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Efficacy of Yiqiyangxin Chinese medicine compound combined with cognitive therapy in the treatment of generalized anxiety disorders

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ABSTRACT

Objective: To observe the clinical efficacy of Yiqiyangxin Chinese medicine compound combined with cognitive therapy on generalized anxiety disorders. **Methods:** A total of 202 generalized anxiety disorders patients were randomly allocated to a control condition (Paroxetine combined with cognitive therapy) or a treatment condition (Yiqiyangxin Chinese medicine compound combined with cognitive therapy). Subsequently, scores of Hamilton Anxiety Scale (HAMA), Zung Self-rating Anxiety Scale (SAS) and blood routine, urine routine, liver function, renal function, electrocardiogram were detected before treatment, 3 months, 6 months after treatment and 6 months after medicine withdrawal, respectively. **Results:** HAMA and SAS scores were significantly reduced in two groups ($P < 0.001$) after treatment, but the differences in HAMA and SAS scores, apparent effect and effectiveness were not significant ($P > 0.05$). HAMA and SAS scores were significantly increased in two groups ($P < 0.05$) after medicine withdrawal, and there were significant differences in HAMA and SAS scores, recurrent disease and adverse reaction ($P < 0.001$). The incidence of recurrent disease and adverse reaction in treatment group was low. Both two groups showed no apparent abnormality in blood routine, urine routine, liver and renal function, and electrocardiogram. **Conclusions:** Yiqiyangxin Chinese medicine compound combined with cognitive therapy can significantly reduce the recurrence after medicine withdrawal and is effective on generalized anxiety disorders. Furthermore, the incidence of adverse reactions is low. The treatment program is worthy clinic application in the further.

1. Introduction

Generalized anxiety disorders (GAD) is an anxiety disorders that is characterized by excessive, uncontrollable and often irrational worry about everyday things that is disproportionate to the actual source of worry. GAD is also a chronic and impairing disorder, independent of its comorbidity with other mental disorders[1]. It is a common neurosis. GAD patients at premorbid have a certain qualities and personalities, and it is related to psychosocial factors

frequently. They constantly perceive threat, and show a preattentive bias to threat-related information. These excessive worries often interfere with daily functioning, as individuals suffering GAD typically anticipate disaster, and are overly concerned about everyday matters such as health issues, money, death, family problems, friend problems or work difficulties. Individuals often exhibit a variety of physical symptoms, including fatigue, fidgeting, headaches, nausea, numbness in hands and feet, muscle tension and aches, difficulty swallowing *etc*[2–6]. In addition, GAD patients typically score higher than normal people on a wide variety of interpersonal problems assessed by the Inventory of Interpersonal Problems[7]. At the same time, this worry prompted GAD patients keep up to seek for all things could be safety guarantee and smoothly. They have more requirements to the sense of determination.

Anxiety occurred when people perceive the threat or danger. Therefore, the pathogenesis of anxiety is considered be a psychogenic phenomenon. The occurrence of anxiety,

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development, maintenance and aggravation are closely related of their cognitive process. In this cognitive appraisal process, the brain alert system of excessive activation and the internal and external stimulus information as “excess dangerous” is considered to be the foundation of anxiety. Researchers considered that the individuals of high generalized anxiety have difficulties in transferring attention as emotional stimulate. Moreover, the uncertain situation will excitate the sense of uncertainty to GAD patients. In the end, it made GAD patients more easily in a nervous state. So the patients showed more sensitive to negative stimulate^[8,9].

Consequently, patients with anxiety disorders have always preferentially selected psychotherapy. However, in practice, we found that learn to master the psychotherapeutic technique have many difficulties. And, when we adopted the method, it must spend a lot of time during the treatment. Hence, at present, pharmaceutical treatment is still adopted for anxiety disorders in clinic^[10,11]. Selective serotonin reuptake inhibitors (SSRIs) are a class of compounds typically used as antidepressants in the treatment of depression, anxiety disorders, and some personality disorders. Paroxetine is a SSRIs type of antidepressant drugs, because of its characteristics with excellent clinical efficacy and few side effects relatively, which are widely used in study and clinic^[12]. However, after administration, once it takes effect, it must have a long-term maintenance treatment. As a rule, patients with anxiety disorders also need a long-term maintenance treatment, but its efficacy remains to be further improved. In China, Chinese herbal medicine in the treatment of anxiety disorders is of a certain characteristics. It has been accepted for many patients now, but we still lack of large-scale, standardized, rigorous clinical controlled study.

In this study, we compared the clinical efficacy between Yiqiyangxin Chinese medicine compound combined with cognitive therapy and paroxetine combined with cognitive therapy.

2. Materials and methods

2.1. Participants and inclusion criteria

In this study 202 GAD patients from outpatient department who were from East China Sanatorium between March, 2006 and October, 2011 were selected. All participants consented to participate in this trial and were randomly assigned to treatment group ($n=93$) and control group ($n=109$). Patients in control group were treated by paroxetine combined with cognitive therapy, while patients in treatment group by

Yiqiyangxin Chinese medicine compound combined with cognitive therapy.

All patients were diagnosed according to DSM-IV criteria^[13], thus enhancing the probability of reasonably homogeneous samples. Measures included in this analysis were interview [typically the Hamilton Anxiety Scale (HAMA)] and self-report questionnaires [the Zung Self-Rating of Anxiety (SAS)]. Entry criteria were as following: (a) HAMA total score >14 , (b) excluded from the severe physical illness and severe personality disorder, and (c) patients and their families had informed consent. The general data compared with treatment group and control group as follows (Table 1), and there was no significantly differences ($P>0.05$) in gender, age, course of disease, *etc.*

2.2. Treatments

In this study, GAD patients had cognitive therapy, and took different medicine according to different groups.

Patients in treatment group took Yiqiyangxin Chinese medicine compound, which can supplement Qi and nourish heart. It consists of 14 crude drugs: American ginseng 30 g, red ginseng 30 g, baical skullcap root 30 g, cochinchinese asparagus root 30 g, dwarf lilyturf tuber 30 g, Chinese magnoliavine fruit 30 g, danshen root 30 g, panax notoginseng 30 g, drug sweet flag rhizome 30 g, thin leaf milkwort root-bark 30 g, gardenia jasminoides 30 g, fermented soybean 30 g, amber 30 g, spina date seed 30 g.

The above listed drugs were ground into power, and were administrated to patients on an empty stomach with 10 g, two times daily. The course of treatment should last six months. Six months after medicine withdrawal, the condition was observed to decide if further steps should be taken.

Patients in control group took paroxetine hydrochloride tablets, which were provided by Sino-American Tianjin SmithKline Pharmaceutical Ltd. In this group, the course of treatment also lasted six months. Firstly, the dose as only 10 mg, and was increased to 20 mg at the second week. And the dose may have changes at times according to the efficacy or side effects. But the limitation was at 20 to 60 mg a day. Furthermore, the minimum therapeutic dose should not be below 20 mg a day. During this treatment period, the mean dose was (24.9 ± 8.9) mg.

Cognitive therapy is based on the theory that the disorder stems from constant perceptions of the world as dangerous place, resulting in a process of maladaptive and habitual interactions among cognitive, behavioral and physiological responses^[14]. Consequently, cognitive therapy included identifying and labeling irrational thoughts and replacing them with positive self-statements or modifying them

Table 1

Comparison of background variables.

Groups	Gender		Age (years)	Educational degree		Marital status		COD(m)
	Male	Female		SHSOL	JCOH	Unmarried	Married	
Control group	49	60	36.7 ± 12.9	62	47	51	58	34.6 ± 11.9
Treatment group	44	49	38.0 ± 13.1	57	36	39	54	33.9 ± 12.7

SHSOL: Senior high school or lower; JCOH: Junior college or higher; COD: Course of disease.

by challenging their veracity. The cognitive modification approaches are often combined with behavioral treatments such as exposure or relaxation training. The behavioral components are viewed either as important in their own right or as a vehicle for practicing cognitive techniques^[15].

Hence, during this phase, firstly, each patient's present information including their feeling, thinking mode and response were collected. This will help understand a wide range of the interactions factors, such as growth experience, core beliefs in cognition, error coping mode (avoidance), and variety reactions of patients with automatic processing mode (thinking, emotion and behavior). Secondly, we tried to find out thinking mode which leads to patients' bad emotion and behavior. This will help them understand the relationship between cognition and psychological problems further. Together with patients, we discussed which mode would be the most perfect for us to understand the world, future and himself. And then, we made therapeutic targets together to find out the mode of thinking, belief and coping conflict with reality life. The cognitive therapy process carried out every half a month, each time lasted about 1 hour. Within 6 months, GAD patients should receive 12 times therapy.

2.3. Clinical evaluation

The efficacy was assessed by HAMA and SAS before the treatment, at the end of 3 months, 6 months (during treatment) and at the end of 6 months after medicine withdrawal. At every period, the evaluation was taken for 1 time. When the treatment was over, the efficacy evaluation according to HAMA reduction rates was assessed by four criteria. After treatment compared with that before treatment, reduction rate $\geq 75\%$ was considered as clinical recovery, rate between 50%–70% as apparent effect, between 25%–49% as effectiveness rate $< 25\%$ as ineffectiveness. The total effective rate = (recovery + apparent effect + effectiveness) / total number of cases $\times 100\%$.

2.4. Laboratory examination

In this study, the laboratory examination consisted of blood routine, urine routine, liver and renal function, and electrocardiogram. All items were measured 1 time before the treatment, at the end of 3 months, 6 months (during treatment) and at the end of 6 months after medicine

withdrawal, respectively.

2.5. Statistical analysis

The difference between treatment and control group were compared using three analysis ways of the calculation of descriptive statistics, *t*-test and χ^2 -test. Statistical analysis was done using SPSS version 19 software.

3. Results

3.1. HAMA scores

As shown in Table 2, after treatment for 3 months and 6 months, both control group and treatment group showed a very significantly decreases in HAMA score (Control group $t=16.280$, 16.504 , both $P<0.001$; treatment group $t=15.707$, 16.764 , both $P<0.001$). However, there was no significantly difference between groups ($P<0.05$). But 6 months after medicine withdrawal there was significantly decrease in HAMA, SAS score in two groups compared with those during medicine taking (Control group $t=9.229$, $P<0.001$; treatment group $t=2.223$, $P<0.001$), and the score was significantly higher in control group than treatment group ($t=6.699$, $P<0.05$).

3.2. SAS scores

As shown in Table 3, after treatment for 3 months and 6 months, both control group and treatment group showed a very significantly decreases in SAS scores (Control group $t=31.052$, 31.155 , both $P<0.001$; treatment group $t=32.030$, 33.137 , both $P<0.001$). However, there was no significantly difference between groups ($P<0.05$). But 6 months after medicine withdrawal there was significantly decrease in HAMA, SAS score in two groups compared with those during medicine taking (Control group $t=13.002$, $P<0.001$; treatment group $t=2.778$, $P<0.001$), and the score was significantly higher in control group than treatment group ($t=9.714$, $P<0.05$).

3.3. Comparison of clinical efficacy

After treatment for 6 months, 30 cases in the control

Table 2

HAMA scores (mean \pm SD).

Group	Before treatment	3 months after treatment	6 months after treatment	6 months after medicine withdrawal
Control group	28.3 \pm 8.6	11.3 \pm 6.7	10.1 \pm 6.8	19.3 \pm 7.9
Treatment group	27.9 \pm 8.4	10.7 \pm 6.4	9.4 \pm 6.5	13.6 \pm 7.5

Table 3

SAS scores (mean \pm SD).

Group	Before treatment	3 months after treatment	6 months after treatment	6 months after medicine withdrawal
Control group	65.8 \pm 9.4	30.4 \pm 7.3	30.1 \pm 7.4	45.8 \pm 8.4
Treatment group	66.3 \pm 8.9	29.1 \pm 6.8	28.9 \pm 6.9	35.8 \pm 7.8

group were in recovery, 37 cases had apparent effect (33.9%), 17 cases showed effectiveness, and 23 cases were ineffectiveness. The total effective rate (recovery + apparent effect + effectiveness) was 78.9%. In contrast, in the treatment group, 21 cases were in recovery, 35 cases had apparent effect (37.6%), 20 cases showed effectiveness, 17 cases were ineffectiveness. The total effective rate was 81.7%.

There was no significantly differences in apparent effect rate and effectiveness rate ($\chi^2=2.575$, $P>0.05$).

3.4. Recurrence rate and adverse reaction incidence

After medicine withdrawal, we found that there were 26 cases with recurrence in the control group, including 7 cases in recovery, 10 cases with apparent effect, and 9 cases with effectiveness. However, only 8 cases with recurrence were reported in the treatment group, including 2 cases in recovery, 3 cases with apparent effect, and 3 cases with effectiveness. There was a significantly difference in recurrence rate between two groups ($\chi^2=9.632$, $P<0.001$).

Laboratory examination showed that in the treatment group, 10 cases had nausea, 3 cases had short-term diarrhea, and 2 cases had dizziness. But after a while, these symptoms gradually disappeared. In the control group, 11 cases had dry mouth, 10 cases had dizziness, 4 cases had insomnia, and 9 cases had nausea. The adverse reaction incidence was significantly lower in control group ($\chi^2=11.840$, $P<0.001$).

4. Discussion

The cause of the anxiety disorder is not very clearly at present. GAD as the most common anxiety disorder has a high prevalence rate (3.6% to 5.1% lifetime and 3.1% 1-year prevalence)^[15]. The current study considered that the cause is relevant to psychological, physical, biochemical and genetic factors. Previous studies found that patients with anxiety disorders could had increase in the content of lactate in blood. Similarity, it could lead to the β adrenaline hyperactivity syndrome or induced locus ceruleus in noradrenergic neurons impulse increased, which could cause anxiety attacked. Moreover, animal experiments found that when electrical stimulated the locus ceruleus it also could cause anxiety reaction^[10].

In cognitive therapy, a variety of approaches have been used to treat GAD patients, such as Ellis' rational-emotive, Meichenbaum's self-instructional training, Beck and Emery's model of cognitive therapy. The basic idea is that cognitive process is the mediate of behavior and emotion. Patients' maladaptive behavior and emotion is relevant to the maladaptive cognitive. Because of this, during the treatment, we emphasized on changing the cognitive process and conception to correct the patients' bad mood and behavior. Furthermore, treatment is especially emphasized on patients' error cognition, not just aimed to theirs abnormal emotion and behavior^[16–22]. The treatment target is to improve patients' clinical symptoms by helping solve resource of error cognition, then to change theirs irrational beliefs and reconstruct theirs thinking mode and outlook on life. Cognitive therapy may be superior to paroxetine because it results in less relapse and recurrence and does not

have risks of pharmacotherapy. In recent years, cognitive therapy in the treatment of anxiety disorder attract a lot of attention^[21].

During the treatment, as a rule, if drug therapy and non-drug therapy show the same effect the non-drug treatment is preferred. However, in practice, there are many difficulties in applying psychotherapeutic technique. Hence, at present, the drug therapy is still of widespread application.

Paroxetine (Paroxetine) is SSRIs and a selective inhibition of presynaptic membrane 5-HT reuptake pumps. However, its effect on the other kinds of neurotransmitters including acetylcholine, adrenaline, noradrenaline, histamine receptors is very little^[11,12]. Because of its characteristic, it is used in treating anxiety disorders, with little adverse reaction and high safety. It is the first-line drug at present. However, it also causes some adverse reactions such as fatigue, constipation, diarrhea, dizziness, headache, dry mouth, and hidrosis symptoms. And many patients refuse to take this medicine.

"Anxiety disorders" is a emotional and psychogenic disorder. It belongs to depression, panic, fear, fright palpitation, heart palpitations, fearful throbbing, insomnia, hysteria, and lily disease in Chinese traditional medicine theory. Recently, it is reported many Chinese herbs which can relieve heat, strengthen the spleen and tonify blood, clear away the heat-evil and phlegm, promote the circulation of blood to remove blood stasis are used to treat this disease^[23–25]. It is proposed that the pathogenesis of anxiety disorders is mainly relevant to deficiency of heart qi, and its dysfunction in moistening and nourishing, and in clearing orifices. This function is very important in regulating our body and mind.

It is stated in "Magic Pivot" that heart stores the spirit and governs the blood vessels. It is named "the office of the monarch" in "Plain Questions: Treatise of the Arcane Book of the Orchid Chamber of the Spirit Tower". Sad and melancholy emotion has negative effect on the body. Deficiency of heart qi will lead to abnormal consciousness. Yiqiyangxin Chinese medicine compound consists of 14 Chinese medicines. Ginseng, sweet, slightly warm, and can invigorate primordial qi to tranquilize and enhance intelligence^[26]. Monomer ginsenoside is a central nerve sedative, and can calm the mind^[26]. American ginseng, bitter, slightly sweet, cold, with meridian tropism to the heart, lung and kidney, and can supplement qi and promote fluid production. Saponin of American ginseng has significant anti-fatigue effect. Baical skullcap root, sweet, slightly warm, and is good at qi supplement^[26]. Combination of cochinchinese asparagus root with dwarf lilyturf tuber can nourish yin and clear the heart^[27]. Chinese magnoliavine fruit, sour, warm, can nourish the heart and yin to tranquilize. Pharmacological studies proved that Chinese magnoliavine fruit has effect on excitatory and inhibitory processes on cerebral cortex, and can balance both processes^[26]. Pulse-Engendering Beverage, consisting of ginseng, dwarf lilyturf tuber and Chinese magnoliavine can invigorate qi and nourish the heart. Danshen root combines with panax notoginseng can promote the circulation of blood, remove blood stasis to promote tissue regeneration, and can nourish the heart to tranquillize. Drug sweet flag rhizome combined with thinleaf milkwort root-bark can

tonify the kidney, strengthen the brain, enhance intelligence and calm the mind^[26]. Gardenia and Fermented Soybean Decoction including gardenia jasminoides and fermented soybean is also a famous for clearing away the heart–fire and eliminating vexation^[27,28]. Amber also has the effect of tranquilizing and calming the mind. Spina date seed, sweet, plain, not only can nourish the heart and tonify the liver but also strengthen the body, and calm the mind^[29]. It is used to treat dysphoria and insomnia used to blood deficiency. Moreover, pharmacological experiments also proved that with jujuboside as active constituents, spina date seed has significant effect of tranquilizing and inducing sleep^[26].

In this study, we use Yiqiyangxin Chinese medicine compound combined with cognitive therapy to treat GAD, which can invigorate the qi, nourish the heart, and tranquilize the mind. The result shows GAD patients are under control to a great extent in clinic. However, this study is lack of large–scale and multicenter clinical verification. Moreover, the oral dosage is high and the administration process is inconvenient. Thus, further studies are needed to find a way to change the dosage form, or find effective monomer or complex instead.

Conflict of interest statement

We declare that we have no conflict of interest.

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