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None declared.

Clinical Efficacy and Safety of various CPMs Combination with western medicine for depression in adults : A Multiple-Treatments Meta-Analysis

Yi, L[1]; Jing, C[2]; Li, S[3]; cui, W[4]; Li, JH[5]; Peng, LB[6]; Peng CY[7].

Review question / Objective: **CPMs in combination with WM for the treatment of adults (≥18 years of age, both sexes, regardless of race, region, or nationality) with a primary diagnosis of depression according to standard operational diagnostic criteria are reported (CCMD-3, DSM -IV, DSM-III-R, DSM-5, or ICD-10).The subjects who were assigned to the control groups were administered solely with WM regimens, including Citalopram, Fluoxetine, Sertraline, Paroxetine, Trazodone Hydrochloride, Doxepin, Flupentixol and Melitracen, Duloxetine Hydrochloride Enteric, mirtazapine, Venlafaxine, Mirtazapine. Patients in the treatment group received CPMs together with WM therapy. The primary outcome was total effective rate (which was calculated using the combination of cure, markedly effective, and effective outcomes), Hamilton Depression Scale (HAMD), Treatment Emergency Symptom Scale (TESS). The secondary outcome were brain-derived neurotrophin factor (BDNF), 5-hydroxytryptamine (5-HT) and norepinephrine (NE). All analyses were documented within 8 weeks of the study, whenever possible. If 8-week data was not available, we used the data that was collected between 4 and 12 weeks, with priority given to the time point closest to 8 weeks. In situations where there were multiple reports, we prioritized the first published report.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 10 June 2023 and was last updated on 10 June 2023 (registration number INPLASY202360032).

INTRODUCTION

Review question / Objective: **Randomized controlled trials of the efficacy and safety of 14 CPMs in combination with WM for the treatment of adults (≥18 years of age, both sexes, regardless of race, region, or nationality) with a primary diagnosis of depression according to standard operational diagnostic criteria are reported**

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Condition being studied: Depression, a psychiatric condition colloquially referred to as depressive disorder, manifests as a persistent state of low mood (Wilkinson et al., 2018; Lee et al.,2020; Buckman et al.,2021). Globally, about 5% of adults suffer from depression; By 2030, depression will become the disease with the highest disability rate in the world, bringing huge mental and economic burdens to society and families(Buckman et al., 2022; Brettschneider et al., 2015; Conejo-Cerón et al., 2021; Breslow et al.,2019).

In most clinical settings, the treatment of depression involves the use of either oral antidepressants or psychotherapy as the primary forms of intervention (Jha et al., 2023;Vas et al.,2023). Psychotherapy has been strongly recommended as the Primary treatment method for adult depression, among which cognitive behavioral therapy has been proven to have comparable effects with drug intervention and may have a more lasting effect (Richards et al., 2016; Cuijpers et al., 2020; Bartova et al., 2022; López-López et al.,2019). However, due to insufficient resources, clinical use is greatly limited (Bartova et al., 2022; Munder et al.,2022). At present, drug therapy is still the most commonly used treatment method for depression (Jha et al., 2023;Vas et al.,2023).Commonly prescribed antidepressants comprise selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), and tricyclic antidepressants (TCAs) , can effectively alleviate depressive symptoms, but with their long medication cycle and obvious side effects, patients have poor drug compliance and poor treatment effect, which greatly affects disease prognosis and clinical application (Jha et al., 2023;Vas et al.,2023; Borbély et al., 2022; Burch et al.,2018; Khawam et al.,2006; Moncrieff et al., 2019). Chinese patent medicines (CPMs) are a form of commercialized traditional Chinese medicine preparations that have been authorized by the national drug regulatory authority, which is made of Chinese medicinal materials as raw materials, under the guidance of the theory of traditional Chinese medicine, in order to prevent and treat diseases, according to the prescribed prescription and preparation process (Ai et al., 2023; Lin et al., 2022; Chen et al., 2023). Chinese patent medicines (CPMs) are essential in the realm of complementary and alternative medicine as adjuvant therapy for adults experiencing depression, these medicines are highly sought after and widely utilized by clinicians across Asia, particularly in China, due to their practical applications and effectiveness (Li et al., 2023; Zhuang et al., 2023; Dai et al., 2022; Fathinezhad et al., 2019; Yu et al.,2022). Numerous studies have noted the effectiveness and security of different kinds of CPMs combined with western medicine (WM) for the purpose of treating depression among adults (Wang et al.,2019;Yan et al., 2020; Wang et al., 2018; Li et al.,2023; Liu et al., 2020). However, the optimal strategy for treating depression with CPMs combined with WM is currently unclear, which may pose challenges for healthcare professionals in selecting treatment options in clinical settings. Multi

treatment meta-analysis (MTMA) is a statistical method that combines information obtained from both direct and indirect sources for comparison and ranking among various treatment options (Riley et al., 2017; Salanti et al., 2011). Therefore, in this study, we aimed to do a MTMA to systematically evaluate the efficacy and Safety of Various CPMs Combined with WM for adult depression disorder. The purpose of this study is to impart valuable knowledge and to provide clinical evidence for optimal drug selection and reliable evidence-based medicine.

METHODS

Search strategy: To ensure a comprehensive and thorough assessment of MTMA, we conducted searches in reputable databases, such as Embase, CINAHL, Chinese Biomedical Literature, China National Knowledge Infrastructure (CNKI), Science and Technology Journal Database (VIP), Wanfang, Cochrane Library, and PubMed. The purpose of this exhaustive search was to collect extensive data for the study and reliable information for the research. Our search included articles from the inception of these databases up to February 2023, and we did not impose any language restrictions. To ensure the comprehensiveness and precision of our investigation, we conducted a manual review of supporting literature, ongoing randomized controlled trials, and contacted pharmaceutical companies that produce and market proprietary Chinese medications for depression. We also emailed study authors to request additional data on unpublished research, however, we regretfully acknowledge that most of these authors did not respond to our inquiries. The search strategy was divided into three parts: CPMs, depression, and RCTs.

Participant or population: Randomized controlled trials of the efficacy and safety of 14 CPMs in combination with WM for the treatment of adults (≥18 years of age, both sexes, regardless of race, region, or nationality) with a primary diagnosis of depression according to standard operational diagnostic criteria are reported (CCMD-3, DSM -IV, DSM-III-R, DSM-5, or ICD-10).

Intervention: The subjects who were assigned to the control groups were administered solely with WM regimens, including Citalopram, Fluoxetine, Sertraline, Paroxetine, Trazodone Hydrochloride, Doxepin, Flupentixol and Melitracen, Duloxetine Hydrochloride Enteric,mirtazapine, Venlafaxine, Mirtazapine. Patients in the treatment group received CPMs together with WM therapy.

Comparator: WM regimens, including Citalopram, Fluoxetine, Sertraline, Paroxetine, Trazodone Hydrochloride, Doxepin, Flupentixol and Melitracen, Duloxetine Hydrochloride Enteric, mirtazapine, Venlafaxine, Mirtazapine.

Study designs to be included: Randomized controlled trials of the efficacy and safety of 14 CPMs in combination with WM for the treatment of adults (≥18 years of age, both sexes, regardless of race, region, or nationality) with a primary diagnosis of depression according to standard operational diagnostic criteria are reported (CCMD-3, DSM -IV, DSM-III-R, DSM-5, or ICD-10).

Eligibility criteria: Randomized controlled trials of the efficacy and safety of 14 CPMs in combination with WM for the treatment of adults (≥18 years of age, both sexes, regardless of race, region, or nationality) with a primary diagnosis of depression according to standard operational diagnostic criteria are reported (CCMD-3, DSM -IV, DSM-III-R, DSM-5, or ICD-10), The subjects who were assigned to the control groups were administered solely with WM regimens, including Citalopram, Fluoxetine, Sertraline, Paroxetine, Trazodone Hydrochloride, Doxepin, Flupentixol and Melitracen, Duloxetine Hydrochloride Enteric,mirtazapine, Venlafaxine, Mirtazapine. Patients in the treatment group received CPMs together with WM therapy. All CPMs treatments for

depression approved by regulatory agencies in China.

Information sources: To ensure a comprehensive and thorough assessment of MTMA, we conducted searches in reputable databases, such as Embase, CINAHL, Chinese Biomedical Literature, China National Knowledge Infrastructure (CNKI), Science and Technology Journal Database (VIP), Wanfang, Cochrane Library, and PubMed. The purpose of this exhaustive search was to collect extensive data for the study and reliable information for the research. Our search included articles from the inception of these databases up to February 2023, and we did not impose any language restrictions. To ensure the comprehensiveness and precision of our investigation, we conducted a manual review of supporting literature, ongoing randomized controlled trials, and contacted pharmaceutical companies that produce and market proprietary Chinese medications for depression. We also emailed study authors to request additional data on unpublished research, however, we regretfully acknowledge that most of these authors did not respond to our inquiries. The search strategy was divided into three parts: CPMs, depression, and RCTs.

Main outcome(s): The primary outcome was total effective rate (which was calculated using the combination of cure, markedly effective, and effective outcomes), Hamilton Depression Scale (HAMD), Treatment Emergency Symptom Scale (TESS). The secondary outcome were brain-derived neurotrophin factor (BDNF), 5-hydroxytryptamine (5-HT) and norepinephrine (NE). All analyses were documented within 8 weeks of the study, whenever possible. If 8-week data was not available, we used the data that was collected between 4 and 12 weeks, with priority given to the time point closest to 8 weeks. In situations where there were multiple reports, we prioritized the first published report.

Quality assessment / Risk of bias analysis: Two researchers (Jianhe Li and Wei Cui) independently assessed the risk of bias in included RCTs according to the risk of bias tool provided in the Cochrane Handbook for Systematic Reviews of Interventions. The following were assessed: 1) selection bias associated with random sequence generation; 2) selection bias associated with allocation concealment; 3) performance bias: blinding of participants and personnel; 4) detection bias: blinding of outcome assessments; 5) attrition bias: completeness of outcome data; 6) reporting bias: selective reporting; and 7) other sources of bias. Each factor was categorized as “low risk”, “high risk”, or “unclear”. All discrepancies that emerged from this study were discussed by a review panel.

Strategy of data synthesis: EndNote was employed to manage the collected trials with a view to organizing and streamlining the gathered data. In cases where published research was found to be a duplicate, we selected the report that contained the most comprehensive and richest data. To thoroughly review the results obtained in this study, we used a network meta-analysis.odds ratio (OR) was used for dichotomous results and the standardized mean difference (SMD, Cohen's d) was used for continuous results.A multinomial likelihood was used for binary results in a MTMA, while a normal likelihood was used for continuous data. Subsequently, a random effects MTMA model was used to thoroughly determine the effect size. R4.3.5 software was utilized for all MTMAs for statistical data processing and investigation, and Bayesian inference was implemented using a Markov chain Monte Carlo model. To arrange the results, both R4.3.5 and Stata MP17 software were used to draw cumulative probability sorting curves (SUCRA) and mean rankings (Watt et al.,2019; Schwingshackl et al.,2019). In addition, clustering analysis was adopted to synthesize and compare interventions with two outcome indicators, thereby allowing for better selection of results. To assess potential publication bias, we employed a comparison-adjusted funnel plot. Additionally, the risk of bias of these

studies was evaluated in line with the Cochrane Intervention System Review Manual.

Subgroup analysis: No.

Sensitivity analysis: No.

Country(ies) involved: Chine.

Keywords: a multiple-treatments meta-analysis,western medicine , Chinese patent medicines, Adult depression disorder , Combined therapy, Traditional Chinese medicine.

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