Hormone Replacement Therapy in Postmenopausal Women with Schizophrenia: Positive Effect on Negative Symptoms?

Laurie A. Lindamer, Dawn C. Buse, James B. Lohr, and Dilip V. Jeste

Background: Some studies of premenopausal women suggest that the severity of psychopathology associated with schizophrenia may be related to levels of estrogen.

Methods: We examined psychopathology in community-dwelling postmenopausal women with schizophrenia who had received \( n = 24 \) versus had never received \( n = 28 \) hormone replacement therapy.

Results: Users of hormone replacement therapy and nonusers did not differ significantly with respect to age, ethnicity, education, age of onset, duration of schizophrenia, global cognitive functioning, or neuroleptic-induced movement disorders. The hormone replacement therapy users received lower average daily doses of antipsychotic medication; they had similar levels of positive symptoms but significantly less severe negative symptoms compared with hormone replacement therapy nonusers, independent of differences in antipsychotic dosage.

Conclusions: Our results suggest that the use of hormone replacement therapy in conjunction with antipsychotic medication in postmenopausal women with schizophrenia may help reduce negative, but not positive, symptoms.

Key Words: Psychosis, aging, estrogen, positive and negative symptoms, antipsychotics

Introduction

Several studies of gender differences in psychopathology associated with schizophrenia suggest that women with schizophrenia tend to have more severe positive symptoms and less severe negative symptoms than men (Andia et al 1995; Goldstein and Link 1988; Gur et al 1996; Lindamer et al 1999; Shtasel et al 1992). The data on gender differences in depressive symptoms are inconsistent (Addington et al 1996; Goldstein and Link 1988). Several explanations for the gender differences in psychopathology have been proposed, including psychosocial factors (Seeman 1997), cerebral lateralization (Seeman 1981), and levels of estrogen (Hafner et al 1993; Lindamer et al 1997; Seeman 1997).

Some of the evidence supporting a role of estrogen comes from studies of changes in psychopathology during different phases of the menstrual cycle in premenopausal women with schizophrenia (Seeman 1996). Researchers have generally found lower scores on measures of psychosis and general psychopathology (Hallonquist et al 1993; Riecher-Rossler et al 1994) or better treatment response (Gattaz et al 1994) during phases of the menstrual cycle when estrogen levels are higher. No relationship of estradiol levels to measures of depression has been observed in women with schizophrenia. The relationship with negative symptoms of schizophrenia has received little attention, however, except for a report of an inverse association between estradiol levels and anergia (Riecher-Rossler et al 1994).

An open-label treatment study of 18 premenopausal women (Kulkarni et al 1995) found a more rapid response in general psychopathology and positive symptom scores in women receiving estrogen supplementation of their antipsychotic medication relative to a group that received only antipsychotic medication. At the end of the 45 days, however, no significant differences between the groups on measures of psychopathology were present. Although there have been studies of estrogen effects on depression (Morrison and Tweedy 2000) and tardive dyskinesia (Glazer and Nasrallah 1988), to our knowledge there have been no published studies examining the association between use of hormone replacement therapy (HRT) and psychopathology in postmenopausal women with schizophrenia.

We investigated the relationship between the use of HRT and psychopathology in community-dwelling postmenopausal women with schizophrenia in a cross-sectional study. It was hypothesized that compared to non-
HRT users, women with schizophrenia who had used HRT would have lower scores on measures of general psychopathology and positive and negative symptoms but that both groups would have similar levels of depression.

**Methods and Materials**

Fifty-seven outpatient women over the age of 45 with the DSM-IV (American Psychiatric Association 1994) diagnosis of schizophrenia or schizoaffective disorder were included in our study. Details of clinical evaluation in our research center have been described elsewhere (Jeste et al 1995). Briefly, exclusion criteria were a history of moderate to severe head trauma or other neurologic disorder, current alcohol or other substance abuse or dependence meeting DSM-IV criteria (American Psychiatric Association 1994), and any systemic medical disease that was judged likely to affect central nervous system functioning. Our study was approved by the University of California at San Diego Human Subjects Committee, and all the patients signed a voluntary written informed consent for research participation. They were interviewed about their gynecological and reproductive history, which included information regarding menopausal status and the use of HRT. Five women who were not yet postmenopausal, as defined by the absence of a menstrual cycle for at least 6 months, were excluded. Of the remaining 52 women, 28 had never received HRT, and 24 had received HRT for at least 1 year.

The following rating scales were used: Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1988) (including the total score and depression, hostility, disorganization and negative symptom subscales), Scales for the Assessment of Positive and Negative Symptoms (SAPS and SANS, respectively; Andreasen 1981, 1984), Positive and Negative Syndrome Scale (PANSS; Kay et al 1987) (including the positive, negative, and general symptoms subscales), Hamilton Depression Rating Scale (HAM-D; Hamilton 1967), modified Simpson–Angus Scale (Simpson and Angus 1970), Abnormal Involuntary Movement Scale (AIMS; National Institute of Mental Health 1976), and the Mini-Mental State Examination (MMSE; Folstein et al 1975). All clinical assessments were performed by raters who were blind to the hormonal status of the subjects.

Continuous variables were transformed, when necessary, to meet the assumptions of normality. Independent t tests were performed to compare the patient groups on continuous variables, and χ² tests were used to compare the groups on categorical variables. Statistical analysis was performed using SPSS (Norusis 1993), and all the statistical tests were two-tailed.

**Results**

Patients who had ever received versus never received HRT were similar with respect to age, ethnicity, diagnosis, education, age of onset, duration of illness, severity of extrapyramidal symptoms and dyskinesia, and global cognitive function (Table 1). Similar proportions (approxi-
mately 90%) of subjects in each group were on antipsychotics (including atypical agents in about a third of the patients) and anticholinergic medications (approximately 20%). More women who had received HRT had a history of hysterectomy (67% vs. 19%, $\chi^2 = 9.617, p = .002$). In addition, the women who had received HRT were on lower mean daily doses of antipsychotic medication.

There were no significant differences between the groups on general measures of psychopathology (BPRS total score or the PANSS general score), measures of depression (BPRS depression subscale or HAM-D), or positive symptoms (BRPS disorganization and hostility subscales, SAPS total, or PANSS positive subscale; Figure 1). The HRT users had lower scores on measures of negative symptoms that were significantly different for the BPRS negative subscale [$t(1,49) = 2.800, p = .007$] and PANSS negative syndrome scale [$t(1,45) = 2.104, p = .041$] and at a trend level for the SANS total [$t(1,45) = 1.886, p = .066$].

Because the HRT users and nonusers differed on the mean current daily dose of antipsychotic medication, the analysis was rerun using an analysis of covariance, with daily neuroleptic dose (mg chlorpromazine equivalent or CPZE; Jeste and Wyatt 1982) as a covariate, on the BPRS negative subscale, the SANS total, and the PANSS negative syndrome scores. The association with the BRPS negative subscale remained significant ($F = 6.409, p = .015$), whereas the results on the PANSS ($F = 3.329, p = .075$) and the SANS ($F = 2.968, p = .092$) became nonsignificant trends.

**Discussion**

No significant differences between women with schizophrenia who had received or had never received HRT were found on measures of overall psychopathology, positive or depressive symptoms, extrapyramidal symptoms, or dyskinesia. Use of HRT appeared to be related to the severity of negative symptoms, however. Women who had never received HRT had higher scores on negative symptoms even when controlling for the amount of antipsychotic medication. The less severe negative symptoms seen in the HRT users could not be explained by group differences in the use of atypical antipsychotic medication because comparable proportions of both groups were taking atypical antipsychotics. Women using HRT required lower doses of antipsychotic medications. Although data are sparse, hormonal status may affect pharmacokinetics of antipsychotic metabolism (Yonkers and Hamilton 1996); however, covarying for the antipsychotic dose did not neutralize the significant difference in BPRS negative symptoms subscale, which has been shown to have valid-
ity in older outpatients with schizophrenia (McAdams et al 1996).

The finding of less severe negative symptoms in postmenopausal women with schizophrenia who received HRT is consistent with the results reported by Riecher-Rossler et al (1994). Estrogen may reduce negative symptoms by several mechanisms, including modulating dopaminergic or other neurotransmitter systems involved in pathophysiology schizophrenia or providing neuroprotective effects (Seeman 1996, 1997). The association between postmenopausal HRT use and less severe negative symptoms in women with schizophrenia may have important clinical implications. The addition of HRT to antipsychotic medication in stable outpatients may have the effect of improving negative symptoms.

Contrary to our hypotheses, our study found no significant difference between postmenopausal HRT users and nonusers on positive symptoms. The lack of differences may be due to the fact that this sample consisted of older outpatients who were stable on antipsychotic medication and who had only mild positive symptoms, thereby restricting variability and the ability to detect differences. Positive symptoms have been shown to decrease with age possibly because of age-related decreases in dopaminergic activity, whereas negative symptoms persist (Eyler-Zorrilla et al 2000; Harvey et al 1997; Schultz et al 1997).

This study has several limitations. First, the differences on the SANS and PANSS negative subscale were significant at the trend level only when neuroleptic dose was taken into account. The consistency of the finding of lower scores on the three different negative symptom measures in HRT users was striking, however. The lack of a relationship between HRT and global cognition could reflect our use of a crude measure (i.e., MMSE) that might lack sensitivity to detect such differences. A recent randomized controlled trial of estrogen replacement therapy found no effect on cognition in patients with mild to moderate Alzheimer’s disease (Mullard et al 2000). The cross-sectional design is another limitation of this study. Although we found less severe negative symptoms in HRT users, it is not possible to conclude that this result is due to the use of HRT directly. It is possible that the severity of negative symptoms may affect the interest in or ability to seek medical care, resulting in women with higher negative symptoms not receiving HRT. Finally, this was a sample of convenience, and available information on the type, dosage, or duration of HRT was limited. Consequently, the sample may be biased.

Double-blind, placebo-controlled studies of estrogen supplementation in postmenopausal women with schizophrenia are needed for more definitive conclusions to be drawn about the effects of estrogen on the psychopathology and functioning in these patients.

This work was supported, in part, by National Institute of Mental Health Grants Nos. MH43693, MH51459, MH45131, MH40671, and MH01580; by the National Alliance for Research on Schizophrenia and Depression; and by the Department of Veterans Affairs.

References


Andreasen NC (1981): The Scale for the Assessment of Negative Symptoms (SANS). Iowa City: The University of Iowa.


