Comparative efficacy and safety of traditional Chinese patent medicine for anxiety disorders in children or adolescence

A protocol for systematic review and network meta-analysis

Zhenyuan Jiang, MD\textsuperscript{a}, Jiahao Wang, MD\textsuperscript{a}, Xiaowen Yu, PhD\textsuperscript{b}, Chuancheng Li, MD\textsuperscript{a}, Yuze Shao, MD\textsuperscript{a}, Zhonglin Wang, PhD\textsuperscript{b,}\textsuperscript{c}

Abstract

Background: Anxiety is the most common mental illness among adolescents and children, and its incidence is increasing year by year, which has a serious adverse effect on the academic and growth of adolescents and children. Conventional treatment methods such as oral administration of western medicine and psycho-behavioral therapy have obvious limitations. Chinese patent medicines play an irreplaceable role in the treatment of this disease. At present, there is no comparison of the safety and effectiveness of various Chinese patent medicines curing anxiety in adolescents. So we take advantage of the method of network meta-analysis to systematically compare the efficacy of various Chinese patent medicines curing this disease.

Methods: We will systematically and comprehensively search the following databases, including PubMed, Web of Science, EMBASE, The Cochrane Library, China BioMedical Literature (CBM), China National Knowledge Infrastructure (CNKI), Chinese Scientific Journals Database (VIP), and Wanfang database. We will include all RCT trials that meet the inclusion criteria, starting from the establishment of the database until August 2020. Two researchers will independently screen the literature based on inclusion criteria. While extracting data, we also assess the risk of bias in the included studies. All the data and evidence obtained will be evaluated by the method of Bayesian network meta-analysis. STATA and WinBUGS software will be used.

Results: This study will evaluate the effectiveness and safety of various TCPMs for anxiety disorders in children or adolescence.

Conclusion: The results of this study will provide valuable references for the clinical application of Traditional Chinese patent medicines, and assist clinicians in formulating more reasonable diagnosis and treatment strategies.

Ethics and dissemination: This study does not require ethical approval.

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Abbreviations: CBM = Chinese biomedical literature database, CI = confidence interval, CNKI = Chinese national knowledge infrastructure, MD = mean difference, NMA = network meta-analysis, OR = odds ratio, RCT = randomized controlled trial, SE = standard error, SMD = standardized mean difference, TCPM = traditional Chinese patent medicine.

Keywords: anxiety disorders in childhood or adolescence, network meta-analysis, protocol, traditional Chinese patent medicine (TCPM)

1. Introduction

Anxiety is the appearance of inner fear and restlessness for no obvious reason, often accompanied by autonomic dysfunction, and the clinical symptoms are persistent mental stress or episodic panic.\textsuperscript{[1-4]} Adolescents and children are in a special period of physical and mental development. Due to their young age and poor mental endurance, they are vulnerable to adverse life events.\textsuperscript{[5]} Therefore, Anxiety symptoms are very common especially in adolescents and children. Relevant research shows that about 5\% to 20\% of children and adolescents worldwide have anxiety disorders.\textsuperscript{[6]} A Norwegian survey on the stability, changes, and incidence of anxiety symptom clusters among 13 to 16-year-olds found that the incidence of high-level anxiety was 8.2\%.[7] Children suffering from anxiety disorders are vulnerable to other mental problems and related physical symptoms in the later growth process than other children.\textsuperscript{[8-11]}

The cause of this disease is very complex and closely related to genetic factors\textsuperscript{[12,13]} researches have confirmed that if 1 parent suffering from anxiety disorder, the risk of their children suffering...
Many clinical trials and systematic reviews have confirmed the clinical efficacy of TCPM in the treatment of anxiety. Traditional Chinese patent medicines which are wildly used for treating anxiety include Xiaoyao Pills, Wuling Capsules, Shugan Jieyu Capsules, and Xuefu Zhiyu Oral Liquid. Basic research has shown that Xiaoyao Pill can reduce the expression of NSF and PICK1 protein by increasing GluR2/3 in the brain, inhibiting neuroinflammation induced by lipopolysaccharide, and alleviating anxiety symptoms. Xuefu Zhiyu Oral Liquid can improve the mental symptoms of model rats by increasing the content of monoamine neurotransmitter 5-HT and BDNF. Network meta-analysis can compare the advantages and disadvantages of 3 or more treatment methods, making full use of clinical data than traditional meta-analysis. Therefore, we use it to compare the effectiveness and safety of each traditional Chinese patent medicine in treating anxiety disorders in adolescents and children.

2. Methods

We will use Bayesian NMA. Then we compliant PRISMA-P guidelines to conduct this study.

2.1. Study registration

This NMA has been registered on the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY) and the registration number is INPLASY202080048 (URL = https://inplasy.com/inplasy-2020-8-0048/).

2.2. Inclusion criteria

2.2.1. Type of study. We will include all RCTs using TCPM for the treatment of anxiety in adolescents and children, as well as related clinical trials, such as I/II early stage, stage III trials, prospective and retrospective observational studies. The language is limited to Chinese and English.

2.2.2. Participants. Adolescents and children diagnosed with anxiety disorders will be included. The diagnosis of anxiety will follow the Hamilton Anxiety Scale (HAMA) and Anxiety Self-Rating Scale (SAS).

2.2.3. Interventions. The experimental group was treated with traditional Chinese patent medicines combined with conventional Western medicine. Chinese patent medicines included Xiaoyao Pills, Wuling Capsules, Shugan Jieyu Capsules, and Xuefu Zhiyu Oral Liquid. The control group received Western medicine treatment, including oral medication or mental behavior therapy. RCTs that use 2 or more proprietary Chinese medicines or combined acupuncture, moxibustion, and other traditional Chinese medicine methods are excluded.

2.2.4. Outcomes. According to the Hamilton Anxiety Scale, a 5-point scale of 0– is adopted. The main indicators are: total clinical effective rate, improvement of anxiety mood, insomnia remission rate, improvement of cognitive function; secondary indicators including relapse rate, plant Nervous system symptoms and the rate of improvement in behavior when talking to people. The included literature must cover 1 or more main indicators.

2.3. Database and search strategy

We will search the Cochrane Library, PubMed, Embase, Clinical Trials, CNKI Database, VIP, Wanfang Database, and China
Biomedical Database. The search strategy will be constructed in the form of Medical Subject Headings (MeSH) combine with keywords, including “Traditional Chinese patent medicine, TCPM, Anxiety disorders in children or adolescence, Adolescent generalized anxiety, Panic Disorder in childhood or adolescence, social phobia in children or adolescence, Randomized controlled,” etc. The search time limit is from the establishment of each database to August 2020. (The retrieval scheme of the PubMed database is listed in Table 1.)

### 2.4. Study selection and data extraction

The literature will be screened by 2 independent researchers according to the inclusion and exclusion criteria, and cross-checked them. In case of disagreement, they will discuss and negotiate with the third investigator. The extracted data include: (1) the fundamental information of the included study (research title, first author, sample size, age, year, course of disease, treatment period); (2) baseline characteristics and intervention measures of the research object; (3) key elements of bias risk evaluation; (4) outcome indicators.

### 2.5. Risk of bias assessment

The quality of each trial will be assessed by 2 researchers independently based on the Cochrane Risk of Bias Risk Assessment Tool recommended by Cochrane Handbook version 5.1.0. Use the decision words “high risk”, “low risk”, and “unclear risk” to evaluate the quality of the input article in 7 aspects, including: whether the random sequence is sufficient; whether there is hidden allocation; whether blinding is used; whether the result data is complete; whether there is selective reporting; whether there is publication bias; others.

### 2.6. Statistical analysis

We will use Stata 14.0 software and Markov chain-Monte Carlo (MCMC) method to conduct Bayesian meta-analysis. Three Markov chains will be used for simulation, and the number of iterations will be set at 50,000 (the first 20,000 are used for annealing to eliminate the effect of the initial value, and the last 30,000 are used for sampling).

The reticular diagram will be drawn by Stata 15.0 software to show the direct and indirect comparison between different interventions. The relative odds ratio (RoR) and its 95% confidence interval (CI) are calculated to evaluate the consistency of each closed loop. The lower limit of 95% CI is equal to 1, indicating good consistency. If RoR is close to 1, direct evidence and indirect evidence are consistent, and the fixed effect model is adopted for analysis. Otherwise, the closed-loop is considered to have obvious inconsistencies, and the random effect model is used for analysis. Dichotomous data will be represented by odds ratio (OR) and 95% CI, and P < .05 was considered statistically significant. WinBUGS 1.4.3 will be used to rank the efficacy of different interventions and the area under the curve will be recorded (the area under the curve will be expressed as a percentage, the larger the value, the better the effect).

### 2.7. Assessment of heterogeneity

If (P > .10 and I² < 50%), we will use the fixed-effect model. Otherwise, we will further explore the source of heterogeneity, and if the source cannot be found, the random-effects model will be used for analysis.

### 2.8. Subgroup analysis and sensitivity analysis

Subgroup analysis will be considered if sufficient data is available. Sensitivity analysis will be conducted with symptom improvement rate to evaluate clinical similarity and methodology of included studies to determine the reliability of the results of this study.

### 2.9. Evaluation of publication bias

Total effective rate, anxiety after treatment, degree of nervousness after treatment, and sleep status after treatment will be taken as indicators, and the inverted funnel plot will be drawn with
each effect amount as the horizontal coordinate and the standard error of effect amount as the vertical coordinate. If the inverted funnel plot is symmetric, it suggests that there is a small sample effect or a slight possibility of publication bias in this study.

2.10. Grading the quality of evidence
We will use GRADE to evaluate the quality of evidence from the following 5 aspects: risk of bias, indirectness, inconsistency, imprecision, and publication bias.

3. Discussion
Teenagers are not fully mature mentally and are vulnerable to adverse life events. Mental health problems are common among children and adolescents, and anxiety disorder is the most common mental illness. Failure to receive timely and effective treatment will result in children’s academic frustration, substance abuse, and poor social function, which will seriously affect personal development. Whether it is cognitive-behavioral-therapy (CBT) or oral psychiatric drugs, there are obvious limitations. Traditional Chinese patent medicine are under the strict supervision of relevant national departments, according to traditional Chinese medicine theories, the prescriptions are selected with rigorous compatibility, and have been effective after long-term clinical application. The Chinese medicine decoction pieces are processed through scientific preparation techniques to produce pills, tablets, capsules, granules, and other different dosage forms are convenient to take, widely used, and have good therapeutic effects. At present, there is no comparison of the advantages and disadvantages of various Chinese patent medicines for the treatment of anxiety in adolescents, so it is necessary to use the method of network meta-analysis to study this topic. In this study, we will introduce the network meta-analysis on the basis of the existing RCT to evaluate the advantages and disadvantages of various Chinese patent medicines, so as to provide clinicians with more complete diagnosis and treatment plans.

Author contributions
Conceptualization: Zhenyuan Jiang, Zhonglin Wang.
Data curation: Zhenyuan Jiang, Xiaowen Yu.
Formal analysis: Zhenyuan Jiang, Yuzhe Shao, Zhonglin Wang.
Funding acquisition: Zhonglin Wang.
Investigation: Zhenyuan Jiang.
Methodology: Zhenyuan Jiang, Jiahao Wang, Chuancheng Li.
Project administration: Zhenyuan Jiang.
Resources: Zhenyuan Jiang.
Software: Zhenyuan Jiang, Jiahao Wang, Xiaowen Yu.
Validation: Zhenyuan Jiang.
Visualization: Zhenyuan Jiang.
Writing – original draft: Zhenyuan Jiang, Jiahao Wang.
Writing – review & editing: Zhenyuan Jiang, Zhonglin Wang.

References
[1] Bokema WA, Wetzer G, Gehrels JB, et al. Aligning the many definitions of treatment resistance in anxiety disorders: a systematic review. Depress Anxiety 2019;36:801–12.
[2] Hallion LS, Ruscio AM. Should uncontrollable worry be removed from the definition of GAD? A test of incremental validity. J Abnorm Psychol 2015;122:369–75.
[3] Kretler S. The meaning profiles of anxiety and depression: similarities and differences in two age groups. Cogn Emot 2018;32:1499–513.
[4] Perusini JN, Fanselow MS. Neurobehavioral perspectives on the distinction between fear and anxiety. Learning Memory (Cold Spring Harbor, NY) 2015;22:417–25.
[5] Turner S, Harvey C, Hayes L, et al. Childhood adversity and clinical and neurocognitive outcomes in psychosis. Epidemiol Psychiatric Sci 2019;29:e78.
[6] Wehry AM, Beesdo-Baum K, Henneley MM, et al. Assessment and treatment of anxiety disorders in children and adolescents. Curr Psychiatry Rep 2015;17:52.
[7] Leikanger E, Larsson B. One-year stability, change and incidence in anxiety symptoms among early adolescents in the general population. Eur Child Adolesc Psychiatry 2012;21:493–501.
[8] Bushnell GA, Gaynes BN, Compton SN, et al. Incidence of mental health hospitalizations, treated self-harm, and emergency room visits following new anxiety disorder diagnoses in privately insured U.S. children. Depress Anxiety 2019;36:179–89.
[9] Essau CA, Lewinsohn PM, Lim JX, et al. Incidence, recurrence and comorbidity of anxiety disorders in four major developmental stages. J Affect Disord 2018;228:248–53.
[10] Goodwin RD, Ferguson DM, Horwood LJ. Panic attacks and psychotica. Am J Psychiatry 2004;161:88–92.
[11] Nelson S, Simons LE, Logan D. The incidence of Adverse Childhood Experiences (ACEs) and their association with pain-related and psychosocial impairment in youth with chronic pain. Clin J Pain 2018;34:402–8.
[12] Hettema JM, Neale MC, Kendler KS. A review and meta-analysis of the genetic epidemiology of anxiety disorders. Am J Psychiatry 2001;158: 1568–78.
[13] Lieb R, Wittchen HU, Hofler M, et al. Parental psychopathology, parenting styles, and the risk of social phobia in offspring: a prospective-longitudinal community study. Arch Gen Psychiatry 2000;57:859–66.
[14] Roberts JE, Tonnesen BL, McCary LM, et al. Trajectory and predictors of depression and anxiety disorders in mothers with the FMR1 premutation. Biol Psychiatry 2016;79:850–7.
[15] Chorot P, Valiente RM, Magaz AM, et al. Perceived parental child rearing and attachment as predictors of anxiety and depressive disorder symptoms in children: the mediational role of attachment. Psychiatry Res 2015;235:287–95.
[16] Bright M, Parker S, French P, et al. Metacognitive beliefs as psychological predictors of social functioning: an investigation with young people at risk of psychosis. Psychiatry Res 2018;262:320–6.
[17] Wainberg ML, Scorza P, Shulz JM, et al. Challenges and opportunities in global mental health: a research-to-practice perspective. Curr Psychiatry Rep 2017;19:28.
[18] Kumar JR, Rajkumar R, Lee LC, et al. Nucleus incertus contributes to an anxiogenic effect of buspironate in rats: involvement of 5-HT1A receptors. Neuropharmacology 2016;110(Pt A):1–4.
[19] Albert PR, Vahid-Ansari F, Luckhart C. Serotonin-prefrontal cortical circuitry in anxiety and depression phenotypes: pivotal role of pre- and post-synaptic 5-HT1A receptor expression. Front Behav Neurosci 2014;8:199.
[20] Gresack JE, Rischbourgh VB. Corticotropin-releasing factor and noradrenergic signalling exert reciprocal control over startle reactivity. Int J Neuropsychopharmacol 2011;14:1179–94.
[21] Sun H, Jia N, Guan L, et al. Involvement of NRI, NR2A different expression in brain regions in anxiety-like behavior of prenatally stressed offspring. Behav. Brain Res 2013;257:1–7.
[22] Ge JF, Xu YY, Qin G, et al. Resveratrol Ameliorates the Anxiety- and Depression-Like Behavior of Subclinical Hypothyroidism Rat: Possible Role of p38 MAPK and Activation of Fyn and NMDA Receptors. Front Pharmacol 2017;8:360.
[23] Roeb RG, Kronenberg S, Carmel M, et al. Additive effects of 5-HTTLPR (serotonin transporter) and tryptophan hydroxylase 2 G-703T gene polymorphisms on the clinical response to citalopram among children and adolescents with depression and anxiety disorders. J Child Adolesc Psychopharmacol 2013;23:117–22.
[24] Kronenberg S, Aptar A, Brent D, et al. Serotonin transporter polymorphism (5-HTTLPR) and citalopram effectiveness and side effects in children with depression and/ or anxiety disorders. J Child Adolesc Psychopharmacol 2007;17:741–50.
[25] Brent D, Meliem N, Ferrell R, et al. Association of FMR1 polymorphisms with suicidal events in the Treatment of Resistant Depression in Adolescents (TORDIA) study. Am J Psychiatry 2010; 167:190–7.
[26] Silverman WK, Pina AA, Viswesvaran C. Evidence-based psychosocial treatments for phobic and anxiety disorders in children and adolescents. J Clin Child Adolesc Psychol 37 2008;105–30.

[27] Kendall PC, Settipani CA, Cummings CM. No need to worry: the promising future of child anxiety research. J Clin Child Adolesc Psychol 2012;41:103–15.

[28] Xiong TW, Wu Q, Liu J, et al. [Research progress of effect of anxiolytic traditional Chinese medicines and formulas on neurotransmitters]. Zhongguo Zhong yao za zhi = Zhongguo zhongyao zazhi = China journal of Chinese materia medica 2020;45:14–9.

[29] Shi B, Luo J, Fang Y, et al. Xiaoyao pills prevent lipopolysaccharide-induced depression by inhibiting inflammation and protecting nerves. Front Pharmacol 2019;10:1324.

[30] Lu LL, Shen XH, Chen JX. [Xuefu zhuyu oral liquid intervened stress-stimulated depression model rats]. Zhongguo Zhong xi yi jie he za zhi Zhongxiyi jiehe zazhi 2013;33:638–40.

[31] Puhan MA, Schünemann HJ, Murad MH, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analyses. BMJ 2014;349:g630.