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A prospective study of hormonal treatment and anxiety disorders in community-dwelling elderly women (The Esprit Study)

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Abstract

Background: The impact of hormone therapy use on late-life anxiety disorder in elderly women has not been evaluated.

Methods: Anxiety disorders were evaluated in 838 community-dwelling postmenopausal women aged 65 years and over, randomly recruited from electoral rolls. Anxiety disorders were assessed using a standardized psychiatric examination based on DSM-IV criteria, at baseline and as part of the 2- and 4-year follow-up.

Results: Multivariate logistic regression analyses adjusted for socio-demographic variables, measures of physical health and cognitive impairment, as well as current depressive symptomatology indicated no significant association between hormone therapy and anxiety disorders at baseline or after the 4-year follow-up period, regardless of type of treatment. Compared to women who have never taken hormonal therapy, no significant difference was observed for women taking continuously hormone therapy over the follow-up or those who stopped their treatment.

Conclusions: The use of hormone therapy was not associated with improved anxiety symptomatology in elderly postmenopausal women.

KEY WORDS: Anxiety; Estradiol; Postmenopausal; Progestogen; Transdermal

1. **Introduction**

Given the extensive protective effects of estrogens on neurotransmitter systems (see for reviews (Behl, 2002; Garcia-Segura et al., 2001)), the question currently being raised is whether hormonal therapy (HT) may play a role in the management of neuropsychiatric disorders in elderly women whose steroid levels, particularly estrogen, are dramatically lowered after the menopause. The majority of previous studies in this area have focused on the effects of HT on dementia and in the treatment of depression (see for reviews (Ancelin and Ritchie, 2005; Ancelin et al., 2007). Despite methodological limitations and contradictory reports, most recent trials in women with clinically diagnosed depression, report a positive effect of short-term transdermal estrogen therapy (ET) in perimenopausal women (Schmidt et al., 2000; Soares et al., 2001), with the antidepressant response in depressed postmenopausal women being much weaker (Cohen et al., 2003; Morrison et al., 2004).

The specific effect of HT on anxiety disorders remains largely unknown. Studies conducted to date have seldom used validated psychiatric instruments or clinical diagnosis, relying principally on questionnaires evaluating psychosomatic menopausal symptoms, well-being, or quality of life. Frequent anxiety and depression co-morbidity further complicates the issue. A beneficial effect of estrogen on anxiety disorders might however, be expected, considering its role on various brain targets as well as it anxiolytic properties observed in animal models (see for recent review (Walf and Frye, 2006)). On the other hand, progestogen or its active metabolites, found in the majority of combined HT preparations, appear to have opposing anxiolytic and anxiogenic behaviors (Rupprecht, 2003; Strous et al., 2006).

Given the relatively high prevalence of anxiety disorders in older women (Ritchie et al., 2004), and differences in vulnerability across individuals, the potential effects of HT in treating these disorders remain an important question to be addressed. However, while it is unlikely to be answered in the near future by large-scale RCTs of long-term HT users, it is currently feasible to use existing data from longitudinal population-based studies with adequate information on hormone exposure and psychiatric evaluation.

The present study aimed to determine whether HT could alleviate anxiety symptomatology in a population-based cohort using validated instruments. In this study we controlled for socio-demographic

variables, measures of physical health including insomnia, as well as cognitive impairment, which may independently contribute to anxiety disorder and HT prescription. We also took into account depression co-morbidity, as well as the type of HT used.

2. Subjects and Methods

2.1. Study population

The data used for this analysis were derived from a longitudinal study of neuropsychiatric disorder in community-dwelling French elderly (the Esprit study) (Ritchie et al., 2004). Eligible participants, who were at least 65 years of age and non-institutionalized, were recruited from the electoral rolls of Montpellier (southern France), between 1999 and 2001. Ethics approval for the study was given by the national ethics committee. After obtaining written informed consent from all participants, interviews were administered by trained staff at baseline and every two years thereafter. Of the women recruited as part of the Esprit Study, only non-demented women with complete follow-up, who were assessed for current anxiety disorders, had detailed information relating to the use of HT and had no missing data for the main covariates considered in the multivariate logistic models (n=838) were included in this analysis.

2.2. Anxiety Disorder

The diagnosis of lifetime anxiety disorders (general anxiety disorder (GAD), phobia, obsessional compulsive disorder, panic and post-traumatic stress disorder) was made using the Mini-International Neuropsychiatry Interview (MINI), a standardized psychiatric examination which has been validated in the general population (Sheehan et al., 1998) according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria (Ritchie et al., 2004). Cases detected by the MINI were reviewed by a panel of psychiatrists to validate the initial diagnosis. In longitudinal analyses, incident cases of anxiety symptomatology were identified from women free of anxiety disorder at baseline but who subsequently had incident anxiety disorder during at least one of the two follow-up examinations.

2.3. Hormone therapy and menopausal characteristics

All types of medications 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 and duration of use, as well as age at menopause (defined as one year without menses) and type of menopause (*i.e.* natural *vs.* surgical or following a treatment such as chemotherapy or radiotherapy).

2.4. Other measures

Participants were classified as disabled if they were unable to complete at least one task from either the Instrumental Activities of Daily Living (IADL) (Lawton, 1988) or the Activities of Daily Living (ADL) (Katz et al., 1963) scales. Cognitive function was assessed using the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) and those scoring less than 26 (corresponding to the 15th percentile) were classified as having lower cognitive function. Insomnia was defined as scoring positive on at least two questions from the 5-item sleep subscale of the Nottingham Health Profile questionnaire (Ribet and Derriennic, 1999). Chronic disorders were defined as having a history of respiratory disorder, cancer, hypertension, hypercholesterolemia, diabetes, and vascular diseases (including angina pectoris, myocardial infarction, stroke, cardiovascular surgery, bradycardia or palpitations). History of chronic disorder was established according to standardized questions with additional information obtained from general practitioners where necessary. The Centre for Epidemiology Studies Depression Scale (CES-D) is a validated questionnaire which was used to measure current depressive symptoms in the elderly population (Berkman et al., 1986). It has been suggested that a cutoff point of 23 or more can be used to identify major depressive disorder (MDD) (Radloff and Locke, 1986).

2.5. Statistical Analysis

Two-tailed chi-squared tests or t-tests were used to compare categorical and continuous characteristics respectively, between women with and without anxiety disorder. Of all the socio-demographic or health variables examined (listed in Table 1), those which were found to be significantly associated with anxiety at $p<0.15$ were considered in the multivariate analysis. The final models were adjusted for education level, widowhood, cognitive impairment, insomnia, current depressive symptomatology and antidepressant treatment. In longitudinal analysis we used multi-adjusted logistic regression models to evaluate the predictive value of HT taken at baseline on incident anxiety disorder

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 multi-adjusted models. SAS version 9.1 (SAS Institute, Inc., North Carolina) was used for the statistical analysis with a significance level of $p<0.05$.

3. Results

3.1. Population characteristics

The 838 women included in the present analysis had a mean age of 72.4, ranging from 65 to 93 years. In our sample, 15.9% currently used HT and 20.5% reported past use. Transdermal estradiol was used by the majority of current HT users either unopposed (16.5%) or combined with oral progesterone (22.6%) or synthetic progestin (38.3%). Oral estradiol was used by only 15.8% of women, with 0.8% using unopposed, 0.8% combined with progesterone and 14.2% with synthetic progestin. None of these French women used other estrogen derivatives (*e.g.* ethinylestradiol, or conjugated equine estradiol), however a small proportion (6.8% overall) were prescribed other forms of HT (*e.g.* tibolone, cyproterone, or progestogen alone).

3.2. Prevalence and correlates of anxiety disorders

The prevalence of current anxiety disorders evaluated using the MINI was 22.3%, mainly consisting of GAD (7.0%) and phobia (16.8%), which may be co-morbid. Obsessional compulsive disorder, panic or post-traumatic stress disorder, each accounted for less than 0.6% of current anxiety disorders. Women with current anxiety were more likely to have lower education level ($p=0.001$), to be widowed ($p=0.05$), to have a higher frequency of cognitive impairment ($p<0.0001$), insomnia ($p<0.001$) and current depression ($p<0.0001$), and to be more frequently treated with antidepressants ($p=0.05$) (**Table 1**).

3.3. Associations between HT and anxiety disorders

We first examined the cross-sectional associations between HT use and anxiety disorders at baseline, while adjusting for educational level, widowhood, cognitive impairment, insomnia, current

depressive symptomatology and antidepressant use. There was no significant association between anxiety disorder and past or current HT use, and regardless of the type of HT currently used (**Table 2**). The same results were observed when specifically GAD or phobia was examined (data not shown).

The effect of current HT on incident anxiety was evaluated longitudinally during the 4-year follow-up (Table 2). Regardless of the type of HT, no significant association was observed between current HT use and incident anxiety disorder during follow-up. The same results were observed after further adjustment for past anxiety disorders (using the MINI) or for anxiety symptomatology (assessed by Spielberger Trait evaluation (Spielberger, 1983)) as well as for anxiolytic treatment (data not shown). In addition, stratification by depression comorbidity did not modify the findings although as there were only a small number of anxious women with comorbid depression (n=27), definite conclusions could not be made concerning this group. Among HT users who were free of anxiety disorder at baseline, 27% of women continuously took HT during the 4-year follow-up, 73% ceased treatment, and only two women started a treatment after inclusion. Neither cessation of treatment or continuous treatment modified risk compared to women who had never used HT.

4. Discussion

The present study indicates that HT use was not significantly associated with a modified risk of incident anxiety disorder in elderly postmenopausal women. Given the size of our sample, a power calculation indicates that the minimal difference in ORs which could have been detected is 50-75% (in absolute values). This absence of an association could reflect a decreased susceptibility of older postmenopausal women, compared to perimenopausal women, to the beneficial effects of HT, as reported in the case of depression (Cohen et al., 2003; Morrison et al., 2004).

To our knowledge, this is the first epidemiological study that has evaluated both the cross-sectional and longitudinal effect of HT on anxiety disorders, diagnosed using a validated standardized psychiatric examination. Previous studies have principally used arbitrary scores or non-specific questionnaires focusing on quality of life, well-being, or menopausal symptoms, rather than anxiety disorder specifically. We did not observe a significant association between HT use and anxiety disorders (*e.g.* GAD or phobia),

even when considering women without co-morbid depression (data not shown). Women with anxiety symptoms may be more likely to complain or to seek treatment and thus to be prescribed HT (bias by indication), however, controlling for a history of anxiety symptomatology did not modify the results.

Furthermore we observed no difference between opposed and unopposed HT. Global anxiety symptomatology has been evaluated (using the State-Trait-Anxiety Inventory) in one RCT, with 120 menopausal women treated by transdermal estradiol combined or not with progestin. Of four progestins evaluated (medroxyprogesterone acetate, nomegestrol acetate or norethisterone acetate, and dydrogesterone), only dydrogesterone was shown to decrease anxiety compared to controls treated with estradiol plus placebo (Cagnacci et al., 2004), although the effect of placebo alone was not examined. In our study, the number of women using unopposed estradiol was too low to test this possibility.

Our study has certain limitations. The data concerning some of the covariates were self-reported which may be subject to recall bias with anxious participants responding more negatively about their health. However, similar associations were seen in the unadjusted and adjusted analysis, thus 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, who had overall poorer health (data not shown). In addition, there is a bias of prescription in regards to women who are given HT and therefore, despite controlling for a number of variables related to this, other factors which were not recorded, may have influenced the results.

Despite these limitations, this study has a number of strengths. The data concerning anxiety disorder used in this analysis are derived from a population-based prospective study of women aged 65 years and over and therefore the results are relevant to elderly women living in the community. The diagnosis of lifetime anxiety disorders was made using the MINI, a standardized psychiatric examination which has been validated in the general population (Sheehan et al., 1998) according to the DSM-IV criteria, which also enabled the distinction between GAD and phobia. The cohort design of this study allowed evaluation of long-term HT use. Current HT use was verified at 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 anxiety disorder, thus minimizing any

confounding, particularly measures of physical or mental health. Finally, we controlled for past anxiety symptomatology as well as for co-morbidity with depression, which may confound the association between anxiety and HT.

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TABLE 1: Characteristics of participants with or without anxiety disorder.

Characteristic	No Anxiety Disorder (n =651)	Current Anxiety Disorder[a] (n =187)	p-value[b]
Age (Mean (SD))	72.4 (5.1)	72.3 (5.0)	0.98
≥12 years of schooling (%)	46.9	33.7	0.001
Widowed (%)	26.0	33.2	0.05
Disability[c] (%)	2.1	3.9	0.17
Cognitive impairment (%)	13.4	26.3	<0.0001
Insomnia (%)	22.1	34.5	<0.001
Chronic disorders[d] (%)	66.5	65.8	0.85
BMI (%)	37.7	33.9	0.34
Current depressive symptomatology[e] (%)	11.9	34.22	<0.0001
Antidepressant use (%)	7.2	11.8	0.05
Age at Menopause (Mean (SD))	49.3 (5.7)	49.0 (5.3)	0.30
Type of Menopause			0.81
Natural (%)	81.3	80.7	
Surgical (%)	9.8	11.3	
Other (i.e. treatment-related) (%)	8.9	8.1	
Hormonal Treatment (HT)			0.79
Never (%)	64.1	62.0	
Past (%)	20.6	20.3	
Current (%)	15.4	17.7	
Duration of HT (Median (min-max))	10.0 (1-43)	10.0 (1-31)	0.63

[a] According to the MINI. [b] Test-statistic were χ^2 or t-test statistics for categorical or continuous variables, respectively. [c] According to IADL and ADL criteria. [d] Includes vascular diseases, other heart problems, respiratory disorders, or cancer diagnosed within the last 2 years. [e] Having CESD score ≥ 23

TABLE 2: Adjusted models for the association between HT use and current anxiety disorders at baseline or after 4-year follow-up.

		Current anxiety at baseline (cross-sectional)			Incident anxiety after 4-year follow-up (longitudinal)		
HT use		**n, % with anxiety**	**OR[a] [95% CI]**	**p-value**	**n, % with anxiety**	**OR[a] [95% CI]**	**p-value**
Lifetime HT use	**Never**	533, 21.8%	1.0				
	Past	172, 22.1%	0.95 [0.61-1.47]	0.95			
	Current	133, 24.8%	1.32 [0.81-2.15]	0.27			
Current HT use[b]	**Never**	533, 21.8%	1.0		409, 21.5%	1	
	Unopposed transdermal	22, 22.7%	0.62 [0.17-2.29]	0.47	17, 23.5%	1.13 [0.34-3.84]	0.84
	Unopposed oral	1	Nd		0	Nd	
	Opposed transdermal	81, 24.7%	1.46 [0.80-2.66]	0.21	61, 18.0%	0.78 [0.36-1.69]	0.53
	- *with progesterone*	*30, 23.3%*	*1.37 [0.54-3.43]*	*0.51*	*23, 26.1%*	*1.26 [0.43-3.74]*	*0.67*
	- *with synthetic progestin*	*51, 25.5%*	*1.52 [0.73-3.18]*	*0.26*	*38, 13.2%*	*0.55 [0.20-1.56]*	*0.26*
	Opposed oral	20, 15.0%	0.80 [0.22-2.91]	0.74	17, 5.9%	0.27 [0.03-2.07]	0.21
HT use 4-year after inclusion	**Never**				409, 21.5%	1.0	
	Continuing				27, 18.5%	1.03 [0.36-2.94]	0.98
	Discontinuing				73, 17.8%	0.77 [0.37-1.58]	0.48
	Starting				2, 0%	Nd	

[a] Adjusted for educational level, widowhood, insomnia, cognitive impairment, current depressive symptomatology and antidepressant use. [b] Corresponds to opposed and unopposed estradiol-based HT (excluding the women taking other unrelated HT types, 9 in baseline analysis, and 5 in longitudinal analysis).
Nd: not determined