Journal of Affective Disorders 170 (2015) 71–77

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

Herbal medicine for hospitalized patients with severe depressive episode: A retrospective controlled study

Lan-Ying Liu [a], Bin Feng [a,*], Jiong Chen [a], Qing-Rong Tan [b], Zheng-Xin Chen [a], Wen-Song Chen [a], Pei-Rong Wang [a], Zhang-Jin Zhang [c,**]

[a] Department of Psychosomatics, Tongde Hospital of Zhejiang Province, Hangzhou 310012, Zhejiang, China
[b] Department of Psychiatry, Fourth Military Medical University, Xi'an 710032, Shaanxi, China
[c] School of Chinese Medicine, LKS Faculty of Medicine, The University of Hong Kong, 10 Sassoon Road, Pokfulam, Hong Kong, China

ARTICLE INFO

Article history:
Received 24 March 2014
Received in revised form
8 August 2014
Accepted 12 August 2014
Available online 27 August 2014

Keywords:
Herbal medicine
Severe depressive episode
Psychotherapeutic agents
Clinical trial

ABSTRACT

Herbal medicine is increasingly used in depressed patients. The purpose of this retrospective controlled study was to evaluate the efficacy and safety of herbal medicine treatment of severe depressive episode. A total of 146 severely depressed subjects were selected from patients who were admitted to the Department of Psychosomatics of Tongde Hospital at Hangzhou, China between 1st September 2009 and 30th November 2013. While all were medicated with psychotropic drugs, 78 received additional individualized herbal medicine. The severity of depressive symptoms was measured using 24-item Hamilton Rating Scale for Depression (HAMD-24) at admission and thereafter once weekly during hospital stay. The proportion of patients achieving clinical response and remission and incidence of adverse events were compared. The two groups had similar average length of hospital stay for approximately 28 days and were not different in the use of psychotropic medications. Survival analysis revealed that patients with herbal medicine had significantly higher chance of achieving clinical response [relative risk (RR)=2.179, $P<0.001$] and remission (RR=5.866, $P<0.001$) compared to those without herbal medicine. Patients with herbal medicine experienced remarkably fewer incidences of physical tiredness, headache, palpitation, dry mouth and constipation, but had a significantly higher incidence of digestive discomfort compared to patients without herbal medicine. These results indicate that additional treatment with individualized herbal medicine enhances antidepressant response and reduces certain side effects associated with psychotropic medications. Herbal medicine is an effective and relatively safe therapy for severe depressive episode (Trial Registration: ChiCTR-OCH-13003864).

1. Introduction

Depression is a serious mental illness that affects 8–20% of the worldwide population (Ferrari et al., 2012). Although a variety of antidepressant drugs have been developed for the treatment of depressive episode, there still remains a large portion of depressed patients who do not make a full response and experience relapse, often resulting in the worsening and hospitalization (Arroll et al., 2005). A high incidence of adverse side effects has largely hampered the clinical use of conventional agents (Arroll et al., 2005). These limitations have led to a search of alternative treatment strategies.

Over the past two decades, herbal medicine has been increasingly introduced into psychiatry practice (Zhang, 2004). This is particularly apparent in China where Chinese medicine has become an important component in public mental healthcare. For instance, Chinese herbal medicine is often recommended as an adjuvant to depressed patients in order to augment antidepressant efficacy, reduce side effects and comorbid symptoms while they are treated with conventional psychotropic medications (Butler and Pilkington, 2013). Indeed, empirical and experimental evidence suggests that there are numerous herbal medicines possessing the antidepressant potential (Zhang, 2004). There are a large number of clinical studies showing the benefits of herbal medicine in the treatment of various depressive disorders (Butler and Pilkington, 2013). Our controlled trials have demonstrated the clinical efficacy of one herbal preparation called Free and Easy Wanderer Plus (FEWP) in reducing bipolar and unipolar depression and adverse event rates (Zhang et al., 2007a, b). Despite these, the effectiveness and safety of herbal medicine for depression are

* Corresponding author. Tel.: +86 571 8997 2003; fax: +86 571 8885 3199.
** Corresponding author. Tel.: +852 2589 0445; fax: +852 2872 5476.
E-mail addresses: fengbintd@aliyun.com (B. Feng), zhangzj@hku.hk (Z.-J. Zhang).

http://dx.doi.org/10.1016/j.jad.2014.08.027
0165-0327/

not yet fully delineated, as most published clinical trials lacked rigorous protocol design with significant methodological flaws (Butler and Pilkington, 2013).

Tongde Hospital is a leading specialty psychiatric hospital in Zhejiang Province of China. It has long been dedicated to integrating Chinese medicine and conventional medication for individuals with complex mental illness (http://www.zjtongde.com/cms/Default.aspx). Since 2009, the Department of Psychosomatics of this Hospital has developed an herbal medicine treatment protocol for depressed patients. In this retrospective controlled study, we sought to evaluate the efficacy and safety of additional treatment with herbal medicine in severely depressed patients in comparison with conventional psychotropic treatment alone.

2. Methods

2.1. Settings and selection of subjects

This retrospective controlled study was conducted in Department of Psychosomatics of Tongde Hospital at Hangzhou, China. Subjects were selected from patients who were admitted to the Department between 1st September 2009 and 30th November 2013, on the basis of electronic database. The study protocol was approved by the Medical Ethical Committee of Tongde Hospital and retrospectively registered in www.chictr.org (Trial Registration: ChiCTR-OCH-13003864). All patients and/or their guardians were required to give voluntary, written, informed consent when they were admitted to the Hospital.

Subjects were selected for this study if they: (1) were either gender aged 16–75 years; (2) had a diagnosis of severe depressive episode based on the International Classification of Diseases (10th version) (ICD-10), as evidenced by a score of ≥ 35 on the 24-item Hamilton Rating Scale for Depression (HAMD-24) (Hamilton, 1960) or having depression-associated suicidal attempts; and (3) were admitted to the Hospital due to a severe depressive episode between September 1, 2009 and November 30, 2013.

Subjects were excluded from the study if they had: (1) herbal medicine treatment for over 7 days prior to admission; (2) herbal medicine treatment, but the compliance was less than 75% within the designated schedules during hospital stay; (3) received brain stimulation therapy, such as electroconvulsive therapy (ECT), psychotherapy or acupuncture treatment during hospital stay; (4) severe comorbid cardiac, hepatic or renal condition, brain tumors or intracranial space-occupying lesions; (5) a history of alcohol or substance abuse within the previous 12 months; or (6) an investigational drug treatment within the previous 6 months.

2.2. Psychotropic and herbal medicine treatment

Patients who were not medicated at admission immediately received orally administered venlafaxine (VLX), a dual serotonin–norepinephrine reuptake inhibitor (SNRI). VLX dose was initiated at 75 mg/day and escalated to an optimal dose (150–225 mg/day in most cases) within 1 week, depending upon individual patient response, but the maximum dose could not exceed 300 mg/day. This dosing regimen has been widely used for depressive episodes in China (Fang et al., 2010). Patients who were already taking VLX would continue his/her VLX regimen. Those who were taking other psychotropic medications, including other antidepressants, were otherwise required to continue, rearrange or remove certain drugs, depending on patients' condition and psychiatrists' discretion.

During hospital stay, most patients were prescribed a combination of VLX and other psychotropic medications for comorbid psychiatric symptoms, such as sleep disturbance, anxiousness and hallucination. Other psychotropic medications included other antidepressants, hypnotics, anxiolytics, antipsychotics and mood stabilizers. The determination of dose, frequency and time of day

Table 1
Herbal medicine formulae for various TCM subtypes of patients with depressive episode.

TCM subtypes	Formula name	Latin binomial and Chinese names of herbs and dosage (g)
Liver stagnation with spleen-qi deficiency	A combination of Free Wanderer Powder and Pinellia–Magnolia Decoction	*Bupleurum chinense* DC. [Chai-Hu, 12], *Angelica sinensis* (Oliv.) Diels. [Dang-Gui, 9], *Paeonia lactiflora* Pall. [Shao-Yao, 12], *Glycyrrhiza uralensis* Fisch. [Gan-Cao, 6], *Pinellia ternata* (Thunb) Breit. [Fa-Ban-Xia, 9], *Magnolia officinalis* Rehd. et Wils [Hou-Po, 12], *Poria cocos* (Schw.) Wolf. [Fu-Ling, 12], *Zingiber officinale* Rosc. [Sheng-Jiang, 10], *Perilla frutescens* (Linn.) Brito. [Zi-Su-Ye, 12].
Liver stagnation with qi stagnancy	Bupleuri-improved Mood Powder	*Bupleurum chinense* DC. [Chai-Hu, 12], *Poria* cocos (Schw.) Wolf. [Fu-Ling, 12], *Cyperus rotundus* L. [Xiang-Fu, 12], *Citrus aurantium* L. [Zhi-Ke, 12], *Bupleurum chinense* DC. [Chai-Hu, 9], *Citrus reticulata* Blanco. [Chen-Pi, 9], *Prunus mume* (Sieb.) Sieb. *et* Zucc. [Lv-E-Mei, 12], *Lilium pumilum* DC. [Bai-He, 12], *Albizia julibrissin* Durazz [He-Huan-Hua, 12], *Cynanchum paniculatum* (Bge.) Kitag. [Xu-Chang-Qing, 12], *Citrus medica* L. var. *sarcodacylis* Swingle [Fo-Shou, 12], *Ligusticum chuanxiong* Hort. [Chuan-Xiong, 10], *Glycyrrhiza uralensis* Fisch. [Gan-Cao, 6].
Deficiency of both heart and spleen	Digestion and Mind invigorated Decoction	*Codonopsis tangshen* Oliv. [Dang-Shen, 12], *Poria* cocos (Schw.) Wolf. [Fu-Ling, 12], *Atractylodes macrocephala* Koidz [Bai-Zhu, 12], *Astragalus membranaceus* (Fisch.) Bunge. [Huang-Qi, 20], *Angelica sinensis* (Oliv.) Diels. [Dang-Gui, 9], *Polygala tenuifolia* Willd. [Yuan-Zhi, 12], *Curcuma longa* L. [Yu-Jin, 12], *Ziziphus jujuba* Mill. var. *spinosa* (Bunge) Hu ex H.F. Chow [Suan-Zao-Ren, 20], *Aucklandia lappa* Decne. [Mu-Xiang, 6], *Ziziphus jujuba* Mill. [Da-Zao, 15], *Glycyrrhiza uralensis* Fisch. [Gan-Cao, 6].
Deficiency of Yin (vital essence) of the liver and kidney	A combination of Six-herb Plus Rehmannia Pill and Yi-Guan Decoction	*Rehmannia glutinosa* Libosch [Sheng-Di-Huang, 12], *Ophiopogon japonicus* (L.f.) Ker-Gawl. [Mai-Dong, 12], *Rehmannia glutinosa* Libosch [Shu-Di-Huang, 12], *Cornus officinalis* Sieb. Et Zucc. [Shan-Zhu-Yu, 12], *Dioscorea opposita* Thunb. [Shan-Yao, 12], *Angelica sinensis* (Oliv.) Diels. [Dang-Gui, 9], *Lycium barbarum* L. [Gou-Ji-Zi, 15], *Paeonia suffruticosa* Andr. [Mu-Dan-Pi, 12], *Ziziphus jujuba* Mill. var. spinosa (Bunge) Hu ex H.F. Chow [Suan-Zao-Ren, 20], *Polygala tenuifolia* Willd. [Yuan-Zhi, 12], *Acorus tatarinowii* Schott [Shi-Chang-Pu, 12], *Melia toosendan* Sieb. et Zucc. [Chuan-Jian-Zi, 6].
Dampness and heat in the liver and gallbladder	Decoction of Gentian Root for Purging the liver-heat	*Gentiana manshurica* Kitag. [Long-Dan-Cao, 12], *Scutellaria baicalensis* Georgi [Huang-Qin, 6], *Gardenia jasminoides* Ellis [Zhi-Zi, 12], *Alisma orientale* (Sam.) Juz. [Ze-Xie, 12], *Angelica sinensis* (Oliv.) Diels. [Dang-Gui, 9], *Rehmannia glutinosa* Libosch [Sheng-Di-Huang, 12], *Bupleurum chinense* DC. [Chai-Hu, 12], *Glycyrrhiza uralensis* Fisch. [Gan-Cao, 6], *Plantago asiatica* L. [Che-Qian-Zi, 10], *Cristaria plicata* (Leach) [Zhen-Zhu-Mu, 30], *Apatite* [Long-Chi, 20].