EVIDENCE-BASED INTEGRATIVE MEDICINE

Wendan Decoction (温胆汤) for Treatment of Schizophrenia: A Systematic Review of Randomized Controlled Trials*

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ABSTRACT Objective: To assess the beneficial and adverse effects of Wendan Decoction (温胆汤, WDD) for the treatment of schizophrenia. Methods: Five electronic databases were searched until May 2014, including the Chinese National Knowledge Infrastructure, the Chinese Biomedical Literature Database, the Chinese Scientist Journal Database, PubMed, and the Cochrane Central Register of Controlled Trials in the Cochrane Library. The randomized controlled trials (RCTs) testing WDD against placebo, antipsychotic drugs, or WDD combined with antipsychotic drugs against antipsychotic drugs alone were included. Study selection, data extraction, quality assessment, and data analyses were conducted according to the Cochrane standards. Results: Thirteen RCTs (involving 1,174 patients) were included and the methodological quality was evaluated as generally low. The pooled results showed that WDD combined with antipsychotic drugs were more effective in clinical comprehensive effect, Positive and Negative Syndrome Scale (PANSS) scores and Brief Psychiatric Rating Scale scores compared with antipsychotic drugs alone. However, WDD had less effectiveness compared with antipsychotics in clinical comprehensive effect; and WDD was not different from antipsychotic drugs for PANSS scores. The side effects were significantly reduced in the intervention group compared with the control group. Conclusions: WDD appears to be effective on improving symptoms in patients with schizophrenia. However, due to poor methodological quality in the majority of the included trials, the potential benefit from WDD needs to be confirmed in rigorous trials and the design and reporting of trials should follow the international standards.

KEYWORDS Wendan Decoction, schizophrenia, randomized controlled trial, systematic review

Schizophrenia is a common and severe mental illness with a chronic course. It is characterized by basic personality change, division of thinking, emotion and behavior, inharmonious of mentation and the environment. A comprehensive global survey concluded that schizophrenia affects approximately 1% of the population worldwide, which usually presents in early adulthood or late adolescence, and patients dramatically lose their labor capacity. All of these bring significant burden for both families and society. According to the World Health Organization (WHO) in 2001, the total direct costs of schizophrenia are estimated to be about 2.8% of the total healthcare budget.

Schizophrenia is commonly treated with antipsychotic drugs. In addition, other kinds of psychological interventions, such as cognitive behavior therapies, interpersonal therapy, psychotherapy and counseling, were also used. Antipsychotics therapy effect is primarily to block the D2 receptors, affects the brain cortex midbrain dopamine-pathway and the midbrain-limbic system. Nine categories, more than 40 species antipsychotic drugs have been used clinically, including phenothiazines, thioxanthone class, butyrophenones, benzamides and two phenoxy nitrogen level classes. The common side effects include somnolence, fatigue, insomnia, nausea, nervousness, dry mouth, weight gain and blurred vision.

Wendan Decoction (温胆汤, WDD) comes from an ancient book of Chinese medicine (CM), Valuable Prescriptions for Emergency (Qian Jin Fang) in 652 AD. In this book, it was said that WDD was usually used to treat some mental symptoms such as auditory hallucination, sleep disorders, and irritable. WDD...
was composed of *Rhizoma Pinelliae*, *Pericarpium Citri Reticulatae*, *Poria*, *Radix Glycyrrhizae*, *Rhizoma Coptidis*, *Fructus Aurantii Immaturus*, and *Caulis Bombusae in Taeniam*, which could invigorate the Spleen (Pi), harmonize the Stomach (Wei), regulate qi, and dispel phlegm. Biochemically, WDD may increase the ability of learning and memory through improving the content and function of central glutamate, and preventing or delaying the degeneration of hippocampal neuronal cells.\(^{(7)}\)

Studies have shown that Chinese herbal medicine has been used to treat millions of people with schizophrenia for thousands of years; it may improve some outcomes in schizophrenia.\(^{(6)}\) Now, in many CMs in the treatment of schizophrenia, the use of WDD or integrated with antipsychotic drugs is the most common. To assess the position and function of WDD in treating schizophrenia, this paper conducted system evaluation based on the randomized controlled trials (RCTs) of WDD in treating schizophrenia, in order to obtain the evidence of the effect and safety of WDD in the treatment of schizophrenia, providing evidence of evidence-based medicine for the treatment of CM.

**METHODS**

**Database and Search Strategies**

Five databases were selected for all the clinical trials about WDD or WDD combined with antipsychotic drugs for the treatment of schizophrenia, including the Chinese National Knowledge Infrastructure (CNKI), the Chinese Biomedical Literature Database (CBM), the Chinese Scientist Journal Database (VIP), PubMed, and the Cochrane Central Register of Controlled Trials in the Cochrane Library (until May 2014). The reference lists of retrieved papers were also searched. The search terms were used alone or combined. The most frequent ones were as follows: "schizophrenia," "Wendan Powder," "Wendan San", "Wendan Pills", "Chinese medicine", "combined with," "controlled clinical trial," "clinical trial," and "randomized controlled trials."

**Inclusion and Exclusion Criteria**

Inclusion criteria included all published studies or RCTs comparing modified WDD with at least one control group that used the conventional Western medicine (WM) or placebo. Participants should be diagnosed as schizophrenia by investigators. Population characteristics, gender, age, language, or disease duration of the participants were not limited in the trials. The control intervention has to be either WM or placebo. There was no limitation for treatment durations. Herbal decoction used in the original trials should be labeled by the trial authors to be "WDD" or "modified WDD". Duplicated publications of the same groups of participants were excluded.

Outcome measures included the clinical comprehensive effect (CCE), Positive and Negative Syndrome Scale (PANSS) scores, Brief Psychiatric Rating Scale (BPRS) scores, and clinical global impression (CGI) scores. The criteria "cure, significant effective, effective, or ineffective" was also included in the outcome measurement.

**Data Extraction and Quality Assessment**

Che YW and Yao KY had extracted some valuable data from some specific research independently. The extracted data included authors, year of publication, total number of cases, diagnosis standard, intervening measure, control measures, treatment course, follow-up, outcome indicator for each study. Disagreements between the investigators were resolved by discussion and reached agreements through a third party.

Cochrane Handbook for Systematic Review of Interventions, Version 5.1.0 was used by Xi YP and Chen ZJ independently as the trial criteria of methodological quality.\(^{(9)}\) The items contained random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other biases. The quality was classified to 3 types of bias including "low", "unclear" and "high". Accordingly, there were 3 levels: low risk of bias (all the items were in low risk of bias), high risk of bias (at least one item was in high risk of bias), and unclear risk of bias (at least one item was in unclear).

**Data Analysis**

The statistical package (RevMan5.2.0) provided by Cochrane Collaboration was used for data analyses. Dichotomous data were expressed as risk ratio (RR), with their 95% confidence intervals (CIs), respectively. Meta-analysis was performed if the intervention, control and outcome were the same or