A Prospective Study of Hormone Therapy and Depression in Community-Dwelling Elderly Women: The Three City Study

Jacqueline Scali, MSc; Joanne Ryan, MSc; Isabelle Carrière, PhD; Jean-François Dartigues, MD; Béatrice Tavernier, MD; Karen Ritchie, PhD; and Marie-Laure Ancelin, PhD

Background: The potential benefits of hormone therapy (HT) in treating depressed postmenopausal women are controversial, and data on depression (re)emergence in the context of HT discontinuation are lacking.

Objective: To determine whether HT is associated with a modified risk of new-onset depressive symptoms in elderly women.

Method: Current depressive symptomatology was evaluated in 4,069 community-dwelling postmenopausal women aged 65 years and over who were randomly recruited from 3 French cities between 1999 and 2001. Depressive symptomatology was assessed using the Center for Epidemiologic Studies-Depression Scale at baseline and as part of the 2- and 4-year follow-up.

Results: Over the follow-up period, multivariate logistic regression analyses adjusted for sociodemographic variables, measures of physical health, and cognitive impairment failed to find a significant association between HT at baseline and the incidence of depressive symptoms. However further analysis indicated an increased risk of incident depressive symptoms for women using transdermal estradiol treatment combined with synthetic progestin specifically (odds ratio [OR] = 1.59; 95% CI, 1.01–2.50; $P = .046$). In addition, while women taking HT continuously over the 4-year follow-up did not show an increased risk of depressive symptoms, women who stopped their treatment early after study inclusion, had a significantly higher risk (OR = 2.63; 95% CI, 1.52–4.55; $P = .0005$).

Conclusions: Hormone therapy was not associated with a protective effect against the emergence of depressive symptoms in elderly postmenopausal women. However, discontinuing treatment could increase the risk of depressive symptoms. Data on the appropriate management of depression in the context of HT discontinuation among postmenopausal women require further investigation.

J Clin Psychiatry 2010;71(12):1673–1679

Submitted: *March 4, 2009; accepted July 7, 2009.*
Online ahead of print: *August 10, 2010 (doi:10.4088/JCP.09m05188blu).*
Corresponding author: *Marie-Laure Ancelin, PhD, Inserm U888, Hopital La Colombiere, pav 42, 39, avenue C. Flahault, BP 34493, 34093 Montpellier Cedex 5, France (marie-laure.ancelin@inserm.fr).*

Although the neuroprotective effects of estrogen have been demonstrated experimentally, the benefits of hormone therapy (HT) in treating depressed menopausal women remain controversial (see Ancelin et al[1] for review). Recent trials in women with clinically diagnosed depression report a positive effect of short-term transdermal estrogen therapy in perimenopausal women,[2,3] with the antidepressant response in depressed postmenopausal women being much weaker.[4,5] However, no trials have evaluated the effect of different treatment regimens on depressed elderly women—especially those containing progestogen, which could decrease estrogen's antidepressant effect,[6–8]—or the impact of long-term use. A history of psychiatric disorder or other individual characteristics could also influence the response to HT and the decision to start or discontinue treatment. Nevertheless, data on depression (re)emergence after HT discontinuation are lacking, especially following the results of the much-publicized Women's Health Initiative (WHI) study[9] in 2002, which has led to a worldwide decrease in HT prescriptions. While differences in vulnerability to psychiatric disorders and the role played by HT remain important questions to be addressed, they are, however, unlikely to be answered in the near future by large-scale, randomized controlled trials (RCTs) with long-term HT users. On the other hand, it is currently feasible to use existing data from large-scale, longitudinal, population-based studies with adequate information on hormone exposure and psychiatric evaluation. The present study aimed to determine whether HT could be associated with a lower incidence of depressive symptomatology in a large population-based cohort of postmenopausal women. The impact of HT discontinuation on depressive symptoms was also evaluated. In this study we controlled for sociodemographic variables, measures of physical health, including insomnia, and cognitive impairment, which may independently contribute to both depression and HT prescription. We also considered the history of depression and the type of HT used.

METHOD

Study Population

The data used for this analysis were derived from a general population study of neuropsychiatric disorders in community-dwelling French elderly men and women (the Three-City [3C] Study). Eligible participants, who were at least 65 years of age and noninstitutionalized, were recruited from the electoral rolls of 3 French cities (Bordeaux, Dijon, and Montpellier) between 1999 and 2001. The study protocol was approved by the Ethical Committee of the University Hospital of Kremlin-Bicêtre. After obtaining written informed consent from all participants, trained staff administered interviews at baseline and every 2 years

thereafter. The 3C study has been described in further detail elsewhere.[10]

Outcome Measures

The Center for Epidemiologic Studies-Depression Scale (CES-D) is a 20-point questionnaire, designed to measure current depressive symptoms in the general population, that has been validated in the elderly.[11] It has been suggested that a cutoff point of 23 or more can be used to identify major depressive disorder (MDD).[12] The diagnosis of lifetime psychiatric disorders was made using the Mini-International Neuropsychiatry Interview, a standardized psychiatric examination that has been validated in the general population[13] according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*) criteria.[14]

Women scoring 23 or higher on the CES-D or those taking antidepressants were considered as having current depressive symptomatology in this analysis. Incident cases of depressive symptoms were identified from subjects who had neither depressive symptoms (CES-D score < 23) nor antidepressant use at baseline but who subsequently presented with high depressive symptomatology or reported antidepressant treatment during at least 1 of the 2 follow-up examinations.

Hormone Therapy and Menopausal Characteristics

All types of medication used during the preceding month (including HT and antidepressants) were validated by presentation of the prescription or the medication itself. Information was also recorded on past HT type, time of initiation, duration of use, age at menopause (defined as 1 year without menses) and type of menopause (ie, natural, surgical, or following a treatment such as chemotherapy or radiotherapy).

Sociodemographic and Clinical Variables

The standardized interview included questions on demographic characteristics, education level, and height and weight. Information was obtained on type and quantity of alcohol consumption (g/d) and tobacco use. Participants were classified as disabled if they were unable to complete at least 1 task from either the Instrumental Activities of Daily Living[15] or the Activities of Daily Living[15,16] scales. Cognitive function was assessed using the Mini-Mental State Examination,[17] and those scoring less than 26 were classified as cognitively impaired. Women were questioned about their sleeping habits, and insomnia was defined as scoring positive on at least 2 questions from the 5-item sleep subscale of the Nottingham Health Profile questionnaire.[18] Blood pressure was measured during the interview using a digital electronic tensiometer OMRON M4 (Omron Healthcare Europe, Hoofddorp, The Netherlands). Detailed medical questionnaires (with additional information when necessary from general practitioners) were used to obtain information on history of vascular diseases, including ischemic pathologies (eg, angina pectoris, myocardial infarction, stroke, cardiovascular surgery), nonischemic pathologies (eg, bradycardia or palpitations), and other chronic illnesses (eg, asthma, diabetes [fasting glucose ≥ 7.0 mmol/L or reported treatment]), hypercholesterolemia (total cholesterol ≥ 6.2 mmol/L), hypertension (resting blood pressure ≥ 160/95 mm Hg or treated), and thyroid problems. Participants were classified as having a chronic health disorder if they suffered from 1 or more of these illnesses.

Statistical Analysis

Two-tailed χ^2 tests were used to compare categorical variables and *t* tests, and analyses of variance were used to compare continuous variables. For subsequent subgroup comparisons, Bonferroni adjustment for multiple comparisons was used. Among all the sociodemographic or health variables recorded, those that were found to be associated with depressive symptoms at the 15% significance level ($P < .15$) were considered in the multivariate analysis. In the final models, we thus adjusted for center, age (continuous), education level (≥ 12 years of schooling), widowhood, cognitive impairment, insomnia, history of chronic disorders, disability, age at menopause (continuous), and past depression. For the variables that were treated as continuous, the linearity assumption was checked. In longitudinal analysis, we used multiadjusted logistic regression models to evaluate the predictive value of HT use at baseline on new-onset depressive symptoms over 4-year follow-up. We also evaluated these risks for women who have taken HT continuously, or those who have stopped during the 4-year follow-up compared to never users, using the multiadjusted models (see above). SAS version 9.1 (SAS Institute, Inc, Cary, North Carolina) was used for the statistical analysis, with a significance level of $P < .05$.

RESULTS

Population Characteristics as a Function of HT Use

Of the women recruited as part of the 3C Study (n = 5,644), only nondemented women (diagnosed using the revised criteria of *DSM-IV*[19]), with complete follow-up data, who were assessed for depressive symptomatology, who had information relating to the use of HT, and who had no missing data for the main covariates considered in the multivariate logistic models (N = 4,069) were included in this analysis. Women not included in this analysis had a lower educational level, were older, were more likely to have disabilities and cognitive dysfunction ($P < .001$), and were more frequently widowed ($P = .002$). They were also more likely to have lifetime depression and to use antidepressants ($P < .01$) and less likely to use or to have used HT ($P < .0001$). There were no significant differences regarding the other variables between the excluded subjects and those included in this analysis.

The 4,069 women included in the present analysis had a mean (SD) age of 73.6 (5.0), ranging from 65 to 93 years. In our sample, 14.7% currently used HT, and 19.9% reported past use. The median (range) duration of past HT use was 5 years (1–39) and 12 (1–43) for current users. Transdermal estradiol was used by the majority of current HT users (78.6%) either unopposed (16.9%) or combined with oral progesterone (29.9%) or synthetic progestin (31.8%). Oral

Table 1. Baseline Characteristics of Participants According to Hormone Therapy (HT) Use (n = 4,069)

Characteristic	Never Used (n = 2,662)	Past Use (n = 808)	Current Use (n = 599)	*P* Value[a]	Significant 2 × 2 Comparisons
Center, %				< .0001	Never vs past or current, past vs current
Bordeaux	26.0	21.9	15.4		
Dijon	50.7	50.7	59.8		
Montpellier	23.3	27.4	24.9		
Age, mean (SD), y	74.5 (5.0)	73.1 (4.8)	70.3 (3.4)	< .0001	Never vs past or current, past vs current
≥ 12 y of schooling, %	33.3	33.4	45.6	< .0001	Current vs never or past
High current tobacco intake (> 5 cigarettes/d), %	2.6	2.7	3.0	.88	
Current high alcohol consumption (> 24 g/d), %	10.9	8.7	12.7	.05	Past vs current
Widowed, %	38.9	32.7	20.9	< .0001	Never vs past or current, past vs current
Disability,[b] %	8.8	8.0	2.8	< .0001	Current vs never or past
Cognitive impairment,[c] %	16.4	17.5	11.6	.006	Current vs never or past
Insomnia, %	32.1	36.4	23.2	< .0001	Current vs never or past
Chronic disorders, %	73.2	71.5	68.1	.04	Current vs never
Ischemic cardiopathology	8.8	8.7	3.2	< .0001	Current vs never or past
Stroke	3.4	3.0	1.5	.03	Current vs never or past
Arteritis	2.5	1.9	1.4	.20	
Non-ischemic pathologies (bradycardia, palpitations)	17.6	18.0	12.6	.009	Current vs never or past
Thyroid dysfunction	11.3	11.8	16.8	.001	Current vs never or past
Diabetes	6.4	5.5	2.2	.0003	Current vs never or past
Hypertension	43.4	40.7	31.8	< .0001	Current vs never or past
Asthma	7.7	8.4	9.1	.47	
Hypercholesterolemia	35.6	39.0	38.9	.11	
Breast cancer, %	4.8	7.0	0.5	< .0001	Current vs never or past
Body mass index > 25 kg/m^2, %	49.2	46.9	37.1	< .0001	Current vs never or past
Current depressive symptoms (CES-D score ≥ 23), %	15.3	17.8	13.7	.09	
Current antidepressant use, %	9.7	9.9	9.0	.97	
Past major depression,[d] %	12.9	15.5	15.9	.06	
Age at menopause, mean (SD), y	49.4 (5.3)	48.3 (6.6)	50.1 (5.5)	< .0001	Never vs past or current, past vs current
Type of menopause, %				< .0001	Never vs past or current
Natural	81.9	70.8	76.3		
Surgical	6.0	12.5	9.6		
Other (ie, treatment-related)	12.2	16.7	14.1		
Age at HT initiation, median (range), y	…	50 (20–77)	56 (25–80)	< .0001	Past vs current
Duration of HT, median (range), y	…	5 (1–39)	12 (1–43)	< .0001	Past vs current

[a]Test statistics were χ^2 or analysis of variance for categorical or continuous variables, respectively. For subsequent subgroup comparisons, Bonferroni adjustment for multiple comparisons was used.
[b]According to Instrumental Activities of Daily Living and Activities of Daily Living criteria.
[c]Mini-Mental State Examination score < 26.
[d]According to the Mini-International Neuropsychiatry Interview.
Abbreviation: CES-D = Center for Epidemiologic Studies-Depression Scale.

estradiol was used by only 18.0% of women, with 2.0% using unopposed, 3.6% combined with progesterone and 12.4% with synthetic progestin. None of these French women used other estrogen derivatives, such as ethinylestradiol, or conjugated equine estradiol (CEE). However a small proportion (3.3% overall) were prescribed other forms of HT (eg, tibolone, cyproterone, or progestogen alone).

Current, past, and never HT users differed significantly on most sociodemographic and clinical characteristics except tobacco consumption, current antidepressant use, hypercholesterolemia, and asthma (Table 1). Never users were significantly older, more frequently widowed, and more frequently reported natural menopause than ever (current or past) users. Never and past users did not differ significantly regarding the other health variables (including the vascular ones). On the other hand, current users of HT appeared different from both past and never users. They were younger, less frequently widowed, had significantly higher education levels, a higher age at menopause, and a lower body mass index (BMI). They were also less likely to have physical disabilities, cognitive impairment, insomnia, chronic disorders (eg, ischemic or nonischemic pathologies, diabetes, high blood pressure), and breast cancer. Current users were more frequently alcohol consumers, had used HT later and for longer than past users, and were more likely to have thyroid dysfunction.

Population Characteristics as a Function of Depressive Symptoms

At baseline, 21.9% of women were identified as having depressive symptoms (CES-D score ≥ 23) or were currently using antidepressants. Depressed women were older and more frequently widowed, with a higher percentage of physical or cognitive impairments, insomnia, and past major depression (Table 2). They also reported a lower age at menopause. Among the women who were not depressed at baseline (CES-D score < 23 and not using antidepressants), 17.4% were identified as having depressive symptoms over the 4-year follow-up period. Women who developed new-onset depressive symptoms were older and with a higher percentage of disability, insomnia, and past major depression than women without depressive symptoms. Compared to women having baseline depressive symptoms, they were, however, less frequently widowed and with a lower

percentage of physical or cognitive impairment, insomnia, or past depression, and they reported a higher age at menopause.

Associations Between Current HT and Incident Depressive Symptoms

The effect of current HT on incident depressive symptoms was evaluated longitudinally during follow-up after controlling for a large number of covariates, eg, age, education level, center, widowhood, age at menopause, insomnia, physical disabilities, cognitive impairment, chronic disorders and past depression (Table 3). Overall, there was no significant adjusted association between baseline HT use and new-onset depressive symptoms ($P = .06$). Hormone therapy duration was not significantly associated with depressive symptoms ($P = .78$, data not shown). However, further examination of the type of treatment used revealed that opposed transdermal HT was associated with the incidence of depressive symptomatology, the effect of which appeared specifically related to the presence of synthetic progestin (OR = 1.59; 95% CI, 1.01–2.50). Other HT types, such as unopposed transdermal estrogen treatment or opposed oral treatment, were not significantly associated with a modified risk of depressive symptoms. No significant associations were found with unopposed oral HT either, although in this case, the low numbers precluded the drawing of definite conclusions.

Among HT users without depressive symptoms at baseline, 34.5% of women continuously took HT during the 4-year follow-up, and 65.5% ceased treatment; 16.2% stopped early in the follow-up, between study inclusion and the first 2-year follow up, and 49.3% stopped between the first and the second 2-year follow-up. Only 5 women started a treatment after study inclusion. Among all the sociodemographic and health variables examined, early discontinuing women only differed from those having continuously used HT by a higher BMI (48.0% vs 32.10%, $P = .02$). Notably, they did not differ significantly regarding HT type ($P = .86$) or insomnia ($P = .28$).

In fully adjusted models, we found no significant association between the continuous use of HT and new-onset depressive symptoms (Table 4). The results were the same regardless of the type of HT used (data not shown); however, with such small numbers in each of the subgroups, this lack of significant association could result from a lack of statistical power. On the other hand, women who stopped their treatment early after study inclusion were at significantly increased risk of new-onset depressive symptomatology (OR = 2.63; 95% CI, 1.52–4.55).

Table 2. Main Baseline Characteristics of Participants According to the Presence of Depressive Symptoms[a] at Baseline or Follow-Up

Characteristic	No Depressive Symptoms (n = 2,104)	Depressive Symptoms at Baseline (n = 714)	New-Onset Depressive Symptoms During Follow-Up (n = 443)	*P* Value[b]
Center, %				.05
Bordeaux	24.43	23.25	23.48	
Dijon	53.33	48.88	53.27	
Montpellier	22.24	27.87	23.25	
Age, mean (SD), y	73.4 (5.0)	74.3 (4.9)	74.3 (5.2)	< .0001
≥ 12 y of schooling, %	36.8	33.1	33.7	.15
Widowed, %	33.5	41.9	35.2	.0003
Disability,[c] %	5.0	14.6	9.3	< .0001
Cognitive impairment,[d] %	12.6	22.4	18.1	< .0001
Insomnia, %	23.0	49.8	36.0	< .0001
Chronic disorders, %	71.3	74.7	73.1	.20
Breast cancer, %	3.9	4.8	2.7	.35
Past major depression,[e] %	9.8	24.6	15.2	< .0001
Age at menopause, mean (SD), y	49.7 (5.3)	49.1 (5.3)	49.5 (5.7)	.006

[a]Center for Epidemiologic Studies-Depression Scale score ≥ 23.
[b]Test statistics were χ^2 or analysis of variance for categorical or continuous variables, respectively.
[c]According to Instrumental Activities of Daily Living and Activities of Daily Living criteria.
[d]Mini-Mental State Examination score < 26.
[e]According to the Mini-International Neuropsychiatry Interview.

DISCUSSION

HT and Depressive Symptoms in Postmenopausal Women

The present study indicates that current HT use is not significantly associated with a decreased risk of depressive symptoms in elderly postmenopausal women. Given the size of our sample, a power calculation indicates that the minimal difference in ORs that could have been detected was 30%–40% (in absolute values). Since the median duration of current HT use was 12 years, our results are not compatible with the hypothesis that postmenopausal women require prolonged treatment to obtain a satisfactory antidepressant effect. This conclusion is also suggested by the absence of significant association between HT duration and depressive symptoms. These results are consistent with previous clinical trials of short-term estradiol treatment, which primarily found a weaker association, if any, between treatment and depression in postmenopausal women compared to perimenopausal women.[4,5] This finding adds further weight to the hypothesis that there is a critical window of estrogen susceptibility, limited to the perimenopausal period, during which HT may have maximal antidepressant and neuroprotective effects.[20,21]

Our results differ from those of a large cross-sectional study of 6,602 postmenopausal women in which a decreased risk of depressive symptoms was reported in current HT users.[22] In that study, 76% of the women were taking estrogen alone (mainly oral CEE), and a lower risk was observed in women using unopposed oral estrogen only but not in combined HT users (estrogen combined with medroxy progesterone acetate [MPA]). The small number of women currently using unopposed estrogen in our sample (especially for women using oral estrogen, n = 9, of whom none used CEE) compared to those using opposed estradiol (80% of current users) could explain the inconsistencies. However, since we did not observe a protective effect with

Table 3. Adjusted Models for the Association Between Hormone Therapy (HT) Use and New-Onset Depressive Symptoms After 4-Year Follow-Up, Among Women Without Depression at Baseline

HT Use at Baseline[a]	n	Depressive Symptoms, %	OR[b] (95% CI)	*P* Value
Never	2,072	17.13	1.0	
Current	470	18.38	1.35 (1.00–1.83)	.06
Never	2,072	17.13	1.0	
Unopposed transdermal	80	16.25	1.06 (0.56–2.03)	.85
Unopposed oral	9	11.11	0.95 (0.11–7.85)	.96
Opposed transdermal	292	19.18	1.48 (1.03–2.12)	.03
With progesterone	134	18.66	1.36 (0.82–2.26)	.24
With synthetic progestin	158	19.62	1.59 (1.01–2.50)	.046
Opposed oral	79	20.25	1.47 (0.78–2.77)	.23
With progesterone	13	23.08	1.90 (0.51–7.07)	.34
With synthetic progestin	66	19.70	1.38 (0.68–2.81)	.37
Other unrelated HT types	10	ND	ND	ND

[a]Corresponds to opposed and unopposed estradiol-based HT.
[b]Adjusted for age, educational level, center, widowhood, age at menopause, insomnia, disability, cognitive impairment, chronic health disorders, and history of depression.
Abbreviation: ND = not determined.

Table 4. Adjusted Models for the Association Between Hormone Therapy (HT) Use After Study Inclusion and New-Onset Depressive Symptoms After 4-Year Follow-Up, Among Women Without Depression at Baseline

HT Use 4 y After Study Inclusion	n	Depressive Symptoms (%)	OR[a] (95% CI)	*P* Value
Never	2,037	15.95	1.0	
Continuing	162	17.90	1.34 (0.84–2.15)	.22
Discontinuing (early)[b]	76	30.30	2.63 (1.52–4.55)	.0005

[a]Adjusted for age, educational level, center, widowhood, age at menopause, insomnia, disability, cognitive impairment, chronic health disorders, and history of depression.
[b]Discontinued between study inclusion and the first 2-year follow-up.

transdermal unopposed estradiol, one explanation could be related to differences in the depression measures used. Whooley et al[22] measured depressive symptoms using the short-form, self-report Geriatric Depression Scale, whereas we used the CES-D, which covers a fuller range of depressive symptoms and has better criterion validity in the identification of MDD.[13,23]

Interestingly, the results of our work do suggest that the effects of HT on depression in postmenopausal women may vary depending on the type of treatment used. Conjugated equine estradiol, for example, is most commonly used in the United States but not necessarily elsewhere around the world,[24] which may help explain some inconsistencies in findings across studies. We also found that women who used transdermal estradiol associated with a synthetic progestin had an increased risk of depressive symptoms, while transdermal estradiol alone or in combination with natural progesterone was not significantly associated with the incidence of depressive symptoms. Although we could not definitively conclude a specific deleterious effect of associated progestin compared to progesterone, our data are supported by previous studies that have shown that the effects of HT on mood can be modified by changing the progestogens compound that is used. Synthetic progestin has been suggested to be an antagonist to estrogen that mitigates its mood-enhancing effect in postmenopausal women.[7,8,25] A negative effect on mood pattern was also reported in nondepressed postmenopausal women treated with progestogen in combination with estrogen, whereas no significant change or improvement in mood was observed with estrogen alone.[26–29] Other studies, however, reported no negative effects on mood or even mood improvement with progestogen alone or combined with estrogen.[30,31] Although the results of our study do not suggest that the use of transdermal estradiol with synthetic progestin actually causes depressive symptoms, the presence of a significant association warrants further investigation to help clarify the long-term effects of specific subtypes of progestins on depression.

Discontinuing HT and New-Onset Depressive Symptoms in Postmenopausal Women

An intriguing finding from this study was the observed increased risk of new-onset depressive symptoms (OR = 2.63; 95% CI, 1.52–4.55; *P* = .0005) among women who stopped HT early in the follow-up period; however, there was no significant difference between continuous HT users and never users. This finding raises the question of why women stopped using HT. Examining group differences, past HT users at baseline differed from never users by being younger and less frequently widowed. Compared to current users, past users were older, less educated, more likely to be widowed, and they reported more frequent insomnia and a higher level of chronic disorders and disability, ie, a priori they were at higher risk of depression. However, among current users at baseline, women who discontinued HT early after study inclusion did not differ significantly from those having continuously used HT during the 4-year follow-up period except for a higher BMI in the early discontinuation group. In addition, this association between discontinuing HT and the incidence of depressive symptoms persisted after adjustment for all potential confounders. In our multiadjusted model, BMI was not considered as an adjustment variable, since it was not significantly associated with depressive symptoms in univariate analysis (*P* = .32). However, since continuing and early discontinuing women only differed by BMI among all the variables examined, we performed an additional multivariate model further adjusting for BMI; this model did not modify the strength of the association, and the same odds ratio (OR) was observed (OR = 2.66; 95% CI, 1.54–4.60; *P* = .0005).

Another possibility is that discontinuation of HT increases the risk of depressive symptoms due to the (re) emergence of menopause-associated symptoms, particularly in those women who first initiated treatment for the control of menopause-associated depression. Vasomotor symptoms, for example, have been independently associated with an increased risk of depression in perimenopausal women,[32] although this association appears less likely in our older postmenopausal women, who are, on average, 20 years

postmenopause.[33] We also observed no difference regarding the frequency of insomnia between continuing and discontinuing women. Women with depressive symptoms may also be more likely to complain of menopausal symptoms and thus to be prescribed HT in the first place. We effectively observed that ever users of HT tended to have a more frequent history of past MDD, although controlling for a past history of depression did not modify the significance of the association. On the other hand, the risk was not significant for those having continued HT.

Early or current stressful events have been reported to be associated with depression, notably during the menopausal transition.[34] We have no information concerning specific stressful life events during the follow-up except bereavement, in which case there was no difference in the frequency of widows between women who developed depressive symptoms during the follow-up period and those with no depressive symptoms. Hence, the underlying biologic, neurochemical, or psychological mechanisms associated with re-emergence of depressive symptoms remain to be determined but could include other processes altering the quality of life and overall functioning, eg, increased proinflammatory activity or sexual dysfunction.[35]

An increase in mood disturbance among postmenopausal women due to declining prescriptions of HT may thus be anticipated. Interestingly, McIntyre et al[36] reported that the decrease in the number of HT prescriptions following the WHI results in 2002 was associated with a statistically significant concomitant increase in prescriptions of serotonergic antidepressants, suggesting that antidepressants were being prescribed for symptoms (psychological and physical) previously controlled with the use of HT. Data on the appropriate management of depression in the context of HT discontinuation are, however, lacking, and the subject requires further investigation.[37,38]

Limitations

This study has several limitations. Women taking antidepressants were classified as depressed, although it is possible that the treatment was prescribed for another psychiatric condition, which could have resulted in misclassification bias. However, we have ensured that the findings were comparable if we considered only CES-D scores and adjusted for antidepressant use in the analysis (data not shown). The data concerning some of the covariates were self-reported and may thus be subject to recall bias, with depressed participants responding more negatively about their health. However, similar associations were seen in the unadjusted and adjusted analysis, suggesting that any bias did not have a substantial influence on the results. There is also the potential for bias in this analysis due to the exclusion of women with missing data. These women were older, had lower education levels, were more frequently widowed, and had overall poorer health. In addition, there is prescription bias in regard to women who are given HT, and we have shown that current users were significantly healthier than both past and never users. Therefore, despite the fact that a number of variables related to this were controlled for, other factors that were not recorded may have influenced the results.

Strengths

Despite these limitations, this study has a number of strengths. The data used in this analysis came from a large, multicenter, population-based, prospective study of women aged 65 years and over, and therefore the results are relevant to elderly women living in the community. Psychiatric evaluation was assessed by trained staff using a measure of depressive symptoms that has been validated in the elderly,[11] and it appears to be a good indicator of MDD.[12] The cohort design of this study allowed evaluation of long-term HT use, and current HT use was verified at study inclusion and at each follow-up by examining the prescriptions and medications themselves, thus minimizing exposure misclassification. We controlled for a large number of covariates linked to depression, thus minimizing any confounding, particularly measures of physical health (physical incapacities and chronic health conditions), insomnia, and cognitive impairment. Finally, in contrast to the majority of community-based studies, we controlled for a history of past depression, which may confound the association between depressive symptoms and HT.

CONCLUSION

HT is still the first-line of treatment for the approximately 75% of women who experience menopausal symptoms, and it remains an important therapeutic option for first episodes of mild and moderate depression occurring at the perimenopause, at least for women with no contraindications for estrogen treatment.[39] Older postmenopausal women, however, often stop HT after prolonged use, and this discontinuation was dramatically exacerbated after the results of the WHI trial were published in July 2002.[9] It is, however, now generally acknowledged that the type of HT used in the WHI's RCT (CEE and MPA) could most likely result in a higher risk of adverse effects than natural HT formulations based on 17β-estradiol and progesterone.[24,40] In fact, while much previous research has focused on whether all women should or should not use HT, our study suggests that practitioners may need to monitor women who decide to discontinue HT treatment more closely, in particular with regard to breakthrough psychiatric symptoms, and to offer possible alternative treatments in the case of (re)emergence of depressive symptoms.[38,41]

Drug names: estradiol (Menostar, Estrace, and others), conjugated estrogens combined with medroxyprogesterone (Prempro, Premphase, and others), progesterone (Prometrium and others).

Author affiliations: Institut National de la Santé et de la Recherche Médicale (Inserm) U888, Montpellier (Mss Scali and Ryan and Drs Carrière, Ritchie, and Ancelin); Inserm U593, Bordeaux (Dr Dartigues); and Geriatric Medical Center Champmaillot, Dijon (Dr Tavernier), France.

Potential conflicts of interest: None reported.

Funding/support: The 3C Study was conducted under a partnership agreement between Inserm, the Victor Segalen Bordeaux II University, and Sanofi-Synthélabo. The Fondation pour la Recherche Médicale funded the preparation and first phase of the study. The 3C Study was also supported by the Caisse Nationale Maladie des Travailleurs Salariés, Direction Générale de la Santé, MGEN, Institut de la Longévité, Agence Française de Sécurité Sanitaire des Produits de Santé, the Regional Governments of

© Copyright 2010 Physicians Postgraduate Press, Inc.

Aquitaine, Bourgogne and Languedoc-Roussillon, and the Fondation de France, the Ministry of Research-Inserm Programme "Cohorts and collection of biological material." Part of this project was financed by a grant from the Agence Nationale de la Recherche project 07 LVIE 004.

REFERENCES

1. Ancelin ML, Scali J, Ritchie K. Hormonal therapy and depression: are we overlooking an important therapeutic alternative? *J Psychosom Res*. 2007;62(4):473–485.
2. Schmidt PJ, Nieman L, Danaceau MA, et al. Estrogen replacement in perimenopause-related depression: a preliminary report. *Am J Obstet Gynecol*. 2000;183(2):414–420.
3. Soares CN, Almeida OP, Joffe H, et al. Efficacy of estradiol for the treatment of depressive disorders in perimenopausal women: a double-blind, randomized, placebo-controlled trial. *Arch Gen Psychiatry*. 2001;58(6):529–534.
4. Cohen LS, Soares CN, Poitras JR, et al. Short-term use of estradiol for depression in perimenopausal and postmenopausal women: a preliminary report. *Am J Psychiatry*. 2003;160(8):1519–1522.
5. Morrison MF, Kallan MJ, Ten Have T, et al. Lack of efficacy of estradiol for depression in postmenopausal women: a randomized, controlled trial. *Biol Psychiatry*. 2004;55(4):406–412.
6. Zweifel JE, O'Brien WH. A meta-analysis of the effect of hormone replacement therapy upon depressed mood. *Psychoneuroendocrinology*. 1997;22(3):189–212.
7. Rymer J, Morris EP. Extracts from "Clinical evidence": menopausal symptoms. *BMJ*. 2000;321(7275):1516–1519.
8. Soares CN, Arsenio H, Joffe H, et al. Escitalopram versus ethinyl estradiol and norethindrone acetate for symptomatic peri- and postmenopausal women: impact on depression, vasomotor symptoms, sleep, and quality of life. *Menopause*. 2006;13(5):780–786.
9. Rossouw JE, Anderson GL, Prentice RL, et al. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288(3):321–333.
10. 3C Study Group. Vascular factors and risk of dementia: design of the Three-City Study and baseline characteristics of the study population. *Neuroepidemiology*. 2003;22(6):316–325.
11. Berkman LF, Berkman CS, Kasl S, et al. Depressive symptoms in relation to physical health and functioning in the elderly. *Am J Epidemiol*. 1986;124(3):372–388.
12. Radloff LS, Locke BZ. *The Community Mental Health Assessment Survey and CES-D scale*. New Brunswick, NJ: Rutgers University Press; 1986.
13. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*. 1998;59(suppl 20):22–33, quiz 34–57.
14. Ritchie K, Artero S, Beluche I, et al. Prevalence of DSM-IV psychiatric disorder in the French elderly population. *Br J Psychiatry*. 2004;184(2):147–152.
15. Lawton MP. Scales to measure competence in everyday activities. *Psychopharmacol Bull*. 1988;24(4):609–614.
16. Katz S, Ford AB, Moskowitz RW, et al. Studies of illness in the aged: the index of ADL: a standardized measure of biological and psychosocial function. *JAMA*. 1963;185:914–919.
17. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189–198.
18. Ribet C, Derriennic F. Age, working conditions, and sleep disorders: a longitudinal analysis in the French cohort E.S.T.E.V. *Sleep*. 1999;22(4):491–504.
19. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition. Washington, DC: American Psychiatric Association; 1994.
20. Resnick SM, Henderson VW. Hormone therapy and risk of Alzheimer disease: a critical time. *JAMA*. 2002;288(17):2170–2172.
21. Zandi PP, Carlson MC, Plassman BL, et al. Cache County Memory Study Investigators. Hormone replacement therapy and incidence of Alzheimer disease in older women: the Cache County Study. *JAMA*. 2002;288(17):2123–2129.
22. Whooley MA, Grady D, Cauley JA. Postmenopausal estrogen therapy and depressive symptoms in older women. *J Gen Intern Med*. 2000;15(8):535–541.
23. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas*. 1977;1(3):385–401.
24. Ancelin ML, Ritchie K. Lifelong endocrine fluctuations and related cognitive disorders. *Curr Pharm Des*. 2005;11(32):4229–4252.
25. Fitzpatrick LA, Pace C, Wiita B. Comparison of regimens containing oral micronized progesterone or medroxyprogesterone acetate on quality of life in postmenopausal women: a cross-sectional survey. *J Womens Health Gend Based Med*. 2000;9(4):381–387.
26. Sherwin BB. The impact of different doses of estrogen and progestin on mood and sexual behavior in postmenopausal women. *J Clin Endocrinol Metab*. 1991;72(2):336–343.
27. Björn I, Bixo M, Nöjd KS, et al. Negative mood changes during hormone replacement therapy: a comparison between two progestogens. *Am J Obstet Gynecol*. 2000;183(6):1419–1426.
28. Andréen L, Bixo M, Nyberg S, et al. Progesterone effects during sequential hormone replacement therapy. *Eur J Endocrinol*. 2003;148(5):571–577.
29. Odmark IS, Bäckström T, Jonsson B, et al. Well-being at onset of hormone replacement therapy: comparison between two continuous combined regimens. *Climacteric*. 2004;7(1):92–102.
30. Cummings JA, Brizendine L. Comparison of physical and emotional side effects of progesterone or medroxyprogesterone in early postmenopausal women. *Menopause*. 2002;9(4):253–263.
31. Cagnacci A, Arangino S, Baldassari F, et al. A comparison of the central effects of different progestins used in hormone replacement therapy. *Maturitas*. 2004;48(4):456–462.
32. Cohen LS, Soares CN, Vitonis AF, et al. Risk for new onset of depression during the menopausal transition: the Harvard study of moods and cycles. *Arch Gen Psychiatry*. 2006;63(4):385–390.
33. Col NF, Guthrie JR, Politi M, et al. Duration of vasomotor symptoms in middle-aged women: a longitudinal study. *Menopause*. 2009;16(3):453–457.
34. Woods NF, Smith-DiJulio K, Percival DB, et al. Depressed mood during the menopausal transition and early postmenopause: observations from the Seattle Midlife Women's Health Study. *Menopause*. 2008;15(2):223–232.
35. Soares CN. Depression during the menopausal transition: window of vulnerability or continuum of risk? *Menopause*. 2008;15(2):207–209.
36. McIntyre RS, Konarski JZ, Grigoriadis S, et al. Hormone replacement therapy and antidepressant prescription patterns: a reciprocal relationship. *CMAJ*. 2005;172(1):57–59.
37. Cohen LS, Soares CN, Joffe H. Diagnosis and management of mood disorders during the menopausal transition. *Am J Med*. 2005;118(suppl 12B):93–97.
38. Soares CN, Joffe H, Viguera AC, et al. Paroxetine versus placebo for women in midlife after hormone therapy discontinuation. *Am J Med*. 2008;121(2):159–162, e1.
39. Altshuler LL, Cohen LS, Moline ML, et al. Expert Consensus Panel for Depression in Women. The Expert Consensus Guideline Series: treatment of depression in women. *Postgrad Med*. 2001;(Spec No):1–107.
40. Skouby SO, Al-Azzawi F, Barlow D, et al. European Menopause and Andropause Society. Climacteric medicine: European Menopause and Andropause Society (EMAS) 2004/2005 position statements on peri- and postmenopausal hormone replacement therapy. *Maturitas*. 2005;51(1):8–14.
41. Grady D, Sawaya GF. Discontinuation of postmenopausal hormone therapy. *Am J Med*. 2005;118(suppl 12B):163–165.