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Efficacy and safety of extract of *Ginkgo biloba* as an adjunct therapy in chronic schizophrenia: A systematic review of randomized, double-blind, placebo-controlled studies with meta-analysis

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ABSTRACT

Our study was to review and evaluate the efficacy and safety of extract of Gb (EGb) as an adjuvant therapy to antipsychotics in chronic schizophrenia treatment. We searched Pubmed/Medline, Embase, PsycINFO, the Cochrane library, and especially the Chinese periodical databases. Finally, eight randomized, double-blind, placebo-controlled trials (RCTs) of 1033 patients were enrolled, with 571 cases in EGb group and 462 in placebo. The result showed that EGb had a significant difference in ameliorating total and negative symptoms of chronic schizophrenia as an adjuvant therapy to antipsychotics. Thus, the EGb therapy plus antipsychotics might be more efficacious. Although the studies describing adverse reactions showed no distinguishable difference between EGb and placebo group in mean total scores of Treatment Emergent Symptom Scale (TESS) or a Rating Scale for Extrapyramidal Side Effects (RSESE), the results of subscores varied in different studies. In addition, the severity of side effects of EGb might be related to its daily dosage. Therefore, the safety of EGb therapy in chronic schizophrenia treatment might need more evidence. And all of these eight trials were carried out in China; thus, the results might be restricted to the race and we need more high-quality studies of multi-center and randomized double-blind clinical trials to compare, analyze, and confirm the findings further.

1. Introduction

Schizophrenia is a serious psychiatric illness with a median incidence of 15.2/100,000 persons, and the rate ratio for males:females was 1.4:1 (McGrath et al., 2008). It is characterized by positive symptoms (such as prominent hallucinations, delusions and persistently bizarre behavior), negative symptoms (such as avolition and psychomotor poverty) (Andreasen and Olsen, 1982), and thought disorder as well as cognitive deficits (Ettinger et al., 2014). However, regrettably, its precise etiology remains largely unknown to date. On the other hand, patients with schizophrenia suffer significantly 10% lifetime risk of suicide (Schultz et al., 2007) and this will affect patients' families and will not be conducive to the economic development and social stability. Current pharmacological treatments of schizophrenia are successful at reducing psychotic symptoms but do not provide a cure and the overall outcome remains suboptimal (Carpenter and Koenig, 2008), especially in neurocognitive deficits and negative symptoms. These treatments are limited to a handful of antipsychotics and otherwise, to the patients with treatment-resistant or chronic illness course, they are more laborious. In addition, almost all the antipsychotics have neurologic or physical side effects virtually (such as weight gain, hypercholesterolemia and diabetes) (Allison et al., 1999; Lindenmayer et al., 2003), which often leads to patients' noncompliance with treatment. Thus, alternative treatment options are urgently needed.

The accumulative results of experimental and clinical studies showed that excessive free radical production or oxidative stress (e.g. an increased superoxide dismutase (SOD) level (Abdalla et al., 1986; Reddy et al., 1991), an increase in lipid peroxides (Mahadik et al., 1998; Yao et al., 2000; Kuloglu et al., 2002), etc.) might be involved in the pathogenesis of patients with schizophrenia (Lohr, 1991; Mahadik and Mukherjee, 1996; Reddy and Yao, 1996; Yao et al., 2001; Flatow et al., 2013). Recently, it was found that the long-term treatments with typical and atypical antipsychotics

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might draw the similar effects on the antioxidant enzymes and lipid peroxidation (Zhang et al., 2006), and additionally, an increase in SOD specific activity was observed mainly in the patients treated with haloperidol and quetiapine (Padurariu et al., 2010). Therefore, some researchers have suggested that the use of free radical scavengers might be a possible approach, and would provide improvement in schizophrenia (Lohr, 1991; Mahadik and Mukherjee, 1996; Mahadik and Scheffer, 1996; Reddy and Yao, 1996; Wu et al., 2013).

It has been found that *Ginkgo biloba* (Gb) has antioxidant properties as a free radical scavenger (Marcocci et al., 1994; McKenna et al., 2001) and has been used to treat patients with schizophrenia usually as an assistant therapy on the basis of the typical (Knable, 2002; Zhang et al., 2006) or atypical (Doruk et al., 2008) antipsychotic medication, especially in the chronic and/or treatment-resistant patients (Zhang et al., 2001a; Knable, 2002; Doruk et al., 2008). The primary results of these studies were usually comfortable but regrettably, they were still scattered in our opinion. Although Singh et al. (2010) and Brondino et al. (2013) pooled analysis of results of studies that extract of Gb (EGb) as an adjunctive therapy to different antipsychotics for the treatment of schizophrenia, while they partially or totally lacked of searching Chinese database, respectively. On the other hand, there were lots of studies of researching EGb in schizophrenia treatment in China in recent decades, many of them were randomized controlled trials (RCTs) and in Chinese language (Meng et al., 1996; Yi et al., 1996; Yu et al., 1996; Zhong et al., 1996; Zhang et al., 1997; Yang et al., 1998), and could not be found in non-Chinese database easily and entirely. Furthermore, the pooled results of negative symptoms reviewed in these two studies were contradictory. Therefore, we retrieved the electronic databases of Pubmed/Medline, Embase, PsycINFO, the Cochrane Library, and especially the Chinese periodical databases and conducted this meta-analysis of randomized, double-blind, placebo-controlled trials to evaluate the efficacy and safety of EGb as an adjuvant therapy in schizophrenia treatment in order to provide important and relatively entire information to expand our current knowledge and further, spawn new research.

2. Methods

2.1. Search strategy

Studies were searched by browsing the following electronic databases independently by two investigators (XCC, YH), supplemented by scanning reference lists of identified original articles and the volumes of abstracts of scientific meetings: Pubmed/Medline, Embase, PsycINFO, the Cochrane Library, and especially the Chinese periodical databases of China National Knowledge Infrastructure (CNKI, website: http://www.cnki.net/), WanFang Data Digital Periodicals (WANFANG, website: http://www.wanfangdata.com.cn/), and Chinese Scientific Journals Database (VIP, website: http://newweb.cqvip.com/) were used to search until March 23rd 2014. The search strategy was as follows: (EGb 761 OR *Gingko biloba* OR ginkgo leaf OR gingko OR ginkgo OR ginko OR bilobalid* OR ginaton OR shuxuening) and (schizophrenia OR mental illness OR psychosis OR psychotic disorder OR delusion) in title/abstract item for searching all the non-Chinese databases, and (yinxing OR yinxingye OR yinxingneizhi OR baiguoneizhi OR shuxuening OR nao'en (trade name) OR sitailong (trade name)) AND (jingshenfenlie OR jingshenzhang'ai OR jingshenbing OR jingshenjibing OR wangxiang) (in Chinese) in title/abstract item for searching Chinese databases. No language restrictions were imposed. The data were updated to Aug. 28th 2014.

2.2. Selection of studies

Potentially relevant studies were independently evaluated by two reviewers (XCC and YH). Reviewers first screened all the titles and then screened the abstracts except articles without these and next, they examined the full text and considered eligible if the published study met the following criteria: (a) was a randomized, double-blind, placebo-controlled study with complete data analysis; (b) included participants diagnosed with chronic schizophrenia; (c) applied EGb as a combined therapy in the experimental treatment of schizophrenia; (d) included no restriction on the race or nationality; and (e) the primary outcome was the Brief Psychiatric Rating Scale (BPRS), Scale for the Assessment of Negative Symptoms (SANS) and Positive and Negative Syndrome Scale (PANSS), and the secondary was the adverse reaction (e.g. Treatment Emergent Symptom Scale (TESS); a Rating Scale for Extrapyramidal Side Effects (RSESE)). However, a study with the following criteria was excluded: (a) was a literature review; and (b) was a duplicate or repeated data article (when two or more publications reported data from the same study populations, we would only keep the most detailed and/or the most recent publication).

2.3. Data exaction

Two authors (XCC, YH) reviewed all the studies independently that met our inclusion criteria, which was guided by the Cochrane Handbook for Systematic Reviews and the PRISMA statement (Moher et al., 2010; Higgins and Green, 2011). Disagreement was finally resolved by discussion with a third author (PPZ). General statement of the studies (such as the first author and year of publication), comprehensive information of patients (such as sample size, age, ethnicity, disease duration and therapy history), and information of the reported outcomes (such as BPRS, SANS, PANSS and adverse reaction) were extracted from the included trials.

2.4. Quality of the studies

Methodological quality of the trials was evaluated as suggested in the Cochrane Handbook on the following areas: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting were classified into low risk, high risk or unclear risk of bias for each item (Higgins and Green, 2011). Two authors (XCC, YH) were independently involved in quality assessment. All discrepancies were resolved by consensus with a third author (PPZ).

2.5. Statistical analysis

The verified data was analyzed by using Review Manager version 5.2 (the Nordic Cochrane Center, Copenhagen, Denmark). Standardized mean difference (*SMD*; inverse variance) and its corresponding 95% confidence intervals (95% *CI*) were computed for continuous outcome data. Statistical heterogeneity between the trials was evaluated by using the I^2 test as well as the χ^2 test (Higgins and Green, 2011). An I^2 value $>50\%$ was considered as substantial heterogeneity. A random-effect model was used for meta-analysis whether existed heterogeneity or not. Significance was assumed if the 95% *CI* did not include the value zero for *SMD*. Funnel plot was used to test potential publication bias. An asymmetric funnel plot indicated the presence of publication bias, whereas a symmetric plot suggested that there was no publication bias.