidepressant treatment (Gualtieri and Johnson, 2007; Mandelli *et al*., 2006; Paleacu *et al*., 2007; Raskin *et al*., 2007; Wroolie *et al*., 2006). In post-menopausal women, antidepressant treatment has been reported to ameliorate the performance in cognitive tasks (Wroolie *et al*., 2006) and estrogen replacement therapy (ERT) has been associated with a better improvement in cognitive performances in depressed (Schneider *et al*. 2001) and non-depressed menopausal women (Carlson *et al*., 2001; Miller *et al*., 2002). Nevertheless, little is known about the improvement of cognitive functions during antidepressant treatment in post-menopausal women with major depressive disorder (MDD) and its relation with hormonal changes.

Hence, this study aimed to investigate the role of menopausal status including the level of sex hormones on cognitive function during antidepressant treatment in pre-menopause women with MDD *versus* post-menopause women with MDD. We hypothesized a poorer cognitive function in post-menopause women with MDD, as compared to pre-menopause women with MDD, and correlated with a reduction of estrogen level. Furthermore, we also hypothesized a poor improvement in cognitive function during antidepressant treatment in post-menopausal women with MDD.

2. SUBJECTS AND METHODS

Design

A prospective, 6-week, open-label naturalistic study for comparison of cognitive function in relation with differential effects of sex hormones in pre-menopausal with MDD *versus* post-menopausal women with MDD.

Subjects

The subjects consisted of 39 Korean female patients who were diagnosed for MDD, according to the Diagnostic and Statistical Manual of Mental Disorders-4th edition (DSM-IV) criteria (American Psychiatric Association 1994). All patients were recruited based on advertisement at 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: amenorrhoea for more than twelve months (McKinlay *et al*. 1992), 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 (McKinlay *et al*. 1992). Exclusion criteria were: serious suicidal risk, pregnancy, lactation, recent 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 (e.g., malignancy), hysterectomy, or oophorectomy. The study was strictly reviewed and approved by the Institutional Review Boards at the Kangnam St. Mary's Hospital and all subjects provided a written informed consent prior to participating in the study after being explained all study procedures.

Psychiatric diagnosis

The AXIS I diagnosis was evaluated by the consensus between the two board-certified psychiatrists upon the study entry, according to the DSM-IV criteria, using the Structured Clinical Interview for DSM-IV Axis I disorders-Clinician Version (First *et al*. 1995).

Medications

Currently available antidepressants (e.g., selective serotonin reuptake inhibitors; serotonin and norepinephrine reuptake inhibitors; noradrenergic and specific serotonin antidepressant and tricyclic antidepressant, 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 individuals' clinical response and tolerability. No other psychotropic medications were permitted during the study with the exception of hypnotics for insomnia and benzodiazepines for anxiety. Over-the-Counter (OTC) medications were only allowed as needed base, e.g., acetaminophen, etc. Since different antidepressant drugs require different dosages, we uniformed doses according to the Antidepressant Treatment History Form (Sackeim *et al*. 1990) and we calculated for each woman the citalopram equivalent dose received during the six-weeks of follow-up.

Assessments

At baseline, all patients were evaluated for depressive symptoms by the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg 1979), the Hamilton rating scale for Depression (HAMD) (Hamilton 1960) and the Clinical global impression, Severity scale (CGI-S) (Guy 1976) and for cognitive function by the Cognitive Failures Questionnaire (CFQ), the subjective test designed to investigate "failures of perception, memory and motor function" (Broadbent *et al*. 1982). The CFQ consists of 25 questions regarding common lapses of cognitive functions including memory, perception and attention. Each question is scored 0 to 4 depending on frequency of occurrence, as rated by the subject. High scores relate to increasing frequency of cognitive lapses. All women were prospectively followed for six weeks during antidepressant treatment and evaluated by the MADRS, the HAMD, the CGI-S, the Clinical global impression, Improvement scale (CGI-I) and the CFQ at week 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 S.A. Nivelles, Belgium).

Statistical analysis

Clinical and demographic features in pre-menopausal and post-menopausal women were analyzed by the Chi-square test, the Student-T test and the correlation analysis. To control for potential confounders we employed the one-way or repeated measures Analysis of covariance (ANCOVA) and the multivariate regression analysis. To test the effect of each variable considered on CFQ scores, we employed the ANCOVA. Cognitive function measured by CFQ scores and its change during antidepressant treatment were analyzed by the one-way/repeated measures ANCOVA, including depressive severity or the rate of improvement from the baseline. The association between change in CFQ scores during antidepressant treatment, menopausal status and hormonal levels, was analyzed by the ANCOVA for repeated measures, including the rate of improvement in depressive severity.

With a standard level of significance (α=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 15.2 points on CFQ scores (explained variance: 14.4%).

3. RESULTS

Demographics and clinical parameters

Post-menopausal women were not different from pre-menopausal women for age at menarche, marital status, history of spontaneous/induced abortions, age at first partum, medical conditions, family history for psychiatric diseases, number of previous depressive episodes, and mean antidepressant dose received during the six-weeks of follow-up. Pre-menopausal women were instead more likely not to have had children (Chi-sq=9.7

Table 1. Hormonal levels and Cognitive Failure Questionnaire (CFQ) scores in pre- and post-menopausal women with MDD

	Pre-menopausal women (n=17)	Post-menopausal women (n=22)	Statistics	
CFQ score				
Baseline	34.1(±16.6)	30.5(±20.5)	F=0.05	*P*=0.82
Week1	29.9(±13.1)	30.5(±14.6)	F=0.06	*P*=0.81
Week3	28.2(±14.9)	24.2(±17.2)	F=0.47	*P*=0.50
Week6	23.6(±17.4)	22.6(±16.6)	F=0.16	*P*=0.69
Sex hormones				
FSH (IU/L)	4.6(±2.2)	62.6(±27.8)	T=8.6	*P*<0.0001
LH (IU/L)	4.9(±3.2)	16.7(±8.4)	T=5.5	*P*<0.0001
E2 (pg/mL)	153.6(±108.0)	40.4(±25.5)	T=-4.8	*P*<0.0001

Data represent mean ± SD. FSH, Follicle Stimulating Hormone; LH, Luteinizing Hormone; E2, estradiol; MDD, major depressive disorder.

p=0.002), but this was probably due to their younger age.

Post-menopausal women were significantly older at their first illness episode (54.7±10.1 years vs. 34.2±7.0 years in pre-menopausal women); anyway, age at onset was not correlated with cognitive impairment at any stage of the follow-up (data not shown, all p values higher than 0.05). The overall mean dosage received during the six weeks of follow-up was not significantly different between pre-menopausal and post-menopausal women (32.0±4.8 mg/d and 37.0±10.6 mg/d citalopram equivalents, respectively).

Post-menopausal women were not different for baseline depressive scores, but they showed a poor response to antidepressant treatment, as compared with pre-menopausal women. As expected, post-menopausal women were markedly different for levels of FSH, LH and E2, with increased levels of FSH and LH and decreased levels of E2 in post-menopausal women (Table 1).

Cognitive function

The CFQ scores at each visit in pre- and post-menopausal women are presented in Table 1**.** In the whole sample, the baseline CFQ score was not associated with age, age at onset, depressive severity and antidepressant drug administered (all *p* values >0.05). The change in CFQ scores during treatment was significant (ANOVA for repeated measures: F=9.73 d.f.=3,108 *p*=0.00001), but a significant effect was exerted also by the rate of improvement in depressive severity (% from baseline) (ANCOVA for repeated measures: MADRS: F=3.70 *p*=0.014; CGI-S: F=2.98 *p*=0.035). Drug administered, as well as other variables, did not affect the improvement of cognitive performances during treatment (all *p* values >0.05).

Cognitive function and menopausal status

Controlling for age, age at onset and depressive severity, baseline CFQ scores were not associated with menopausal status (ANCOVA: *p*=0.90). In both pre- and post-menopausal women, baseline CFQ scores were not associated with any demographic and clinical variables. The course of CFQ scores was not associated with menopausal status (repeated measures ANCOVA: *p*=0.67), even after controlling for improvement in depressive scores during time (repeated measures ANCOVA: *p*=0.11).

Cognitive function and sex hormones

In post-menopausal women, E2 levels were strongly correlated with CFQ scores at each measurement (Table 2). Controlling for severity of depressive symptoms, E2 levels maintained a significant association with the baseline CFQ scores in post-menopausal women (regression analysis: R=–0.54; effect of E2 controlling for MADRS scores β=–0.55 *p*=0.010; effect of E2 controlling for HAMD scores β=–0.53 *p*=0.015; effect of E2 controlling for CGI-S scores β=–0.49 *p*=0.028). In addition, the decline of CFQ scores during antidepressant treatment was significantly associated with E2 levels, also controlling for improvement of depressive severity (Table 3). However, we failed to find any association of CFQ score with sex hormones in pre-menopausal women.

4. DISCUSSION

To our knowledge, this is the first study to investigate a role of menopausal status including the level of sex hormones on cognitive function during antidepressant treatment in pre-menopausal women with MDD versus post-menopausal women with MDD. In the present study, we hypothesized a poor cognitive function

Table 2. Correlation (R) between hormonal levels and cognitive failure at baseline, week 1, week 3 and week 6

	Pre-menopausal women (n=17)			Post-menopausal women (n=22)		
	FSH	LH	E2	FSH	LH	E2
CFQ scores						
Baseline	R=0.06	R=–0.02	R=0.06	R=0.34	R=–0.01	**R=–0.54**
Week1	R=–0.09	R=0.02	R=0.14	R=0.44	R=0.12	**R=–0.48**
Week3	R=0.34	R=0.19	R=0.06	R=0.31	R=0.03	**R=–0.43**
Week6	R=0.01	R=–0.21	R=0.11	R=0.36	R=0.05	**R=–0.45**

Abreviations: FSH, Follicle Stimulating Hormone; LH, Luteinizing Hormone; E2, estradiol; CFQ, Cognitive Failure Questionnaire. Bold characters stand for significant correlations (at the significance level of 0.05).

Table 3. Effect of E2 levels and depression on the reduction of cognitive failure scores (CFQ) in post-menopausal women*

	Statistics	
	F	P
Effect of Time	1.26	0.30
Time x improvement in MADRS scores	7.46	0.0003
Time x E2 level	3.51	0.021

Abbreviations: E2, estradiol; MADRS, Montgomery-Åsberg Depression Rating Scale; CFQ, Cognitive Failures Questionnaire.
*Analyzed by the ANCOVA for repeated measures

in post-menopausal women with MDD, as compared with pre-menopausal women with MDD, because of the known effect of E2 levels on mood symptoms; furthermore, we theorized a slower improvement during antidepressant treatment in post-menopausal women with MDD. However, we failed to prove our hypotheses: first, the cognitive function measured by CFQ score was not different in pre- and post-menopausal women; second, the improvement of cognitive functions was not influenced by the menopausal status and, furthermore, antidepressant drugs did not have differential effects.

Nonetheless, we found eminently intriguing results in relation to E2 level and cognitive function in post-menopausal women with MDD. In post-menopausal women, the CFQ scores were correlated with E2 levels and the reduction of CFQ score during antidepressant treatment was also dependent on E2 levels, even controlling for depressive symptoms severity. This is in line with previous evidence of a significant role of E2 on cognitive functions. Indeed, E2 has been known to interact with brain functioning (Genazzani *et al*., 1997; Joffe and Cohen, 1998; Maggi and Perez, 1985; Silva *et al*., 2001; Thakur and Sharma, 2006) and to favor cognitive performance in post-menopausal women (Costa *et al*., 1999; Dumas *et al*., 2006; Joffe *et al*., 2006; Saletu, 2003; Sherwin, 1994; Smith *et al*., 1999; Smith *et al*., 2001), although controversial data also exist (Almeida *et al*., 2005; Owens *et al*., 2002; Polo-Kantola *et al*., 1998; Thal *et al*., 2003). Recently, estrogen therapy has demonstrated its effect on activation of prefrontal cortex (Joffe *et al*., 2006) and findings from the existing literature also lend a support for a principal role of estrogens in aging men, just as in women (see (Sherwin 2003) for a review). Therefore, our results further support a significant impact of E2 on the improvement of cognitive function measured by CFQ score in post-menopausal women with MDD.

On the whole, in our subjects, cognitive function did significantly improve with antidepressant treatment. This is in line with previous works reporting improvement in cognitive function with treatment (Gualtieri and Johnson, 2007; Mandelli *et al*., 2006; Paleacu *et al*., 2007; Raskin *et al*., 2007; Wroolie *et al*., 2006). In a previous work, depressed patients who were improved with antidepressant treatment were found to perform better in cognitive tests than subjects who were not improved (Mandelli *et al*. 2006); accordingly, in this sample also the decline of cognitive impairment was dependent from that of depressive severity.

On the other hand, we could not detect an effect of menopausal status and old age on performances at the CFQ. The CFQ provide a self-evaluation of cognitive deficits and not much is known about the performance at the CFQ in clinical populations to use it as a measure of change (Wagle *et al*. 1999). The CFQ was originally devised to measure perception, memory, and motor lapses in daily life. In depressed subjects, a high incidence of cognitive failures has been reported (Farrin *et al*. 2003) and it has been found to correlate with current mood state in a study (van den Bosch *et al*. 1993), but not in others (Burdick *et al*., 2005; MacQueen *et al*., 2002). Age and meta-memory abilities can influence

the performance in self-administered test on cognitive function (Reese and Cherry 2006). However, the CFQ has been reported to be scarcely influenced by age and, furthermore, performance at the test has been reported counter-intuitively better in old people as compared with younger (Rabbitt and Abson 1990). Accordingly, though not significantly, CFQ performance was slightly worse in pre-menopausal women at the baseline, while no difference was observed at the end of treatment. Depressive severity may also account for the slight difference, but our pre- and post-menopausal women were not different for baseline severity and it influenced neither the slight baseline divergence nor the improvement of CFQ scores during treatment in the two groups. Moreover, in order to minimize the problem of comparing young and old people, characterized by different cultural and physiological conditions, we controlled the effect of age on CFQ scores in our sample and we tested the potential difference between pre- and post-menopausal women, founding no differences. Finally we analyzed the effect of hormonal levels and CFQ scores separately in pre- and post-menopausal women. Nevertheless, more sophisticated tools designed to differentiate subtle changes of cognition function independently from age-effect in patients with MDD should be employed in the future studies.

Given the slight divergence at baseline in CFQ performance, while no difference at the end of treatment, the absolute improvement co-occurring with recovery from depression is greater in pre- than in post-menopausal women. We may thus hypothesize that reduced E2 levels may delay improvement of cognitive functions. However, this observation is purely speculative and must be taken with cautiousness.

Some other important limitations underlie in the present study. 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 to detect differences, and given the preliminary nature of our analyses, we did not apply a Bonferroni correction, but this could have lead to false positives. However, we employed two tail analyses though in presence of a specific one tail hypothesis, this should be considered a conservative approach. Since there is a paucity of data in this field, specifically comparing the cognitive function in pre- and post-menopausal women suffering MDD, with or without adjunctive hormonal therapies, during antidepressant treatment, further research on bigger samples is thus needed. Second, our pre- and post-menopausal women had some specific characteristics, which can limit the generalization of result. Our post-menopausal sample was characterized by old age at onset, with a median of 54 and a mode of 58. Even if the old age of these women may have impaired the assessment of previous episodes occurred in young 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. Anyway, age at onset did not affect neither depression severity nor cognitive function. Furthermore, our pre-menopausal women had a high rate of subjects at their first depressive episode (approximately 50%). Thus, the specific composition of our pre- and post-menopausal subjects limits the representativeness and result may not be applicable for earlier onset or recurrent post-menopausal women with MDD. Pre- and post-menopausal women were not different for the incidence of medical conditions, nevertheless we did not take into account the severity of medical problems, which may have been more severe in the older menopausal group. Finally, patients were treated with different antidepressants. However, the type of antidepressant drug was not related with the CFQ scores, and the doses, uniformed as citalopram equivalents (Sackeim *et al.* 1990), were not different in pre- and post-menopausal women.

5. CONCLUSION

The present study further supports a crucial role of E2 on the cognitive function in post-menopause women with MDD, despite of methodological limitations. Moreover, our results suggest that E2 may also influence the improvement of cognitive function in post-menopause women with MDD, during treatment with antidepressants, maybe delaying the progress co-occurring with depression. However, given the above-mentioned weaknesses of both methodology and result, subsequent well-designed, lager trials are warranted to draw more definite conclusion in the near future.

Acknowledgement

This work was supported by a financial support of the Catholic Medical Center Research Foundation made in the program year of 2008.

REFERENCES

1 American Psychiatric Association (1994): *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition.* Washington DC: American Psychiatric Association.
2 Badgio PC, Worden BL (2007): Cognitive functioning and aging in women. *J Women Aging* **19**: 13–30.
3 Broadbent DE, Cooper PF, FitzGerald P, Parkes KR (1982): The Cognitive Failures Questionnaire (CFQ) and its correlates. *Br J Clin Psychol* **21** (Pt 1): 1–16.
4 Daniel JM (2006): Effects of oestrogen on cognition: what have we learned from basic research? *J Neuroendocrinol* **18**: 787–95.
5 Farrin L, Hull L, Unwin C, Wykes T, David A (2003): Effects of depressed mood on objective and subjective measures of attention. J Neuropsychiatry Clin Neurosci **15**: 98–104.
6 First MB, Spitzer RL, Gibbon M, Williams JB (1995): 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.

7 Genazzani AR, Bernardi F, Pluchino N, et al (2005): Endocrinology of menopausal transition and its brain implications. CNS Spectr **10**: 449–57.
8 Guy W (1976): ECDEU Assessment manual for psychopharmacology: revised. Rockville, MD.
9 Hamilton M (1960): A rating scale for depression. J Neurol Neurosurg Psychiatry **23**: 56–62.
10 Mandelli L, Serretti A, Colombo C, et al (2006): Improvement of cognitive functioning in mood disorder patients with depressive symptomatic recovery during treatment: an exploratory analysis. Psychiatry Clin Neurosci **60**: 598–604.
11 McKinlay SM, Brambilla DJ, Posner JG (1992): The normal menopause transition. Maturitas **14**: 103–15.
12 Montgomery S, Asberg M (1979): A new depression scale designed to be sensitive to change. British Journal of Psychiatry **134**: 382–9.
13 Porter RJ, Bourke C, Gallagher P (2007): Neuropsychological impairment in major depression: its nature, origin and clinical significance. Aust N Z J Psychiatry **41**: 115–28.
14 Rabbitt P, Abson V (1990): ‚Lost and found': some logical and methodological limitations of self-report questionnaires as tools to study cognitive ageing. Br J Psychol **81** (Pt 1): 1–16.
15 Reese CM, Cherry KE (2006): Effects of age and ability on self-reported memory functioning and knowledge of memory aging. J Genet Psychol **167**: 221–40.
16 Sackeim HA, Prudic J, Devanand DP, Decina P, Kerr B, Malitz S (1990): The impact of medication resistance and continuation pharmacotherapy on relapse following response to electroconvulsive therapy in major depression. J Clin Psychopharmacol **10**: 96–104.
17 Schneider LS, Small GW, Clary CM (2001): Estrogen replacement therapy and antidepressant response to sertraline in older depressed women. Am J Geriatr Psychiatry **9**: 393–9.
18 Sherwin BB (2003): Steroid hormones and cognitive functioning in aging men: a mini-review. J Mol Neurosci **20**: 385–93.
19 van den Bosch RJ, Rombouts RP, van Asma MJ (1993): Subjective cognitive dysfunction in schizophrenic and depressed patients. Compr Psychiatry **34**: 130–6.
20 Wagle AC, Berrios GE, Ho L (1999): The cognitive failures questionnaire in psychiatry. Compr Psychiatry **40**: 478–84.