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Adjunctive raloxifene for postmenopausal women with schizophrenia: A meta-analysis of randomized, double-blind, placebo-controlled trials

Xiao-Min Zhu [a,1], Wei Zheng [b,1], Xiao-Hong Li [c,d,1], Dong-Bin Cai [e], Xin-Hu Yang [b], Gabor S. Ungvari [f], Chee H. Ng [g], Xiao-Ping Wang [h], Jayashri Kulkarni [i,j], Jasmin Grigg [i,j], Yu-Ping Ning [b,*], Yu-Tao Xiang [k,**]

[a] Suzhou Psychiatric Hospital, The Affiliated Guangji Hospital of Soochow University, Suzhou, China
[b] The Affiliated Brain Hospital of Guangzhou Medical University (Guangzhou Huiai Hospital), Guangzhou, China
[c] The National Clinical Research Center for Mental Disorders, Beijing Anding Hospital, Capital Medical University, Beijing, China
[d] Beijing Key Laboratory of Mental Disorders, Beijing Anding Hospital, Capital Medical University, Beijing, China
[e] Clinics of Chinese Medicine, The First Clinical Medical College of Guangzhou University of Chinese Medicine, Guangzhou, China
[f] The University of Notre Dame Australia/Graylands Hospital, Perth, Australia
[g] Department of Psychiatry, University of Melbourne, Melbourne, Victoria, Australia
[h] Mental Health Institute of the Second Xiangya Hospital, Hunan Province Technology Institute of Psychiatry & Key Laboratory of Psychiatry, Mental Health of Hunan Province, Central South University, China
[i] Monash Alfred Psychiatry Research Centre, Alfred Hospital, Melbourne, Australia
[j] Monash University Central Clinical School, Monash University, Melbourne, Australia
[k] Unit of Psychiatry, Faculty of Health Sciences, University of Macau, Macao SAR, China

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ABSTRACT

Objective: Raloxifene, a selective estrogen receptor modulator, has been used in treating postmenopausal women with schizophrenia with inconsistent results. This meta-analysis of randomized, double-blind, placebo-controlled trials (RCTs) examined its efficacy and safety for postmenopausal women with schizophrenia.
Method: Standardized mean differences (SMDs) and risk ratio (RR) together with their 95% confidence intervals (CIs) were calculated using the random effects model.
Results: The meta-analysis included 5 RCTs ($n = 240$) comparing raloxifene ($n = 125$, 60 or 120 mg/day) with placebo ($n = 115$). Adjunctive raloxifene outperformed placebo with regard to the Positive and Negative Syndrome Scale (PANSS) total psychopathology [$n = 240$, SMD:-0.64 (95%CI:-0.90, −0.37), $P < 0.00001$; $I^2 = 0\%$], positive symptoms [$n = 240$, SMD:-0.49 (95%CI:-0.81, −0.16), $P = 0.003$; $I^2 = 29\%$], negative symptoms [$n = 240$, SMD:-0.43 (95%CI:-0.68, −0.17), $P = 0.001$; $I^2 = 0\%$], and general psychopathology scores [$n = 240$, SMD:-0.66 (95%CI:-0.92, −0.39), $P < 0.00001$; $I^2 = 0\%$]. Both groups had similar rates of adverse events and discontinuation ($n = 159$, RR: 1.32 (95%CI: 0.65, 2.70), $P = 0.44$, $I^2 = 0\%$).
Conclusion: Adjunctive raloxifene appears to be effective and safe in improving psychotic symptoms for postmenopausal women with schizophrenia.
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1. Introduction

Gender differences in schizophrenia have been extensively studied (Heringa et al., 2015). Compared to males, female patients usually have a later onset (Abel et al., 2010; Eranti et al., 2013; Xiang et al., 2010) peaking up to mid-forties (Jackson et al., 2013) and a less severe illness course (Thara and Kamath, 2015). Also, psychotic symptoms in women with schizophrenia are often worse when estradiol levels decline, such as in the peri-menopausal and post-menopausal phases (Gupta et al., 2012; Kulkarni et al., 2012b; Riecher-Rössler, 2012). These findings suggest that estrogen may have a potential neuro-protective role in women who are susceptible to this illness prior to menopause.

A recent review (Gogos et al., 2015) concluded that estrogen had an underlying protective effect on schizophrenia based on clinical, animal and molecular studies. A meta-analysis (Begemann et al., 2012) of randomized controlled trials (RCTs) also found that adjunctive estrogen treatment in female schizophrenia patients could improve both positive and negative symptoms. Furthermore, a large-scale study (Kulkarni et

* Corresponding author.
** Correspondence to: Y.-T. Xiang, 3/F, Building E12, Faculty of Health Sciences, University of Macau, Avenida da Universidade, Taipa, Macau SAR, China.
E-mail addresses: ningjeny@126.com (Y.-P. Ning), ytxiang@umac.mo (Y.-T. Xiang).
[1] These authors contributed equally to the paper.

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al., 2015) found estrogen is efficacious in women of child-bearing age with treatment-resistant schizophrenia.

A major disadvantage of using estrogen augmentation in schizophrenia is the potential serious side effect on breast and uterine tissue in long-term treatment (Kulkarni et al., 2012a). In contrast, estrogen-like actions agents, such as selective estrogen receptor modulators (SERM), have few or negligible negative effects since they are usually tissue-specific and do not stimulate mammary or uterine endometrial tissue (Ellis et al., 2015); therefore they could be a safer adjunctive treatment choice than estrogen. Raloxifene, as the first-generation SERM class medication, was conventionally used as a preventive treatment for postmenopausal osteoporosis (D'Amelio and Isaia, 2013). It also acts as an agonist on serotonin (Cyr et al., 2000), alpha-amino-propionic-acid (AMPA) (Cyr et al., 2001), D2 and D3 dopamine receptors (Landry et al., 2002) in the frontal cortex, striatum, and basal ganglia of rats' brain, all areas of which are impaired in schizophrenia. Therefore, it is postulated that raloxifene could be a potential adjunctive medication for schizophrenia.

Several RCTs (Kianimehr et al., 2014; Kulkarni et al., 2016; Kulkarni et al., 2010; Usall et al., 2011; Usall et al., 2016), mostly conducted in postmenopausal women, found inconsistent results of raloxifene treatment in schizophrenia. A meta-analysis (Heringa et al., 2015) included only 3 RCTs (Kianimehr et al., 2014; Kulkarni et al., 2010; Usall et al., 2011) with a small sample size ($n = 114$), which limits the power of the results. Recently two more RCTs (Kulkarni et al., 2016; Usall et al., 2016) were published, thus we conducted a comprehensive meta-analysis of RCTs to examine the therapeutic effect and safety of adjunctive raloxifene for postmenopausal women with schizophrenia.

2. Methods

2.1. Inclusion criteria

The inclusion criteria of this meta-analysis were based on the *PICOS* strategy according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009): ***P***articipants: postmenopausal women with schizophrenia established by any diagnostic criteria. All patients received antipsychotics (APs). ***I***ntervention: adjunctive raloxifene plus APs. ***C***omparison: APs plus placebo. ***O***utcomes: primary outcome measure was total psychopathology as measured by the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) or the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962). Key secondary outcomes included positive symptoms, negative symptoms, and general psychopathology subscales of the PANSS, the BPRS, the total scores of the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) and/or the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983), neurocognitive function, any cause discontinuation, and adverse

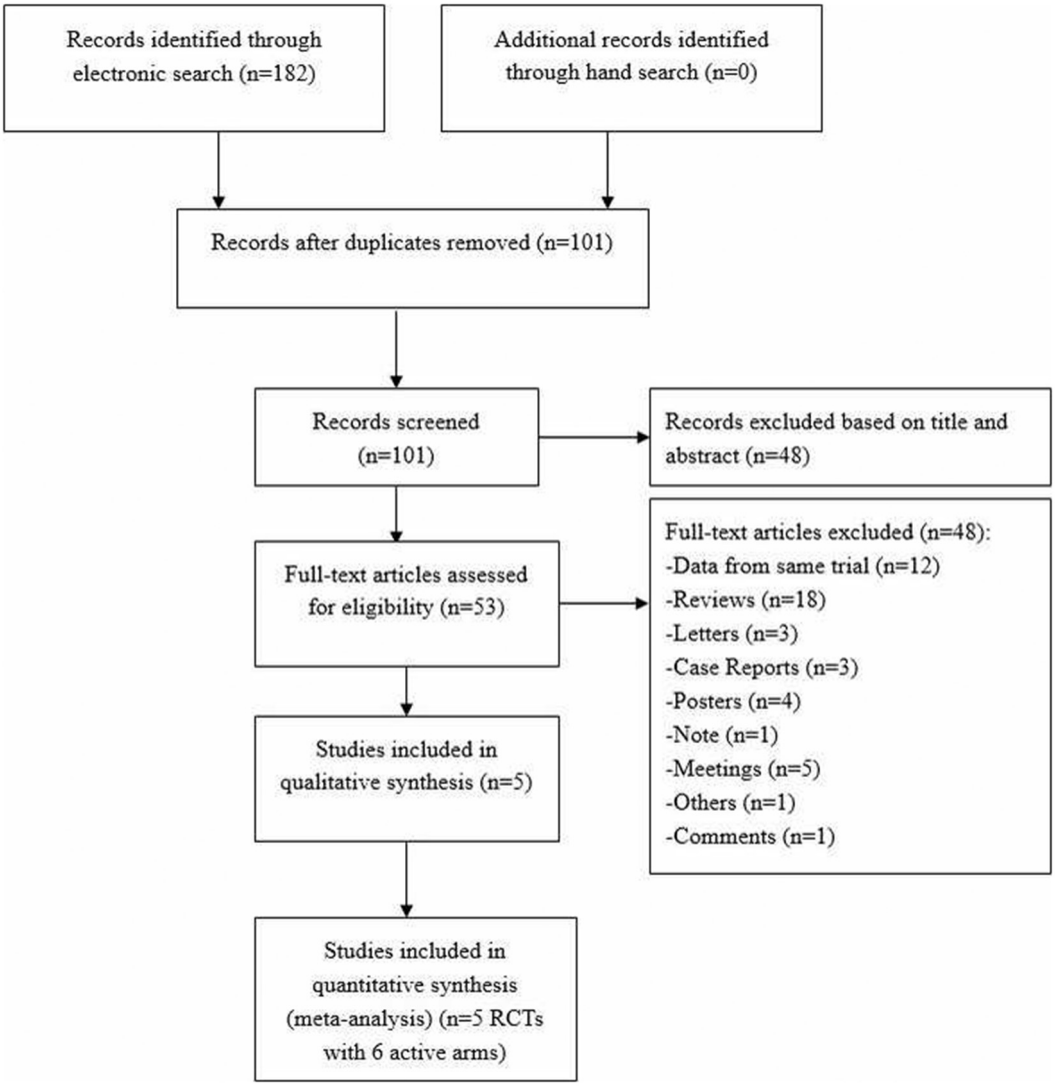

Fig. 1. PRISMA flow diagram.

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