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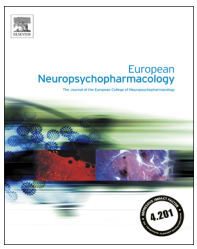

# Effects of raloxifene on cognition in postmenopausal women with schizophrenia: A double-blind, randomized, placebo-controlled trial ☆

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**Abstract**
Studies of estrogen therapy in postmenopausal women provide evidence of an effect of sex hormones on cognitive function. Estrogen has demonstrated some utility in the prevention of normal, age-related decline in cognitive functions, especially in memory. The potential therapeutic utility of estrogens in schizophrenia is increasingly being recognized. Raloxifene, a selective estrogen receptor modulator (SERM), appears to act similarly to conjugated estrogens on dopamine and serotonin brain systems, and may be a better option since it lacks the possible negative effects of estrogen on breast and uterine tissue. We assessed the utility of raloxifene as an adjuvant treatment for cognitive symptoms in postmenopausal women with schizophrenia in a 12-week, double-blind, randomized, placebo-controlled study. Patients were recruited from both the inpatient and outpatient departments. Thirty-three postmenopausal women with schizophrenia (DSM-IV) were randomized to receive either adjuvant raloxifene (16 women) or adjuvant placebo (17 women) for three months. The main outcome measures were: Memory, attention and executive functions. Assessment was conducted at baseline and week

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12. The total sample is homogenous with respect to: age, years of schooling, illness duration, baseline symptomatology and pharmacological treatment. The addition of raloxifene (60 mg) to regular antipsychotic treatment showed: we found significant differences in some aspects of memory and executive function in patients treated with raloxifene. This improvement does not correlate with clinical improvement. The use of raloxifene as an adjuvant treatment in postmenopausal women with schizophrenia seems to be useful in improving cognitive symptoms.


## 1. Introduction

Over recent decades, various studies have reached the conclusion that alterations in neuropsychological functioning are a basic characteristic of schizophrenia and not a consequence of other symptoms, medication side-effects or other aspects of the course of the illness (Kremen et al., 2000; Elvevag and Goldberg, 2000). The neuropsychological profile in schizophrenia is mainly characterized by changes in attention, processing speed, memory, and executive functions although, in some patients, a generalized effect can also be observed (Heinrichs and Zakzanis, 1998; Fioravanti et al., 2012). In addition, an important relationship has been found between these deficits and daily-life functioning (Ucok et al., 2006).

Gender differences in schizophrenia are an important factor and have been well studied in recent years. It has been found that schizophrenia occurs less frequently in women, has a later onset and, in general, a better prognosis (Hafner, 2003; Ochoa et al., 2012). One of the theories proposed to explain these differences in schizophrenia is the "estrogen hypothesis" which postulates that estrogens provide a protective effect in women at risk of presenting this illness (Seeman MV, 1990).

The estrogen hypothesis has been confirmed in various epidemiological studies which have found that levels of estrogens in women with schizophrenia are significantly lower than in healthy women (Riecher-Rossler et al., 1994). Furthermore, illness relapses appear with greater frequency, coinciding with phases of the menstrual cycle where low levels of estrogens are present.

Recent years have also seen an accumulation of evidence on estrogen activity in the brain. It is known that they play a fundamental role in the modulation of neuronal excitability, synaptic plasticity, induce neuronal survival, improve expression with respect to regenerative responses and have a role in neuronal development and regulation (Audesirk et al., 2003; Ciriza et al., 2004). Their role in the Central Nervous System (CNS) has been demonstrated in cognition related processes, especially in memory and learning capacity, mood modulation and other mental activities. Particularly notable are studies which evaluate the effects of estrogens in women with psychiatric pathology and others that assess cognitive decline in the general population (Zec and Trivedi, 2002; Terauchi et al., 2011; Riecher-Rossler and Kulkarni, 2011).

A considerable amount of animal research has also been carried out which shows that estrogens have a modulating effect on the brain's dopaminergic system (Hafner et al., 1991) and an impact on serotonergic activity (Moses et al., 2000). Estrogens also promote neuronal regeneration and block neuronal death mechanisms (DonCarlos et al., 2009). Various studies have been performed which assess the efficacy of estrogen therapy in postmenopausal women and although many indicate a positive association between cognitive functioning and estrogen replacement therapy, others have found none (Wharton et al., 2011; Gorenstein et al., 2011).

Nevertheless, the use of estrogenic treatment appears to have important contraindications for its long-term maintenance (Steinberg et al., 1991) and therefore, the selective estrogen-receptor modulators (SERMs) may be a better option.

Raloxifene is a SERM which acts in a similar way to conjugated estrogens on dopamine and serotonin brain systems, and acts as an agonist on bones and as an antagonist on breast and uterine tissue, avoiding the negative effects of estrogens.

The effects of raloxifene on the CNS have yet to be clarified but recent neuroimaging studies and basic clinical testing on healthy people are shedding new light on the subject. In a study on ovariectomized rats, it was found that raloxifene and tamoxifen increase the density of dendritic spines of pyramidal neurons in prelimbic, infralimbic and prefrontal areas (Velazquez-Zamora et al., 2012). A neuroimaging study (Neele et al., 2001) found changes in cortical activation patterns in frontal areas during a visual memory task in a group of postmenopausal women treated with raloxifene. A further study by Goekoop (Goekoop et al., 2006), carried out on elderly men, found that raloxifene could be acting in tasks that involve the prefrontal area, the anterior cingulate cortex and occipital area; all bilaterally. No differences in medial temporal areas were found (Goekoop et al., 2006).

However, other study (Yaffe et al., 2001) found no significant differences in a group of 7478 postmenopausal women treated with different doses of raloxifene versus placebo although a trend to less cognitive decline in areas related to attention and memory was found in patients in the raloxifene group. On the other hand, a subanalysis in patients over 70 years old did find differences.

In a study we published in 2011, the main objective was to evaluate the effect of raloxifene on psychpathology in patients with schizophrenia using the PANSS scale (Usall et al., 2011). We found a beneficial effect on positive and negative symptoms, and general psychopathology. Similar results were found by Kulkarni et al. (2010) with raloxifene 120 mg.

However, no study has evaluated the influence of raloxifene at the cognitive level in schizophrenia; we were only able to find the case study (Kulkarni et al., 2008). So, we conceived an exploratory study which aim of the present study was to assess the efficacy of raloxifene as an adjuvant antipsychotic treatment on neuropsychological functioning