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Raloxifene as a treatment for cognition in women with schizophrenia: the influence of menopause status

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ABSTRACT

Cognitive impairments cause significant functional issues for people with schizophrenia, often emerging before the onset of hallucinations, delusions and other psychosis symptoms. Current pharmacological treatments do not target cognitive dysfunction. Several lines of evidence support the beneficial effects of estrogens on cognition. Raloxifene hydrochloride, a selective estrogen receptor modulator, has been associated with cognitive improvements in healthy postmenopausal women and in schizophrenia, although findings are inconsistent. Using pooled data from two clinical trials, the aim of the current study was to compare the efficacy of 120 mg/day adjunctive raloxifene to placebo for 12 weeks on cognitive performance in women with schizophrenia who were stratified by menopause status (pre-menopausal; peri-menopausal or post-menopausal). A total of sixty-nine participants with a diagnosis of schizophrenia or schizoaffective disorder were included. Cognition was assessed at baseline and study end using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Results indicated that after stratifying for menopause status (strata) and adjusting for endogenous hormone levels (estrogen, progesterone, follicle stimulating hormone and luteinising hormone), semantic fluency, picture naming and list recognition change from baseline scores for the raloxifene group differed significantly from the placebo group. The findings from the current study highlight the importance of considering menopause status when interpreting the effects of hormonal treatments.

1. Introduction

Cognitive problems are a core feature of schizophrenia, with up to 80% patients showing significant impairment (Keefe and Fenton, 2007). Cognitive deficits are closely aligned with functional outcome and present a significant obstacle in the recovery process (Green, 1996). Current treatment options do not successfully ameliorate cognitive impairments (Green, 2006; Minzenberg and Carter, 2012). The areas of neurocognition that are primarily impaired include attention, working memory, memory as well as executive functioning skills, such as decision making, inhibition and planning (Minzenberg and Carter, 2012).

Sex hormones, particularly estrogen, have been substantially investigated over recent years in relation to their capacity to modify brain function. Findings from animal studies demonstrate that estrogens can influence spine density in the hippocampus and prefrontal brain regions (Tuscher et al., 2016; Woolley et al., 1990), promote neurotrophin synthesis (Milne et al., 2015) and protect the brain against stress and inflammation (Luine, 2016). Animal studies have demonstrated that estrogens have the capacity to enhance cognition, particularly in the areas of learning and memory (Engler-Chiurazzi et al., 2016; Luine, 2014). Human studies have also demonstrated beneficial effects of estrogen therapies, although findings are less consistent (Luine, 2014) and suggest that the effects of estrogens on cognition may be dependent on patient age, menopause status, duration of treatment as well as vary according to the cognitive domain assessed (Weickert et al., 2016).

The development of selective estrogen receptor modulators (SERMs), such as raloxifene, provide an estrogen therapy with mixed agonist/antagonist properties thus avoiding some of the adverse risks that have been associated with estradiol therapy (e.g. Beral et al., 2005). Raloxifene has antagonist effects on the estrogen receptor in the breast and uterus, while maintaining agonistic effects on the estrogen receptors in bone and brain tissue (Shang and Brown, 2002). Raloxifene, currently approved for use in postmenopausal women with osteoporosis, has been associated with mixed effects on cognition, potentially reflecting variations in methodology, dose and study populations (Yang et al., 2013).

A number of placebo-controlled studies in healthy postmenopausal women have shown little or no benefit of 60 mg/day raloxifene on

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cognitive function (Buckwalter et al., 2007; Haskell and Richardson, 2004; Jacobson and Truax, 1991; Nickelsen et al., 1999), with the exception of one study reporting verbal memory improvements in healthy late postmenopausal women (70–80 years) following 60 mg/day of raloxifene treatment at 3, 6, and 12 months (Jacobsen et al., 2010). A higher raloxifene dose of 120 mg/day (Nickelsen et al., 1999) has been associated with an improvement in verbal memory following 1 month of treatment (however this effect was no longer significant at 6 or 12 months). As part of the Multiple Outcomes of Raloxifene Evaluation trial, a large number of postmenopausal women with osteoporosis (n = 7478, mean age: 66) received either 60 mg raloxifene, 120 mg raloxifene or placebo for three years. The combined raloxifene group (60 mg and 120 mg groups combined) demonstrated a trend toward less decline following three years of raloxifene treatment on the two tests of verbal memory and attention (Yaffe et al., 2001). Further analyses revealed a reduced risk of developing mild cognitive impairment and a lower risk of developing Alzheimer's disease at the higher dose of 120 mg/day(Yaffe et al., 2005). A recent systematic review on the effects of raloxifene on cognition in postmenopausal women concluded that a dose of 120 mg/day may have some benefit for cognition in relation to ageing and risk of cognitive decline(Yang et al., 2013).

Clinical trials in schizophrenia have similarly revealed mixed findings. We have previously demonstrated a beneficial effect of 12 weeks of adjunctive raloxifene treatment (120 mg/day) on overall psychosis symptom severity, and positive psychosis symptoms in older women with refractory schizophrenia (Kulkarni et al., 2016, 2010). We did not, however, observe a significant group improvement on any cognitive domain in our RCT (using the Repeatable Battery for Neuropsychological Status, RBANS) (Kulkarni et al., 2016). Similarly, a recent 16-week, double-blind randomised placebo-controlled trial in severely ill postmenopausal women with schizophrenia did not find significant cognitive improvements following 120 mg/day raloxifene on the Composite Brief Assessment of Cognition in Schizophrenia(Weiser et al., 2017). Cognitive enhancing effects of raloxifene in schizophrenia have, however, been demonstrated in several case studies (e.g. (Kulkarni et al., 2008; Usall et al., 2011) and other RCTs (e.g. Huerta-Ramos et al., 2014; Weickert et al., 2015).

Using a dose of 60 mg/day of adjunctive raloxifene for 12 weeks in postmenopausal women with schizophrenia (mean age of raloxifene group = 60.14), Huerta-Ramos et al (Huerta-Ramos et al., 2014) demonstrated a beneficial effect of raloxifene on verbal learning and phonemic fluency, with a small sample size of 26 (14 randomised to raloxifene). Another series of studies have looked at the effects of adjunctive raloxifene treatment (120 mg/day) in a younger mixed sample of males and females and adopted a 13-week randomised, double-blind, placebo controlled crossover design, with analyses conducted following the initial 6 week period (Weickert et al., 2015). This group first demonstrated significant improvements following 6 weeks of raloxifene (n = 40, mean age = 37.4) in immediate and delayed verbal learning (Wechsler Memory Scale Revised Logical Memory I and II) and attention/processing speed (Trail Making Test A) as compared to a placebo group (n = 39, mean age = 34.0). Supplementary analyses looking at the effects of sex reported that females, but not males showed an improvement in phonemic fluency (Controlled Oral Word Association Task), although the number of females and their age and menopause status was not reported.

Using the same 13-week cross-over design, this group has also demonstrated changes in neural activation during facial recognition and emotional inhibition tasks. Specifically raloxifene treatment (n = 10), relative to placebo (n = 10), was associated with significantly greater activation in the left inferior frontal gyrus and right hippocampus during angry face recognition, although there were no changes in performance accuracy (Ji et al., 2016). In a separate study, this group (Kindler et al., 2016) demonstrated that, relative to placebo, six weeks of adjunctive raloxifene treatment (120 mg/day) was associated with increased activity in the left PFC during inhibition of responses to negative words in a mixed male and female schizophrenia sample. They also reported a pharmacogenetics interaction, whereby performance accuracy and the fMRI BOLD in bilateral prefrontal cortex signal increased during inhibition of response to negative words specifically in the raloxifene group with the estrogen receptor-α gene ESR-1 rs9340799 A/A genotype. While this series of studies has demonstrated beneficial effects of 120 mg/day of raloxifene over a six week period on aspects of cognition, the results should be treated with caution given the mixed sex and mixed age sample.

The mixed findings of the effects of raloxifene on cognition in schizophrenia mirrors that found in the general population and is potentially a reflection of methodological differences and differences in participant characteristics. A recent systematic review and meta-analysis of the effects of raloxifene augmentation in schizophrenia failed to demonstrate a beneficial effect of raloxifene on cognition (de Boer et al., 2018); however, the authors concluded that raloxifene could potentially improve cognitive functioning in some cases and recommended further examination. Recent commentaries and reviews have suggested that the potential for hormone therapies, such as raloxifene, to improve cognition may be influenced by factors including treatment duration (de Boer et al., 2018), age and endogenous hormone levels (associated with changes in menopause status) (Bolton, 2016; de Boer et al., 2018).

The aim of the current study is to compare the efficacy of 120 mg/day adjunctive raloxifene for 12 weeks on cognitive performance in women with schizophrenia controlling for menopause status, stratifying women into pre-menopausal; peri-menopausal or post-menopausal status, in a pooled analysis using data from two clinical trials (where the primary aim of the clinical trials was to determine the effects of raloxifene on psychopathology).

2. Methods

2.1. Study design

The data for the present study represents pooled data from two clinical trials where the primary aim of both studies was to determine the effects of adjunctive raloxifene treatment on symptoms of psychosis on older women (Kulkarni et al., 2016) and younger, child bearing aged women with psychosis. In both clinical trials, women underwent assessment for eligibility in inpatient and outpatient settings in two treatment centres, Alfred Health and Barwon Health, in Melbourne, Australia, from January 1, 2006, to December 31, 2015. Both trials were conducted according to the CONSORT (Consolidated Standards of Reporting Trials) guidelines (Moher et al., 2010) and conducted as parallel-design, 12-week, double-blind RCT. Within each study, participants who passed screening were enrolled in the study, assigned by a computer-generated 1:1 block randomization schedule to receive 120 mg/d of raloxifene hydrochloride (administered as 1 capsule containing two 60-mg tablets [Evista; Eli Lilly]) or placebo (an identical capsule containing lactose [UNIVAR; Ajax Finechem]). Further details on study design can be found at Kulkarni et al (Kulkarni et al., 2016) (the psychopathology outcomes of the second clinical trial in pre-menopausal women are unpublished). The Alfred Human Research Ethics Committee approved both study protocols, and all participants gave written, informed consent before entering the study. Both studies are registered at ClinicalTrials.gov Identifier: NCT00361543 andNCT02354001.

2.2. Participants

For both clinical trials, women were eligible for the studies if they met DSM IV criteria for schizophrenia or schizoaffective disorder and were receiving a stable dose of antipsychotics for at least 4 weeks before enrolment. They were required to have normal findings on a mammogram within the last 12 months, and normal results of a Papanicolaou