**INTRODUCTION**

**Review question / Objective:** O: Hamilton Depression scale score (HAMD), clinical effective rate (according to HAMD score reduction rate or HAMA score reduction rate), adverse reactions.

**Condition being studied:** At present, the main treatment measures for depression are: drug therapy, psychotherapy and other treatments. Drugs include selective serotonin uptake inhibitors (SSRIs) and antianxiety or sedative hypnotic drugs. Psychotherapy includes interpersonal psychotherapy (IPT) and cognitive behavioral therapy (CBT). Other treatments such as exercise therapy, repetitive transcranial magnetic stimulation (rTMS) and phototherapy, etc., but there is no clear conclusion on the effect of different drug regimens. Compared with western medicine, traditional Chinese medicine has the advantages of multi-component, multi-target intervention, small adverse effect, comprehensive conditioning and long-lasting effect.

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 09 December 2020 and was last updated on 09 December 2020 (registration number INPLASY2020120052).

**The efficacy and safety of Chinese herbal medicine for depression: a protocol for systematic review and network meta-analysis**

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METHODS

Participant or population: Patients with depression identified by systematic clinical interviews or validated depression scoring system.

Intervention: The treatment group was treated with various prescriptions alone, including Guipi decoction (pill), Chaihu Shugan San (pill), Xiaoyao powder (pill), Huanglian Ejiao decoction, Sini decoction (San), Ganmai Dazao decoction, Shugan Jieyu capsule, Chaihu Shugan San (pill), Bupleuron Oyster soup and so on.

Comparator: C: the control group was treated with blank control group or western medicine alone. Western drugs included antidepressants: serotonin reuptake inhibitors SSRIs (fluoxetine, citalopram, paroxetine and sertraline), norepinephrine reuptake inhibitors (venlafaxine, mirtazapine, duloxetine), and antianxiety drugs: benzodiazepines (diazepam, lorazepam, clonazepam, alprazolam, estazolam). Non-benzodiazepine (buspirone, Deanxin), etc.

Study designs to be included: Randomized controlled trials (RCTs).

Eligibility criteria: Exclusion criteria: 1. repeated published literature; 2. literatures used in combination of two or more treatments; 3. comments and letters; 4. fruitless studies without full-text contacts; 5. studies with unclear efficacy evaluation; 6. in order to ensure literature quality, literature from journals that are not sourced from Peking University's "Overview of Chinese Core Journals" are not included in this study; 7 non-Chinese and English literatures.

Information sources: Pubmed, EMBase, The Cochrane Library, CBM, CNKI, and Wan Fang Data databases were searched by computer to collect the RCT, search time limit of traditional Chinese medicine for the treatment of depression from the establishment of the database to December 9, 2020. In addition, the references included in the literature were retroactively included to supplement the relevant literature.

Main outcome(s): Hamilton Depression scale score (HAMD), clinical effective rate (according to HAMD score reduction rate or HAMA score reduction rate), adverse reactions.

Quality assessment / Risk of bias analysis: According to the Cochrane Handbook, two independent reviewers (CW and YJ) will evaluate the risk of bias in the study, including the generation of random sequences, the concealment of assignments, the blindness of participants, personnel and outcome evaluators, incomplete outcome data, selective reports, and other sources of bias. We divide each area into three levels: high risk of bias, unclear or low. Differences of opinion among reviewers will be resolved through discussion or negotiation with the third reviewer (CY).

Strategy of data synthesis: We will conduct a traditional meta-analysis for direct comparison. The influence of continuous variable data will be calculated by standardized mean difference (SMD), while the impact of binary variable data will be calculated by risk ratio (RR). The 95% confidence interval (CI) of SMD and RR will also be calculated (95%CI). For indirect comparisons, reticular meta analysis is needed to mix the results to improve statistical efficiency. The network meta-analysis will be carried out using the "netmeta" package of the R software. The results of direct and indirect comparisons
will be presented in the form of a network diagram.

**Subgroup analysis:** We will conduct a subgroup analysis to search for potential inconsistencies and heterogeneity, such as depressive level, gender, ethnicity, etc.

**Sensibility analysis:** We will conduct a sensitivity analysis to verify the robustness of the results. Studies with uncertain or high-risk bias risks will be excluded to check whether the results will change.

**Language:** The written language is limited in English or Chinese.

**Country(ies) involved:** China.

**Keywords:** network meta-analysis, Chinese herbal medicine, depression, protocol.

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