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Original Article

Selective serotonin reuptake inhibitor combined with dengzhanshengmai capsule improves the fatigue symptoms: a 12-week open-label pilot study

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Abstract: Objective: This study was to assess the efficacy and safety of selective serotonin reuptake inhibitor (SSRI) plus Dengzhanshengmai capsule in patients with chronic fatigue syndrome (CFS). Methods: SSRI at a moderate dose plus Dengzhanshengmai (n = 134) with SSRI alone (n = 134) were compared for the efficacy and safety in the treatment of CFS. The therapeutic efficacy and safety were evaluated. Results: As compared to monotherapy group, the efficacy in combined therapy group was better and characterized by the improvement of general fatigue (0.8±0.6 *vs.* 1.3±0.7), physical fatigue (0.6±0.3 *vs.* 1.0±0.4) and reduced activity (1.0±0.5 *vs.* 1.3±0.6) since the 2nd week ($P<0.01$) and in reduced motivation (2.1±0.8 *vs.* 2.4±1.0) since the 8th week ($P<0.01$) and the improvement continued thereafter. The mental fatigue score and HAD score were comparable between two groups ($P>0.05$). No significant difference was found in the drop-out rate between SSRI group (15.7%) and SSRI plus Dengzhanshengmai group (18.0%). The reasons for drop out were adverse events (7.5% vs. 9.7%), requests of the patients or career requirement (3.7% vs. 4.5%), loss to follow-up and others (2.2% vs. 3.0%) and lack of efficacy (2.2% vs. 0.7%). Although the patients in combined therapy group experienced a higher rate of hypertension than (5.8% vs. 1.5%), no significant difference was observed ($P = 0.08$). Conclusion: SSRI combined with Dengzhanshengmai capsule may significantly improve the general fatigue, physical fatigue, reduced activity and reduced motivation of CFS patients as compared to monotherapy with SSRI. Furthermore, this combined therapy is safe and tolerable.

Keywords: SSRI, fatigue, dengzhanshengmai

Introduction

Chronic fatigue syndrome (CFS) is a debilitating and complex disorder characterized by profound fatigue that is not improved by bed rest and often associated with substantial disability [1] and a high incidence of comorbidities including depression [2, 3], anxiety, pain, insomnia and poor cognition [4] resulting in low daily activities and pool quality of life. Although pharmacological, psychological and exercise interventions have been used for the therapy of CFS, their efficacy is still unsatisfactory [5], and adverse events and reactions are frequently found in clinical practice [6]. Given the facts that anxiety and depression are common in CFS patients and have similar biological characteristics to some pathological conditions, some first-line antidepressants such as selective serotonin reuptake inhibitor (SSRI) have been recommended by US FDA to treat CFS, but findings from available studies on SSRI (such as flouxetine) are conflicting on the efficacy and most studies report negative aspects including low response rate, delayed onset and presence of adverse effects on high doses. This situation may be ascribed to the differences in the nosological status and etiology of CFS [7]. In the clinical therapy of CFS, additional Chinese traditional medicine to SSRI treatment may be helpful to improve the response rate without increase adverse effects based on the role of immune dysfunction in the pathogenesis of CFS. It has been proposed that Chinese herb Dengzhanshengmai capsule is able to improve the functional deficiency of the 'liver', 'spleen',

Table 1. Clinical and demographic characteristics at baseline

		SSRI (n = 134)	SSRIs plus Dengzhanshengmai (n = 134)	t/χ^2	*P*
Age (yr)		36.8±16.7	35.1±17.1	1.70	0.09
Sex (male: female)		52: 84	59: 75	0.94	0.33
Education (years)		7.5±2.2	7.7±2.8	0.65	0.52
BMI (kg/m^2)		25.6±4.7	25.2±4.1	0.74	0.46
Course of disease (months)		14.5±7.3	15.7±9.9	1.13	0.26
Comorbid complaints	Headache (%)	90 (67.2)	96 (71.6)	0.63	0.43
	Myalgia (%)	91 (67.9)	85 (68.5)	0.60	0.44
	Sore throat (%)	87 (64.9)	80 (59.7)	0.78	0.38
	Tender cervical lymph nodes (%)	81 (60.4)	76 (56.7)	0.38	0.54
	Sleep disturbances (%)	78 (58.2)	87 (64.9)	1.28	0.26
	Memory problems	70 (52.2)	72 (53.7)	0.06	0.81
	HAD-Anxiety (%)	12.3±4.9	12.1±5.3	0.05	0.96
	HAD-Depression (%)	11.2±3.1	10.4±4.0	1.83	0.07
	Other problems (%)	42 (31.3)	51 (38.1)	1.33	0.25
MFI	General fatigue	10.2±4.1	10.7±4.3	0.97	0.33
	Physical fatigue	9.6±3.8	9.4±4.1	0.41	0.68
	Mental fatigue	7.4±3.5	7.6±3.4	0.47	0.64
	Reduced activity	8.6±3.3	8.9±2.8	0.80	0.42
	Reduced motivation	7.2±3.7	7.3±3.0	0.24	0.81

Note: Chi-squared test for categorical variables and *t*-test for quantitative variables; BMI: body mass index; SSRI: selective serotonin reuptake inhibitor; HAD: Hospital Anxiety and Depression Scale; MFI: Multidimensional Fatigue Inventory.

Table 2. Reasons for drop out in two groups

	SSRIs (n = 113)	SSRIs plus Dengzhanshengmai (n = 110)	*P*
Adverse events	10 (7.5)	13 (9.7)	0.77
Request of patients	5 (3.7)	6 (4.5)	1.00
Loss to follow up and other reasons	3 (2.2)	4 (3.0)	1.00
Lack of efficacy	3 (2.2)	1 (0.7)	0.32
Total	21 (15.7)	24 (18.0)	0.74

'kidney', 'heart' and 'brain', exerting therapeutic effects on CFS. Dengzhanshengmai capsule contains four ingredients: erigeron breviscapus herba, ginseng herba, schisandra herba and ophiopogon japonicus herba, which may augment the immune function through supplementing 'Qi' and nourishing 'Yin', promoting blood circulation and clearing disturbing ideas in mind. Thus, we hypothesized combined treatment with Dengzhanshengmai and SSRI is promising to achieve better efficacy for CFS patients as compared to monotherapy with SSRI. This study was to compare monotherapy with SSRI and combined therapy with SSRI and Dengzhanshengmai in terms of efficacy and tolerability.

Methods

Patients

Patients of three centers (First Affiliated Hospital of Zhejiang University, Xiaoying Street Community Health Center and Tongde Hospital of Zhejiang Province) were recruited into this study from September 2012 to October 2014. A total of 268 CFS adults were included in the present study and CFS was diagnosed according to the US Centers Disease Control and Prevention (CDC) Diagnosis criteria for CFS [http://www.cdc.gov/cfs/diagnosis/index.html]. CFS was confirmed when 4 or more of the following 8 symptoms were present: 1) Post-exertion malaise lasting more than 24 h; 2) Unrefreshing sleep; 3) Significant impairment of short-term memory or concentration; 4) Muscle pain; (5) Multi-joint pain without swelling and redness; 6) Headaches of a new type, pattern, or severity; 7) Tender cervical or axillary lymph nodes; 8) Frequent or recurrent sore throat. Exclusion criteria included current

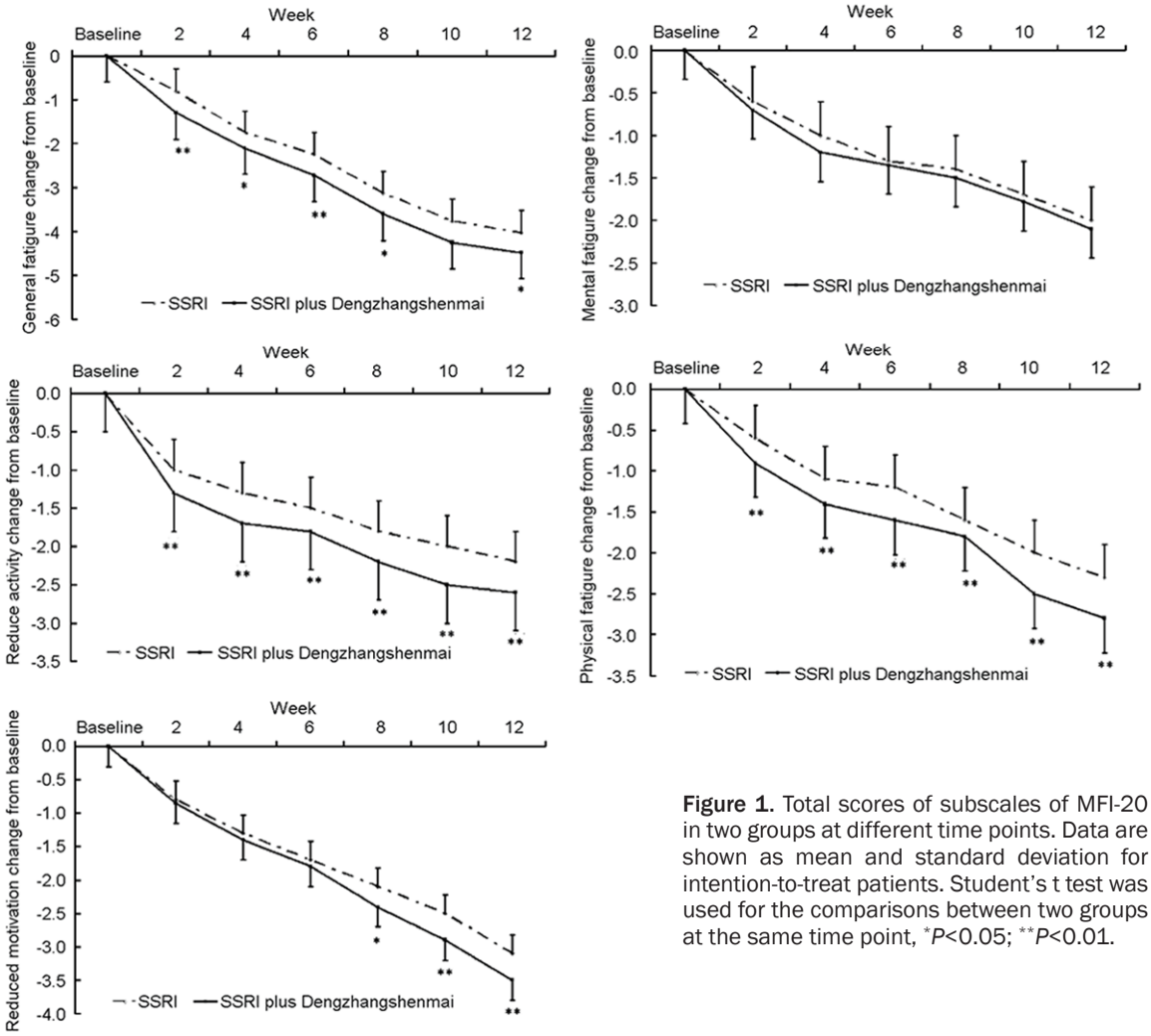

Figure 1. Total scores of subscales of MFI-20 in two groups at different time points. Data are shown as mean and standard deviation for intention-to-treat patients. Student's t test was used for the comparisons between two groups at the same time point, $^{*}P<0.05$; $^{**}P<0.01$.

or past use of antidepressants for any psychiatric condition; concurrent DSM-IV Axis I disorder, vegetarians, nursing women, pregnant women, use of psychotropic medication in the last month, previous or current engagement in CFS or psychiatric research, substance dependence or abuse and clinically significant or unstable medical illness. A structured clinical interview for DSM-IV (SCID-I) was performed to exclude patients with current psychiatric comorbidity.

Study design

This was a prospective open label-controlled 12-week follow-up trial which was designed to compare the combined therapy with Dengzhanshengmai plus SSRI and monotherapy with SSRI in terms of efficacy and safety in CFS outpatients. A total of 268 patients were randomly assigned to monotherapy group (SSRI: Seroxat, Eisai Co. Ltd., Japan Zoloft and Citalopram) (n = 134) and combined therapy group (Dengzhanshengmai capsule: Yunnan BIOVALLY Pharmaceutical Co., China) (n = 134). During the study, all the patients were administered with Seroxat at 10-30 mg/day or Zoloft at 25-100 mg/day or Citalopram at 10-30 mg/day for the first 4 weeks and thereafter the standard dosages were employed for maintenance therapy. In combined therapy group, Dengzhanshengmai capsule was given at 1.08 g/day for 12 weeks. Patients received a regular follow up once every 2 weeks, during which the routine physical and mental examination, psychometric tests (Multidimensional Fatigue Inventory-20 and Hospital Anxiety and Depression Scale), medication compliance evaluation, and adverse events monitoring, ECG (weeks 0, 2, 4 and 12), laboratory assessments (weeks 0, 2, 4, 8 and 12) were conducted. At the end of this study, 223 patients completed

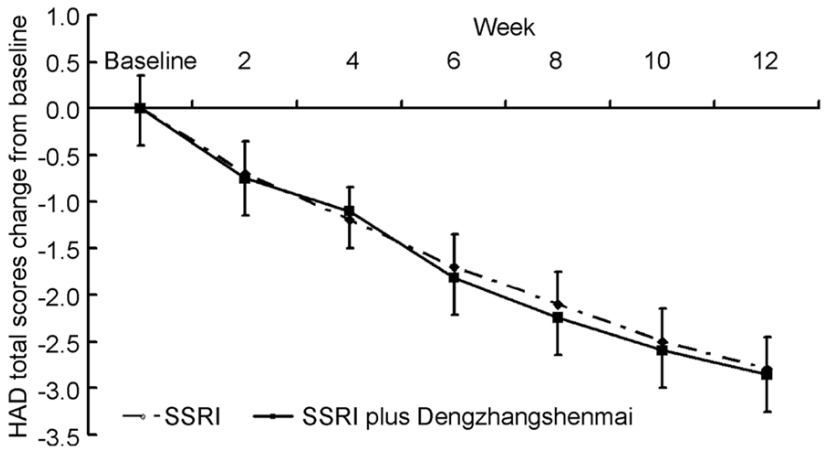

Figure 2. Total scores of HAD in two groups at different time points.

this trial. This study was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient before study.

Assessments

The Multidimensional Fatigue Inventory (MFI)-20 covering general fatigue, physical fatigue, mental fatigue, reduced activity and reduced motivation has been widely used for the evaluation of CFS. MFI-20 has proved to be a valid and reliable instrument for the assessment of fatigue in CFS patients [8] and depression patients [2]. The subscale of MFI-20 consists of 4 items. It is a 5-point scale and patients were scored according to the self-reported fatigue perception (from "never" to "very often"). The total score ranges from 4 to 20. The higher the total score, the more likely to be severe the fatigue severity is. The Hospital Anxiety and Depression Scale (HADS) has been shown to be a useful tool for the assessment of anxiety and depression. It is a 14-item scale and patients are scored on a 4-point Likert scale according to the symptoms of anxiety and depression within the last week. The total score ranges from 0 to 21 for either subscale. Depression and anxiety were defined as a score of >9 on the HADS depression and anxiety subscale [2]. The higher the score, the more severe the mood impairment is.

Statistical analysis

Quantitative data are expressed as mean ± standard deviation and categorical data as frequency. The demographics, lifestyles, and reported fatigue, anxiety, and depressive symptoms at baseline were compared between two groups by *t*-test for quantitative data or Chi-squared test for categorical data. The correlation analysis of the changes in all outcomes between pre- and postintervention and the linear regression analysis was performed by using the change in depression score as a dependent variable and the changes of other outcomes as independent variables. Statistical analysis was conducted with Statistical Package for the Social Sciences (SPSS version 18.0, SPSS Inc., Chicago, IL, USA). A value of $P<0.05$ was considered statistically significant.

Results

Demographics and disease-related characteristics

As shown in **Table 1**, there were no significant differences in the demographics, course of disease, comorbidities and MFI subscale scores. A total of 45 patients (21 in SSRI group and 24 in SSRI plus Dengzhanshengmai group) did not complete this study due to the drug unavailability in the hospital pharmacy. No difference was observed in the drop-out rate between two groups (**Table 2**) (SSRI: 15.7%; SSRIs plus Dengzhanshengmai: 18.0%). The reasons for drop-out included adverse events (7.5% vs. 9.7%; P>0.05), requests of the patients or career requirement (3.7% vs. 4.5% P>0.05), loss to follow-up and other reasons (2.2% vs. 3.0% P>0.05) and lack of efficacy (2.2% vs. 0.7% P>0.05).

Subscale scores of MFI-20

The subscale scores declined since the beginning of treatments in both groups. This indicates that both treatments improve the CFS. Compared to SSRI group, the efficacy in SSRI plus Dengzhanshengmai group increased significantly in the general fatigue (0.8±0.6 *vs.*

Table 3. Frequency of adverse events in two groups (%; Fisher' Exact Test)

	SSRIs (n = 113)	SSRIs plus Dengzhanshengmai (n = 110)	*P*
Total adverse events	56 (41.8)	55 (41.0)	0.95
Dry mouth	7 (5.2)	6 (4.5)	1.00
Nausea	6 (4.5)	7 (5.2)	0.78
Diarrhea	6 (4.5)	5 (3.7)	1.00
Constipation	5 (3.7)	6 (4.5)	0.76
Vomiting	5 (3.7)	3 (2.2)	0.72
Insomnia	5 (3.7)	4 (3.0)	1.00
Agitation/anxiety	4 (3.0)	5 (3.7)	0.74
Headache	4 (3.0)	3 (2.2)	1.00
Weight gain	3 (2.2)	3 (2.2)	1.00
Sexual problems	3 (2.2)	2 (1.5)	1.00
Sweating	3 (2.2)	2 (1.5)	1.00
Problems urinating	2 (1.5)	1 (0.7)	1.00
Hypertension	2 (1.5)	8 (5.8)	0.05

1.3±0.7), physical fatigue (0.6±0.3 *vs.* 1.0±0.4), reduced activity (1.0±0.5 *vs.* 1.3±0.6) since the 2nd week ($P<0.01$, Student's t test, t_{257} = 6.19, 9.14 and 4.39, respectively) and reduced motivation (2.1±0.8 *vs.* 2.4±1.0) since the 8th week ($P<0.01$, Student's t test, t_{251} = 2.64) and this improvement maintained thereafter. No significant difference was found in the improvement of mental fatigue between two groups ($P>0.05$, **Figure 1**). These results indicate SSRI plus Dengzhanshengmai is more effective than SSRI alone to improve CFS since the 2nd week.

Scores of anxiety and depression

The HAD scores declined since the beginning of treatments, but no significant differences were found between groups at same time point ($P>0.05$, **Figure 2**).

Safety

The most common treatment-related adverse events in this study were dry mouth, nausea, diarrhoea, constipation, vomiting, insomnia, headache, weight gain, sweating, sexual problems, urinating problems, hypertension and suicidal tendency/attempts (**Table 3**). Totally, 21 patients in SSRI group and 24 in SSRI plus Dengzhanshengmai group experienced mild to moderate adverse events. No serious adverse events or death were found during the study. The statistical results about the laboratory and auxiliary examination just showed no any significance difference. The dropout rate due to adverse events in SSRIs plus engzhanshengmai group (9.7%) was comparable to that in SSRI group (7.5%). Although SSRI plus Dengzhanshengmai group had a higher incidence of hypertension than in SSRI group (5.8% vs. 1.5%), no significant difference was observed between them ($P = 0.08$).

Discussion

CFS is a disabling condition of unknown cause, and no effective therapy has been developed to date [9]. It has been found that a wide array of immune [10-12], inflammatory [13], stress [14], bioenergetic, hypothalamic-pituitary-adrenal [15] and neurophysiological [16] abnormalities are involved in the pathogenesis of CFS. In addition, studies also reveal that CFS is also associated with altered activities of specific brain regions. Because CFS has many risk factors and is associated with some causes of depressive disorders and many symptoms including mood problems (depression, anxiety and panic attack) [17], cognitive deficits (concentration and memory impairment) and pain (muscle and multiple joints pain) [18] may overlap with symptoms of depression, depressive symptoms are further observed to mediate a moderate relationship fatigue severity [19], and thus antidepressant drugs have been widely used in the treatment of CFS.

Given the strong association between peripheral immune activation and neuroinflammation, together with the subsequent activation of glial cells and mitochondrial damage, likely account for the pathogenesis of intractable fatigue and disability seen in many patients with neuroimmune and autoimmune diseases [20], various agents with the capability to improve energy metabolism or enhance the immune function are used in the therapy of CFS. According to traditional Chinese medicine theory, 'Yang' and 'Qi' are driving forces of biological activities in the human body based on the crucial role of mitochondria in the energy metabolism, and thus Yang- and Qi-invigorating tonic herbs, such as cistanches herba able to regulate mitochondrial function have been recommended for the therapy of CFS [21].

In this study, 268 patients were randomly assigned into SSRI monotherapy group and combined therapy with SSRIs plus Deng-

zhanshengmai group. There were no significant differences in the demographics, clinical manifestations and neuropsychological measurements between two groups, which indicates that patients in two groups matched in these factors. On the basis of subscale scores of MFI-20, SSRIs plus Dengzhanshengmai showed a better therapeutic efficacy as compared to SSRI alone, demonstrated by the significant improvement of general fatigue, physical fatigue, reduced activity since the 2nd week and reduced motivation since the 8th week. Moreover, these improvements maintained thereafter. However, there was no significant difference in the change of HAD score at same time points between groups, which indicates that Dengzhanshengmai capsule has no antidepressive effect and our findings are reliable. Of note, the drop-out rate and incidence of adverse events were comparable between two groups, suggesting that additional Dengzhanshengmai treatment is safe. This might contribute to developing and keeping up to date an evidence-based hierarchy of antidepressants to be used for the therapy CFS and provide a good alternative for the therapy of CFS in terms of its tolerability and efficacy.

However, there were still some limitations in this study. First, these results partly reflected a routine clinical treatment because we failed to define the criteria for effectiveness which may be helpful for the further analysis of the onset time of the treatment in both groups. Of course, the curative standard has not yet formed a unified understanding. In addition, the term "treatment response" also describes a state of improvement in the patient's condition based on the physicians' judgment at least a temporary global improvement; however, this evaluation standard was not used in this study. Second, no single SSRI agent and a fixable dose were employed in this study leading to the consequence that it failed to rule out the influence of unmeasured confounding factors (such as selection bias, detection bias and performance bias) although the patients went closer to the treatment state in a "real world". Different SSRIs were used in this study and each SSRI has little difference in the efficacy and adverse effects. Finally, a short-term and nondouble-blind follow-up was employed in this study, which may also bias our results.

Conclusion

Our results indicate that SSRI plus Dengzhanshengmai capsule can significantly improve the fatigue symptoms. This combined therapy is safe and tolerable, and thus may offer a promising strategy for the therapy of CFS.

Disclosure of conflict of interest

None.

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