Efficacy and Safety of Jiu-Wei-Xi-Feng Granules for Treating Tic Disorders in Children: Study Protocol for A Randomized Controlled Equivalence Trial

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1 **Title page**

2 Efficacy and safety of Jiu-Wei-Xi-Feng granules for treating Tic Disorders in children: study
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7 They conceived the study, design the trial and drafted the manuscript. SYH and QHC were
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Abstract

Background: Tic disorders (TD) is a neuropsychiatric disease with twitch as the main manifestation in childhood. Jiu-Wei-Xi-Feng granules has been marketed in China for treating children with TD. As *Long Gu*(*Os Draconis*) in the composition of this Chinese patent medicine is a rare and expensive medicinal material protected by the Chinese government, therefore, we consider replacing it with *Mu Li*(*Concha Ostreae*) that has the same effect and is cheaper. This study is designed to evaluate the clinical equivalence between Jiu-Wei-Xi-Feng granules (*Os Draconis* replaced by *Concha Ostreae*) (JWXFD) and Jiu-Wei-Xi-Feng granules (original formula) (JWXFO) in children with TD (consumption of renal yin and liver wind stirring up internally syndrome).

Methods/design: This is a multicenter, randomized, double-blind, equivalence trial comparing the efficacy and safety of JWXFD and JWXFO in treating Children with tic disorders (consumption of renal yin and liver wind stirring up internally syndrome). A total of 288 patients will be recruited and randomly assigned to two groups in a 1:1 ratio. The treatment course is 6 weeks, with a 2 weeks follow-up. The primary outcome is the mean change value from baseline to 6th week by the Yale Global Tic Severity Scale total tic score (YGTSS-TTS). Secondary outcomes include total effective rate of tic, Yale Global Tic Severity Scale (YGTSS) scores and its factor scores (the degree of motor tics, phonic tics and social function damage), Clinical Global Impression-Severity scale, and TCM syndrome efficacy.

Discussion: The design of this study refers to a large number of similar research design points,

and asked for opinions of peer experts, and finally reached a consensus. This trial will provide high-quality evidence on the clinical equivalence between JWXFD and JWXFO and provide a basis for the marketing of JWXFD.

Trial registration: ChiCTR2000032312.

Registered on 25 April 2020, <http://www.chictr.org.cn/showproj.aspx?proj=52630>

Keywords: Jiu-Wei-Xi-Feng granules, Tic disorders, Randomized controlled trial, Equivalence trial, Traditional Chinese medicine

Background

Tic disorders is a neuropsychiatric disorder characterized by involuntary, aimless, rapid, repetitive and rigid single or multiple muscle motor tics and / or vocal tics in childhood and adolescent [1,2]. The therapy of tic disorders usually consists of three stages: psychological education, behavior intervention and drug treatment [3,4]. Behavioral therapy has become a first-line treatment for TD, but it is limited by the need for professional intervention personnel and the long intervention time. When patients require an active intervention for these symptoms and behavioral therapy is not available, antidopaminergic drugs (tiapride, haloperidol, aripiprazole, tetrabenazine, etc.) and alpha adrenergic receptor agonists (guanfacine, clonidine) should be considered. However, they often bring many adverse effects. Tiapride, which is safe and good, will still have up to 25% sedation or drowsiness and cause the female prolactin level abnormality or amenorrhea and so on [5-7].

The description and management methods of TD-like symptoms first appeared in ancient Chinese medical documents *Inner Canon of Huangdi* written 2000 years ago. Essays on the therapeutic prescription of TD can be found in *Key to Therapeutics of Children's Diseases* [8],

written by Qian Yi of Song Dynasty. As time goes by, TCM has made a great progress in tic disorders, more abundant experience in syndrome differentiation and treatment, and summarized excellent and effective TCM prescriptions [9,10].Jiu-Wei-Xi-Feng granules, developed by Jiangsu Kanion Pharmaceutical limited company, originated from the clinical experience of treating children's tic disorders with consumption of renal yin and liver wind stirring up internally syndrome. From 2004 to 2009, Jiu-Wei-Xi-Feng granules completed the phase II and phase III clinical trials controlled by tiapride and the supplementary trials controlled by placebo [11-13], and it passed the examination of Center for Drug Evaluation of China. The product was approved for production and marketing on December 31, 2012, by China food and drug administration (CFDA) (approval No.:z20120034).It is composed of *Shu Di Huang(Rehmanniae Radix Preparata)*, *Tian Ma(Gastrodiae Rhizoma)*,*Long Dan(Radix Gentianae)*,*Gui Jia(Carapax et Plastrum Testudinis)*, *Gou Teng(Ramulus Uncariae Cum Uncis)*,*Long Gu(Os Draconis)*,*Jiang Can(Bombyx Batryticatus)*, *Qing Meng Shi(Lapis Chloriti)*,*Fa Ban Xia(Rhizoma Pinelliae Preparatum)*.

Regulations on the protection of fossil paleontology, promulgated by the State Council of China in September 2010, stipulates that no unit or individual shall transact key protected fossils without authorization. The *Long Gu(Os Draconis)*, one of the prescriptions, belongs to first-class key protected fossil of paleontology. In view of the relevant policies and regulations of national *Longgu* protection, in order to save resources, we consider replacing the *Long Gu(Os Draconis)* with *Mu Li(Concha Ostreae)*.Both of them have similar functions in traditional Chinese medicine and basically consistent chemical composition. They often use each other interchangeably in Chinese herbal compound prescription. At the same time, we also studied the pharmacodynamics

of Jiu-Wei-Xi-Feng granules (JWXFD) which substitutes *Concha Ostreae* for *Os Draconis* and original Jiu-Wei-Xi-Feng granules (JWXFO) in three animal models. The results showed that both of them could reduce the score of the relevant evaluation indexes of the tics and without statistical difference between groups. In order to further confirm the feasibility of using *Concha Ostreae* instead of *Os Draconis*, and evaluate the same efficacy and safety of the new prescription (JWXFD) and the original prescription (JWXFO), we design a clinical equivalence test.

Methods/design

Study design

This study is a multicenter, randomized, prospective, double-blind, and parallel group, equivalence trial comparing the efficacy and safety of JWXFD (*Os Draconis* replaced by *Concha Ostreae*) and JWXFO (original formula) in treating TD in Children. Figure 1 shows the flow chart of the trial.

Ethics

This study has been authorized by the China Food and Drug Administration (CFDA) (approval number SFDACYZB1805909), and registered in the Chinese Clinical Trial Registry (ChiCTR2000032312). In addition, the trial was approved by the Ethics Committee of The First Teaching Hospital of Tianjin University of Traditional Chinese Medicine (TCM) (approval number (TYLL2019[Y]-017) and the ethics committees of the other twelve hospitals. To ensure the enough participants and research progress, 13 clinical research center in different provinces of China will conduct this trial: First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, The Affiliated Hospital of Shandong University of TCM, Daqing People's Hospital, Second Affiliated Hospital of Tianjin University of TCM, Wuxi Children's Hospital, Dongzhimen Hospital Beijing University of Chinese Medicine, Children's Hospital of Soochow University, The

First Affiliated Hospital of Henan University of TCM, The Second Hospital of Hebei Medicine University, Taizhou Hospital of TCM, The First Hospital of Hunan University of Chinese Medicine, First Affiliated Hospital of Heilongjiang University of TCM, Deyang People's Hospital. If there is any important modification to the study protocol, it will be submitted to the ethics committee again for review and approval. All eligible participants and their guardian will be fully informed about risks and benefits of the trial and the protocol details; they will sign an informed consent form prior to participation. But If there is any injury or death related to the trial, the sponsor will be responsible for the related treatment costs and financial compensation. After participating in the study, the personal information of the children will be abbreviated to protect their privacy. The data related to the trial process of subjects are only allowed to be viewed by researchers and monitors and will not be used in other studies. The study protocol is based on the SPIRIT checklist [14].

Patient population and setting

Diagnostic criteria

A diagnosis of the TD in Western medicine is established according to DSM-5[15] Standard of TCM syndrome differentiation is based on *Pediatrics of TCM (Second Edition* [16]). The TCM diagnostic differentiation criteria for CEYLWSS are listed in Table 1. Patients should have at least one primary symptom and at least two of the secondary symptoms in order to confirm the syndrome differentiation, as well as refer to tongue and pulse.

According to *Diagnosis and treatment of childhood tic disorders experts consensus (2017)* [1] published by The Neurology Group of Chinese Pediatric Society of Chinese Medical Association, the criteria for the severity of TD based on Yale Global Tic Severity Scale (YGTSS) are as

follows:

1. Mild: YGTSS total scores < 25
2. Moderate: YGTSS total scores between 25 and 50
3. Severe: YGTSS total scores > 50

Inclusion criteria

1. Meeting the diagnosis criteria of TD of mild or moderate based on DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) [15] and confirmed the TCM syndrome pattern criteria of consumption of renal yin and liver wind stirring up internally syndrome (CEYLWSS).
2. Aged between 4 and 14.
3. The participants' TD last for more than a year, and had not used any related therapeutic drugs for TD before 2-4 weeks enrolled (>Six half-lives plus one week for the related drugs).
4. Parents or other legal guardians of the children sign informed consent.

Exclusion criteria

1. Participant with transient tic disorder (TTD), other specific tics or non-specific tics, severe TD, and refractory TD (the TD patients who have been treated with sufficient anti-TD drugs such as tiapride hydrochloride and aripiprazole for more than 1 year without effective and whose course of disease is prolonged[1]).
2. Participants' involuntary movement can be explained by other diseases, such as rheumatic dance, Huntington's dance, Kayser's disease, Hammond's disease, myoclonus, acute dyskinesia, spasm of hysteria, epilepsy and childhood schizophrenia, and drug-induced extrapyramidal diseases.

3. Participant combined with other mental disorders such as attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), and learning disorder, sleeps disorder, etc.
4. Participant with severe primary diseases of heart, liver, kidney, digestion and hematopoietic system.
5. Participant with allergic reaction to composition of experimental drug.
6. Participant cannot cooperate or be participating in other drug trials.
7. The researcher consider that the participant is not suitable to be enrolled.

Withdrawal criteria

1. The investigator can decide the patient to quit in case of allergic reaction or serious adverse events.
2. After 4 weeks of treatment, participant is worsening conditions (YGTSS total scores > 50).
3. During the study, participant with other diseases, or stopping the experimental drug for more than a week.
4. Participant has poor compliance (the compliance is less than 80%), automatically changes the medication or adds the prohibited TCM medicine or western medicine during the study.
5. Breaking blindness.
6. Participant is found to have seriously violated the inclusion and exclusion standards after randomization.
7. Patients have right to withdraw for any reason during the study.
8. The subjects did not explicitly claim withdraw from the study, but they do not take the drug and accept follow-up visit.

Randomization and Blinding

A total of 288 eligible subjects will be randomly allocated in a 1:1 ratio. Randomized sequences was generated by an independent statistical expert in the Epidemiology Department of First Teaching Hospital of Tianjin University of TCM, with 36 blocks of block size 8 based on the computer software SAS 9.2. Randomized sequences is duplicate, which will be concealed in the sealed envelopes, managed by the project managers of each center and sponsor, who are not involved in the recruitment, intervention, assessment, or statistical analysis. Subjects, investigators, CRC and statisticians were blind. The color and taste of the new prescription (NJWXD) and the original prescription (JWXFO) were basically the same after the assessment of school-age children. Therefore, the method of double-dummy was not adopted in this trial. Emergency envelope are kept in each study center, the investigator may only open it under the following conditions: patient occurs serious adverse event (SAE) or serious infection; patient's condition worsened and need for necessary emergency treatment.

Interventions

All the drugs (JWXFD and JWXFO) of this trial are provided and manufactured by Jiangsu Kanion Pharmaceutical Co., Ltd (Jiangsu, China).JWXFD or JWXFO is 6g per bag (batch number: 190701 for JWXFD; 190702 for JWXFO). The Children 4 to 6 year's olds receive 1 bag twice a day Bid, while those 7 to 9 years old take 1.5 bags Bid, while those 10 to 14 years old take 2 bags Bid. The duration of treatment is 6 weeks, with 2 weeks follow-up. During the trial patients will be visited four times by investigators. Subjects' journal will be set to record the medication of children. Each subject's drug was packaged in a separate package for 2 weeks plus 3 days. The surface of each package attach a visible label states "Jiu-Wei-Xi-Feng Granules For Clinical Trial Use Only" and other information: national drug approval number, drug number, drug name,

package dosage, storage conditions, and drug supplier. All test drugs shall be collected and counted by special personnel, and the compliance shall be calculated. Details of the study schedule are in Figure 2.

Concomitant treatments and forbidden medication

During the study, any other therapy or medication may affect the study outcomes is prohibited, such as tiapride, clonidine, haloperidol, valproate, aripiprazole, risperidone, tetrabenazine, pimozide, fluphenazine, sulpiride, inosine, and with the same effect Chinese medicine is also prohibited. Any other treatment during the study will be recorded in the case report form (CRF).

Outcome measures

Primary outcome

The primary outcome is the mean change from baseline to the 6th week in YGTSS total tic score (YGTSS-TTS). YGTSS is a special scale developed by Leckman et al. of Yale University in 1989 to evaluate the severity of Tic disorders. It contains three parts: motor and phonic tics and social function impairment. YGTSS-TTS refers to the integral sum of the first two parts [17].

Secondary outcomes

Secondary outcomes include total effective rate of tic, YGTSS scores and its factor scores (the degree of motor tics, phonic tics and social function damage), Clinical Global Impression-Severity scale (CGI-S), and TCM syndrome efficacy. Effective rate of tic is judged by the change in YGTSS-TSS score from initial assessment to that at the end of the 6th week. Clinical control is defined as $\geq 75\%$ decrease in the YGTSS-TSS score; obvious improvement as $\geq 50\%$ and $< 80\%$ decrease; improvement as $\geq 25\%$ and $< 50\%$ decrease ; and ineffective as $< 25\%$ decrease . Total effective rate of tic = clinical control + obvious improvement + improvement. The CGI-S is used

to evaluate the severity of clinical symptoms and change that ranges from 0 (Normal) to 7 (Extreme) [18,19]. The "effective" of TCM syndromes is defined as the reduction of the total score of TCM syndromes $\geq 50\%$. Change in TCM symptom and sign scores based on Fig 3. The primary symptoms (Motor tics and Phonic tics) was measured as either none (0), mild (2), moderate (4), or severe (6). The secondary symptoms was measured as either none (0), being (1). Total TCM scores is equal to total primary symptoms plus total secondary symptoms.

Safety outcome measures

The primary outcome of safety is the incidence of adverse events. Some physical examinations and laboratory tests will be performed on baseline and after 6 weeks of treatment to assess safety.

The physical examination includes temperature, respiration, blood pressure and heart rate.

Laboratory tests included blood routine, urine routine, liver and renal function, ECG. Adverse events (AE) will be recorded in CRF, "adverse event record" of CRF includes: adverse event occurrence time, end time, duration, severity, measures taken and outcome, and make judgment on the relationship between adverse events and experimental drugs.

Sample size estimation

The placebo-controlled clinical trial of JWXFO showed that the mean difference of YGTSS-TTS was 6.12 (4.12~8.12) and standard deviation was 7.2. We prespecified an equivalence margin of -3 to 3 points. Assuming a 15% dropout rate, the sample size of 144 per group should provide an approximately 80% power at a statistical level of 0.05.

Data management and statistical analysis

Two clinical research coordinators (CRC) independently entry the data into the online Electronic Data Capture (EDC) based on the CRFs, and the data entry time shall not exceed 1 week after

each visit. After this, investigator and data administrator shall audit the data in accordance with the CRFs independently. After the completion of data entry, any data modification in EDC need fill in a reason and the modification record will be left. After that, clinical researchers, data managers and statisticians will hold a data verification conference under the blind state for discussing data process and the partition of data sets including full analysis set (FAS)population, the per-protocol set (PPS) population and safety set (SS) population. Statistical analysts perform data analysis in a blind state. Efficacy analyses will be conducted according to the full analysis set (FAS) population and the per-protocol set (PPS) population. Safety analyses will be conducted by safety set (SS) population. Missing values of primary outcome will be replaced by the last observation carried forward (LOCF) method. T test or non-parametric test will be used for quantitative data, while chi-square test will be used for qualitative data. Cochran-Mantel-Haenszel test or logistic regression model will be used to adjust covariates (center or others).The difference of primary outcome was compared between groups using a two-sided confidence interval approach, a level of equivalence between treatments of ± 3 points and a 0.05 significance level. SAS 9.2 will be used for data analysis.

Quality control and monitoring

Each study hospital will have a professional quality manager. All investigators will receive uniform training about standard operating procedures (SOPs) for trial execution. In particular, the investigators involved in the evaluation, we will conduct conformance training on YGTSS scale, CGI-S and TCM symptom grading scale. CRCs are responsible for contacting subjects regularly to remind them of medication and follow-up. CRA regularly monitors the quality of trial to ensure their authenticity and integrity.

Discussion

TD is a chronic neuropsychiatric disease with a long treatment period. Most of the children with TD had improved symptoms after treatment, while a few cases showed no significant improvement and the symptoms persisted until adulthood or lifelong[20]. The exact etiology and pathogenesis of TD are unclear. It is generally believed that genetic factors and environmental factors work together to cause changes in biological substances in vivo leading to different clinical manifestations and comorbidities. Traditional Chinese medicine holds that the main pathogenesis of TD is consumption of renal yin and liver wind stirring up internally [21]. The treatment of TD is mainly behavioral therapy and drug therapy. When the severity of tic is moderate or severe, behavioral intervention or drug intervention is required. Compared with drug therapy, only a limited number of children can use behavioral therapy [22]. Antidopaminergic drugs [23] (e.g. Haloperidol, pimozide, etc.) are widely used to treat children with tic disorders, but their side effects are obvious and the efficacy is poor. In China, TCM treatment of TD has shown good efficacy [24]. A variety of proprietary Chinese medicines have been developed, among which JWXFO has been proven to be a proprietary Chinese medicine that can significantly improve the status of symptoms of tic disorders in Chinese children, with few side effects [11-13]. The purpose of this study is to prove that JWXFD and JWXFO have the same effect. If verified in this trial, it can reduce the damage to fossil medicines and greatly reduce the cost.

Trial status

Protocol version 1.0, 9 August 2019. The trial is currently in the process of recruiting participants in the thirteen study centers.

Abbreviations

287 TD : tic disorders

288 JWXFD: Jiu-Wei-Xi-Feng granules (*Os Draconis* replaced by *Concha Ostreae*)

289 JWXFO: Jiu-Wei-Xi-Feng granules (original formula)

290 TCM: traditional Chinese medicine;

291 YGTSS-TTS : Yale Global Tic Severity Scale Total Tic Score

292 CGI-S : Clinical Global Impression-Severity scale

293 CRF: case report form;

294 AEs: Adverse events ;

295 CRC: researchers or clinical research coordinator;

296 FAS: full analysis set;

297 PPS: per-protocol set;

298 SS: safety set;

299 95%CI: 95% confidence interval.

300 **Declarations**

301 ***Ethics approval and consent to participate***

302 The protocol, informed consent form, and recruitment poster were reviewed and approved by the

303 Ethics Committee of The First Affiliated Hospital of Tianjin University of Traditional Chinese

304 Medicine (no. TYLL2019[Y]字 017). All participants will provide written informed consent

305 before enrolment.

306 ***Consent for publication***

307 Not applicable.

308 ***Availability of data and materials***

All data will be made available.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SXG and RBL contributed equally to this work and should be considered as equal first coauthors. They conceived the study, design the trial and drafted the manuscript. SYH and QHC were involved in design and modifying the draft. CLZ helped design the trial. RMH contributed to the modifying of the manuscript. All authors read and approved the final manuscript.

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- 388

Fig. 1 Study flow chart

390

391

Fig. 2 Symptoms and signs scale based on TCM syndromes

	Study period				
	Screening	Intervention period			Follow-up
Visit	Visit 0	Visit 1	Visit 2	Visit 3	
Timepoint	Baseline day -7 ~ 0	2weeks±2days	4weeks±4days	6weeks±7days	2weeks after stopping the drug
Enrollment					
Informed consent	√				
Medical history, treatment history	√				
Physical exam and vital signs	√				√*
Random allocation	√				
Intervention					
JWXFO		←	→		

JWXFD
Assessment					
YGTSS	√	√	√	√	√
CGI-S	√	√	√	√	√
CGI-I				√	
TCM syndrome score	√	√	√	√	√
AEs
Vital signs	√	√	√	√	√*
Blood and urine routine	√			√	√*
Hepatic and renal function	√			√	√*
Electrocardiography	√			√	√*
Data collection					
Hand over/reception of drugs	√	√	√	√	
Drug combination		√	√	√	

√*, If there is an AE, patient need be followed up for safety information till reach the endpoint of event.

Fig. 3 Schedule of study procedures

TCM main syndrome	Score grading			
	0	2	4	6
Motor tics	NO	YGTSS-TTS	YGTSS-TTS	YGTSS-TTS
Phonic tics		3 ~ 9	10 ~ 17	18 ~ 25
TCM minor syndrome	Score grading			
	0	1		
Two zygomatic flushing	NO	YES		
Hand, foot and heart is hot	NO	YES		
Hot flashes night sweats	NO	YES		

irritable	NO	YES		
Insomnia and much dream	NO	YES		
Dizziness tinnitus	NO	YES		
Tongue and pulse	Score grading			
	0	1		
Tongue	Light red	Red tongue with less fluid		
Tongue coating	Thin white	Little or no		
pulse	Norma	String thin and weak or fast		

394 Note: For symptoms that cannot be accurately expressed due to the age of the child, fill in NA.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

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