

## Chinese Medicinal Herbs in Relieving Perimenopausal Depression: A Randomized, Controlled Trial

Fan Qu, M.D., Ph.D.,<sup>1\*</sup> Xuefen Cai, B.A.,<sup>1\*</sup> Yinger Gu, B.A.,<sup>1</sup> Jue Zhou, M.D., Ph.D.,<sup>2</sup>  
Runju Zhang, M.D.,<sup>1</sup> Elizabeth Burrows, B.A.,<sup>3</sup> and Hefeng Huang, M.D.<sup>1</sup>

### Abstract

**Objective:** To explore the effects of GengNianLe (GNL, also called perimenopausal depression relieving formula), a defined formula of Chinese medicinal herbs in relieving perimenopausal depression in Chinese women.

**Methods:** Between September 2004 and April 2008, 47 Chinese women were randomized into a GNL group ( $n = 21$ ) and a control group which received tibolone ( $n = 26$ ) using a randomization chart. Depression was rated with the 24-item Hamilton Depression Scale (HAMD). The serum levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), and estradiol ( $E_2$ ) were detected before and after the treatment.

**Results:** After 12 weeks of treatment, HAMD scores in both groups decreased significantly ( $p < 0.05$ ) with no significant difference between the groups ( $p > 0.05$ ). The levels of FSH decreased significantly and the level of  $E_2$  increased significantly in both groups, and they changed more in the control group. No side-effect of treatment was reported in either group during treatment.

**Conclusions:** The Chinese medicinal formula GNL showed promise in relieving perimenopausal depression and merits further study.

### Introduction

Perimenopausal depression is characterized by chronic endocrine and autonomic disturbances during the transition to menopause.<sup>1</sup> Epidemiologic studies have indicated that 8% to 47% of women undergo perimenopausal depression.<sup>1–4</sup> It is reported that up to 46.1% of Chinese perimenopausal women suffered from symptoms of low mood, among whom 30% had moderate or severe symptoms.<sup>4</sup> For women with or without a history of depression, the perimenopausal transition is a time of increasing vulnerability for depressive episodes.<sup>5–9</sup> An association has been found between the increased risk of perimenopausal depression and a history of postpartum depression and premenstrual syndrome.<sup>10</sup>

Studies have suggested that women with perimenopausal depression may respond to specific interventions.<sup>11,12</sup> Antidepressants has demonstrated efficacy in treating perimenopausal depression; however, concomitant sexual dysfunction and weight gain have limited their use.<sup>13</sup> Some studies have found that estrogen augmentation was effective in treating perimenopausal depression,<sup>14–18</sup> while others did not find improvement with estrogen augmentation.<sup>19,20</sup>

With more and more patients actively seeking alternative approaches, alternative and complementary therapies, including Chinese medicinal herbs, have manifested significant curative effects in alleviating perimenopausal depression and other perimenopausal symptoms.<sup>21–25</sup> However, little research has been exclusively conducted on the effect of Chinese medicinal herbs in relieving perimenopausal depression. This study was designed to assess the efficacy of GengNianLe (GNL, also called perimenopausal depression relieving formula), a defined formula of Chinese medicinal herbs, in relieving perimenopausal depression in Chinese women. The formula is based on a combination of the theories of Traditional Chinese Medicine (TCM), the literature, and our clinical experience. In the present study, tibolone was used as a comparison. The TCM terms used are based on the *English-Chinese Chinese-English Dictionary of Chinese Medicine*.<sup>26</sup>

### About tibolone and GNL

Tibolone, an analogue of the progestin norethynodrel, is a drug with tissue-specific effects on receptors and enzymes that influence the synthesis and metabolism of endogenous estro-

<sup>1</sup>Women's Hospital, School of Medicine, <sup>2</sup>College of Pharmaceutical Sciences, Zhejiang University, Hangzhou, Zhejiang, China.

<sup>3</sup>Global College of Long Island University, Brooklyn, NY.

\*The first two authors contributed equally to the present research.

gen, progesterone, and androgen.<sup>27</sup> Although tibolone can protect bone and alleviate perimenopausal symptoms like estrogen does, it has a protective, progesterone-like effect on the uterus and does not increase breast density or tenderness.<sup>28</sup> Tibolone has been found to significantly decrease Hamilton Depression Scale (HAMD) scores and improve menopausal and psychological symptoms in women following surgical menopause.<sup>29</sup> It was postulated that tibolone's effect on mood is mediated via the  $\Delta^4$ -isomer metabolite, which can be locally synthesized in the brain by the  $\beta$ -hydroxysteroid dehydrogenase isomerase enzyme.<sup>30</sup> The significant beneficial effects of tibolone on mood were also thought to be associated with its normalization of beta-endorphin levels and its androgenic properties.<sup>31,32</sup> A consensus was reached at the 4th Amsterdam Menopause Symposium that tibolone is a valuable treatment option for women with climacteric complaints, and it was proposed that tibolone might have added value for a number of subgroups of perimenopausal women, including women with sexual dysfunction, mood disorders, fibroids and urogenital complaints, as well as those with breast tenderness or high breast density due to conventional hormone replacement therapy (HRT).<sup>33</sup> The contraindications to tibolone are the same as to conventional HRT.<sup>33</sup> Tibolone was found to be more effective in improving mood disorders<sup>34</sup> and caused significantly less breast tenderness and mastalgia than conventional HRT.<sup>35–39</sup> Tibolone was associated with a lower incidence of vaginal bleeding than conventional HRT.<sup>40</sup> Investigation of endometrial histology in women treated with tibolone showed a high level of atrophic endometrium instead of hyperplasia.<sup>41,42</sup> No significant increase in endometrial thickness was seen when compared with women receiving conventional HRT.<sup>40,43</sup> In contrast to conventional HRT, tibolone did not increase the size or volume of myomas<sup>44</sup> and its use resulted in a significant reduction in a wide range of complaints, including weight gain.<sup>45</sup> Tibolone has been found to prevent the increase in body fat mass and the decrease in lean body mass that typically occur in postmenopausal women.<sup>46,47</sup> However, although tibolone has been registered in 90 countries for treatment of climacteric symptoms, and in 45 countries for the prevention of osteoporosis, it is not available in the United States because there is no large randomized clinical trial to assess its safety and effectiveness, and further data are needed for approval by the Food and Drug Administration (FDA).<sup>28,48</sup> Tibolone has been found to increase the risk of stroke in older women with osteoporosis although it can reduce the risk of fracture and breast cancer.<sup>49</sup> An elevated risk of endometrial disease has also been found in postmenopausal women treated with tibolone.<sup>50</sup> Other reported side-effects include acne, hair loss, hypertension, and recurrent endometriosis.<sup>45,51</sup> The United Kingdom's Million Women Study found an increased risk of breast cancer in users of all types of hormone-related therapies, including tibolone.<sup>52</sup>

There is no term that corresponds to perimenopausal depression in ancient books of TCM. *Jin Gui Yao Lue* (*The Synopsis of the Golden Chamber*) states "Women with *Zang Zao* (visceral agitation, hysteria) tend to grieve, cry and frequently yawn." "Patients with *Bai He* disease always fall silent and they are unable to walk and eat, although they have the desire to do so."<sup>53</sup> *Zang Zao* and *Bai He* are two terms used in these books for mental disorders. The clinical manifestations are similar to those of hysteria, melancholia, and insomnia. It is generally considered that insufficiency of

Kidney *qi* and disorder of Liver *qi* are the main pathogenesis.

The formula for GNL comes from a combination of the theories of TCM, the literature, and our clinical experience. *Concha margaritifera*, semen *Ziziphi spinosae*, radix astragali, and rhizoma dioscoreae were chosen for their sovereign medicinal roles, meant to regulate the *qi*, Blood, *yin* and *yang* of the Kidney and the Liver in order to relieve depression. Semen platycladi, cortex albizziae, radix sodonopsis, and semen cuscudae acted as the minister (secondary) medicinal roles. *C. margaritifera* was used to calm the Liver, enrich *yin*, repress the sthenic *yang*, and tranquilize the mind.<sup>54,55</sup> It has been found to possess sedative and hypnotic activities and is usually used to treat depression, palpitation, insomnia, amnesia, dementia, neurasthenia, mental retardation, and infantile oligophrenia clinically.<sup>56,57</sup> Semen *Z. spinosae* is used to nourish the Liver and to cause tranquilization.<sup>54,55</sup> Animal studies have suggested that it modulated stress-induced sleep changes in mice<sup>58</sup> and enhanced total sleep time in rabbits.<sup>59</sup> It has also been found to improve immunity in the human body.<sup>56,57</sup> *C. margaritifera* and semen *Z. spinosae* are often used together to treat depression, vexation, restlessness, insomnia, and dreaminess.<sup>54–56</sup> Radix astragali was used to supplement *qi* and Blood. It is commonly added to many tonic formulas, including those containing radix codonopsis, to help build the immune system, stamina, and endurance.<sup>54,57</sup> It has been found to possess immunomodulating effects both *in vitro* and *in vivo*.<sup>56,57</sup> Rhizoma dioscoreae was used to supplement Kidney *yin* and *qi* and improve the functions of the Spleen.<sup>54,55</sup> It has antioxidant properties and is traditionally used to improve immunity.<sup>60</sup> Semen platycladi is used to nourish the Heart in order to calm the mind. It has been found to have a hypnotic effect in rats.<sup>56,57</sup> Semen *Z. spinosae* and semen platycladi are used to nourish the Heart and to tranquilize the mind. Semen *Z. spinosae* tends to act on the Liver, while semen platycladi serves well to nourish the Heart and supplement the Kidney.<sup>54,55,57</sup> Cortex albizziae is used to tranquilize the Five Zang organs, particularly to clear the Liver, harmonize the mind, and make people happy and free of depression.<sup>54,55</sup> It is often used as a sedative and blood activator for the treatment of distractibility, depression, and insomnia.<sup>56,57</sup> Radix codonopsis is used to supplement *qi* and Blood.<sup>54,55</sup> It has been found to improve immunity, memory, and adaptability of the body and has sedative and hypnotic activities.<sup>56,57</sup> Semen cuscudae was used to boost both Kidney *yin* and Kidney *yang*.<sup>54,55</sup> It has been found to improve the function of the hypothalamic-pituitary ovarian (HPO) axis and improve immunity.<sup>54,55</sup> It was found to increase ATP synthesis in aged rat brains.<sup>61</sup> Radix polygalae was used to tranquilize the Heart and mind.<sup>54,55</sup> Tenuifolin, extracted from radix polygalae, has been found to have sedative activities<sup>56</sup> and to increase the levels of norepinephrine and dopamine, thus improving learning and memory in aged mice.<sup>62</sup> Fructus *Ligustri lucidi* is used to supplement the Liver, Kidney, and Heart and to tranquilize the mind.<sup>54,55</sup> It has been found to induce ultrastructural changes on the corticotrophs of the rat pituitary gland, modulate endocrine function, and possess anti-aging activities.<sup>63</sup> All the herbs in GNL act together to supplement the Kidney, regulate the Liver, balance *yin* and *yang*, and supplement *qi* and Blood, thus relieving perimenopausal depression. The disorder of the HPO axis during peri-

menopause has been found to affect the levels of dopamine and serotonin, important mood-stabilizing neurotransmitters.<sup>64,65</sup> The serotonin deficiency hypothesis is the most prominent biological theory of the etiology of depression,<sup>66</sup> and estrogen has been found to modulate serotonergic function, through which estrogen controls mood.<sup>67</sup>

The herbs that supplement the Kidney and regulate the Liver have been found to regulate the synthesis and release of neurotransmitters and improve the reproductive endo-

crine function by acting on the HPO axis,<sup>68</sup> which has been confirmed by clinical research on treating perimenopausal depression with Chinese medicinal herbs.<sup>69</sup> It was then hypothesized that GNL plays its role in relieving perimenopausal depression through regulating reproductive endocrine function and coordinating neuroendocrinal function.

It should be noted that among the ten herbs in the formula of GNL, eight have antineoplastic activities and seven have been found to improve immunity.<sup>56,57</sup>

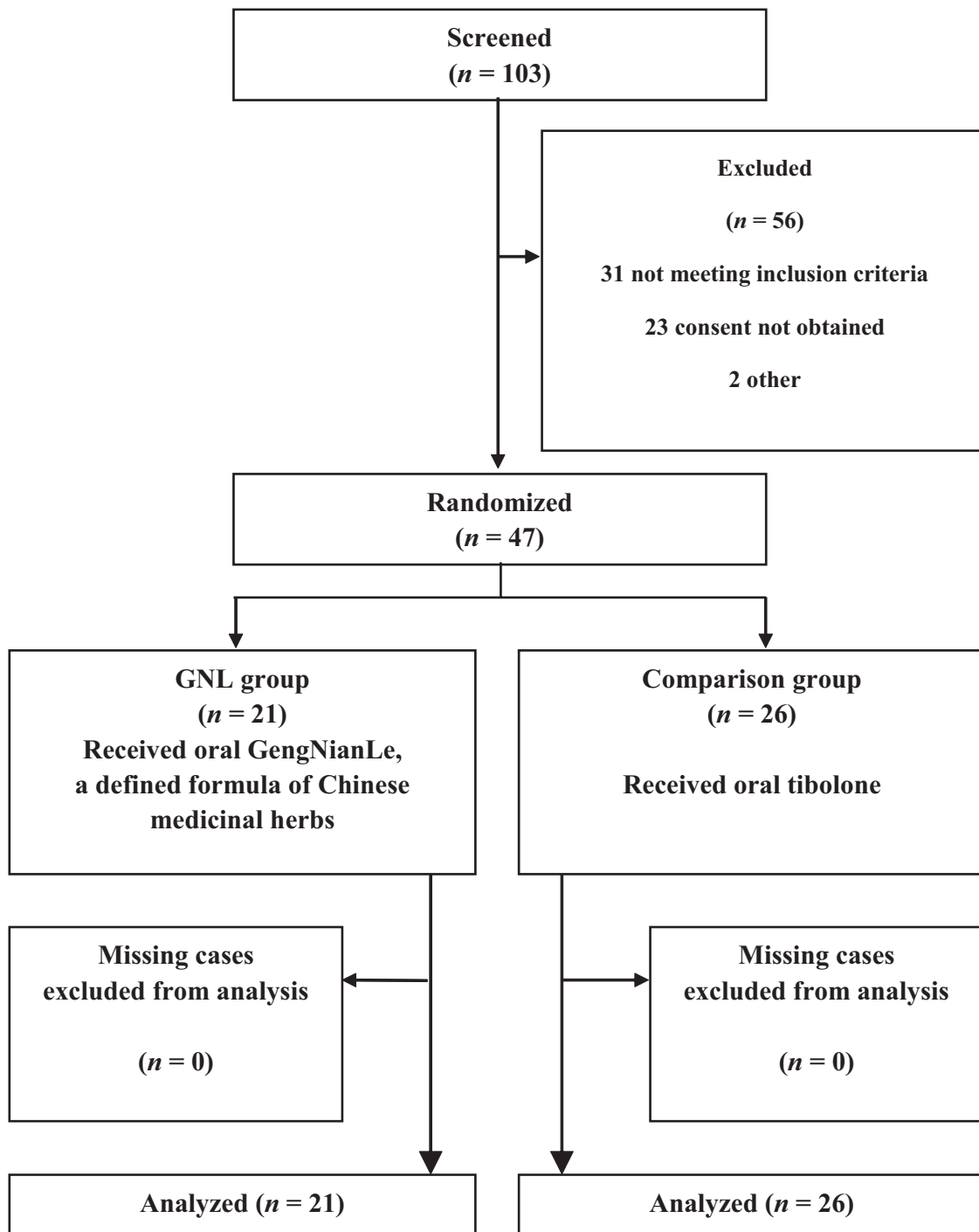


FIG. 1. Study design.

## Subjects and Methods

### Subjects

The study was conducted between September 2004 and April 2008 at the Women's Hospital, School of Medicine, Zhejiang University.

The inclusion criteria were: age 45 to 60 years with at least six consecutive months of amenorrhea with a serum estradiol (E<sub>2</sub>) level < 20 pg/mL and a follicle stimulating hormone (FSH) level > 40 mIU/mL; a minimum of one month of low mood; a total score ≥ 20 on the 24-item HAMD;<sup>70,71</sup> a gynecologic examination and laboratory tests showing that the patient did not suffer from organic diseases of the reproductive system; and no history of depression. Written consent was obtained from each subject stating that the subject would complete the case study. To be considered for the study, patients had to have met all these criteria.

Exclusion criteria were: hormonal medications within the past three months; medical conditions that rendered a patient ineligible for estrogen therapy; structural disease of the central nervous system; cognitive impairment; treatment for depression in the previous three months; alcohol or drug abuse or dependence during the previous six months; serious medical problems resulting in a high probability of death within a year; schizophrenia, bipolar disorder, or early-onset dysthymic disorder; menopause induced by bilateral oophorectomy; pathological conditions; chemotherapy; or behaviors such as extreme exercise or anorexia nervosa and somatic or neurological illnesses impairing psychiatric evaluation. Patients were excluded from the study if they fit any of the above criteria.

The diagnosis of perimenopausal depression in this trial was made by an independent gynecologist and an independent psychologist who were not part of the research team. Another independent researcher allocated the patients into a group with randomization methods. The 24-item HAMD was used to rate the perimenopausal depression.

Subjects were randomized into either the GNL group or the comparison group using Microsoft Excel to randomize numbers into two groups. Ethical approval and permission to conduct the study were obtained from the local ethical committee. The aim and methodology of the study were explained to the patients. Voluntary participation was requested and informed consent was obtained.

The patients were required to record the time they took the medication and to record any adverse effects of the treatment on a standard daily log before going to bed every evening. The standard daily log was structured by the hospital, validated beforehand, and included all possible side effects including pain, weight gain, headache, nausea, hair growth, and greasiness of the skin. Each participant received a physical examination, a routine blood examination, a routine urinoscopy, a liver function test, and a renal function test one day before the treatment started and one day after the treatment ended. In the statistical analysis, all of the women were included with no missing cases (Fig. 1).

There was no significant difference in baseline characteristics between the two groups (Table 1).

### Administration

**GNL group.** The formula of GNL is: 15 g of *C. margaritifera*, 8 g of semen *Z. spinosae*, 12 g of semen platycladi, 10 g of

TABLE 1. BASELINE DEMOGRAPHIC

	GengNianLe group (n = 21)	Comparison (tibolone) group (n = 26)
Age (years)	48.7 ± 8.1	50.4 ± 9.3
Time since last menstrual period (years)	1.1 ± 0.6	1.2 ± 0.5
Married or living as married	15 (71.4%)	19 (73.1%)
Divorced or separated	5 (23.8%)	5 (19.2%)
Never married	1 (4.8%)	2 (7.7%)
Women with children	17 (81.0%)	19 (73.1%)
Educational background		
Less than high school	6 (28.6%)	7 (26.9%)
High school	8 (38.1%)	10 (38.5%)
Some college/university	3 (14.3%)	4 (15.4%)
Occupational diploma/further education	4 (19.0%)	5 (19.2%)
Area of residence		
Urban	15 (71.4%)	18 (69.2%)
Suburban	3 (14.3%)	3 (11.5%)
Small town	1 (4.8%)	0
Rural	2 (9.5%)	5 (19.2%)
Current employment status		
Full-time	5 (23.8%)	4 (15.4%)
Part-time	6 (28.6%)	5 (19.2%)
Unemployed	5 (23.8%)	7 (26.9%)
Retired	5 (23.8%)	10 (38.5%)
Duration of perimenopausal depression (months)	2.6 ± 0.7	2.9 ± 1.0

TABLE 2. HAMILTON DEPRESSION SCALE (HAMD) SCORES AND SERUM LEVELS OF FSH, LH, AND E<sub>2</sub> BEFORE AND AFTER 12 WEEKS OF TREATMENT

	<i>GengNianLe</i> group (n = 21)		<i>Comparison (tibolone)</i> group (n = 26)	
	Baseline	Post-treatment	Baseline	Post-treatment
HAMD scores	33.4 ± 10.3	15.4 ± 6.5*	35.1 ± 12.2	14.1 ± 7.3*
Hormone levels				
FSH (mIU/mL)	58.9 ± 13.9	41.2 ± 9.8*†	61.3 ± 11.4	30.2 ± 12.1*
LH (mIU/mL)	33.5 ± 7.6	30.1 ± 5.5†	34.1 ± 5.9	18.4 ± 5.1*
E <sub>2</sub> (pg/mL)	13.4 ± 5.8	21.7 ± 6.9*†	12.9 ± 6.2	41.9 ± 13.3*

\**p* < 0.05, compared with baseline in the same group.

†*p* < 0.05, compared with the comparison group.

FSH, follicle stimulating hormone; LH, luteinizing hormone; E<sub>2</sub>, estradiol.

radix polygalae, 8 g of cortex albizziae, 15 g of radix astragalii, 10 g of radix codonopsis, 15 g of radix dioscoreae, 15 g of semen cuscutae, and 10 g of fructus *L. Lucidi*, all of which are within the standard dosage levels.<sup>51-54</sup> All the herbs were identified and screened for heavy metal contamination by the College of Pharmaceutical Sciences, Zhejiang University. The herbs were provided and prepared by Huqing Yutang Pharmaceutical Co., Ltd. (Hangzhou, China). The formula was prepared in 200 mL of liquid and then reserved in vacuum bags. Patients were instructed to orally take one dose a day for twelve consecutive weeks. A two-week supply was dispensed at each treatment visit. Subjects were asked not to modify their diet during the study period.

**Comparison group.** The patients were prescribed oral Livial (2.5 mg/tab) (Tibolone, Nanjing Oujianong Pharmaceutical Co., Ltd, Nanjing, China), at the dose of one tablet a day for twelve consecutive weeks.

#### Index and method

Assessment of perimenopausal depression was performed using the 24-item HAMD<sup>70,71</sup> administered at baseline and after twelve weeks of treatment. One day before the treatment and at the end of the treatment, the levels of FSH and

luteinizing hormone (LH) were measured with enzyme-linked immunosorbent assay (ELISA) and the levels of E<sub>2</sub> with double antibiotic ELISA. All reagents were provided by Lianxing Biological Technology Company, Tianjin, China.

#### Data analysis

Results were analyzed by an independent university statistician using SPSS v.13.0 for Windows software. Nonparametric Mann Whitney tests were used to analyze the inter- and intragroup differences of HAMD scores. Analysis of variance (ANOVA) was used to analyze the inter- and intragroup differences of the serum levels of FSH, LH, and E<sub>2</sub>. A 5% significance level (*p* < 0.05) and two-tailed tests were used for all hypothesis tests. Ninety-five percent confidence intervals (95%CI) for the median differences were determined.

## Results

#### HAMD scores

There was no significant difference between the HAMD scores of the two groups at baseline. After twelve weeks of treatment, both groups' HAMD scores decreased significantly (*p* < 0.05) with no significant difference between the

TABLE 3. SCORES OF THE KEY ITEMS IN THE 24-ITEM HAMILTON DEPRESSION SCALE (HAMD)

Item	<i>GengNianLe</i> group (n = 21)		<i>Comparison (tibolone)</i> group (n = 26)	
	Baseline	Post-treatment	Baseline	Post-treatment
Depressed mood	3.4 ± 1.2	1.9 ± 0.5*	3.8 ± 1.2	2.2 ± 0.6*
Feelings of guilt	3.1 ± 0.5	1.9 ± 0.6*	3.2 ± 0.9	2.1 ± 0.6*
Suicide	2.9 ± 1.2	1.5 ± 0.5*	3.0 ± 1.1	1.9 ± 0.7*
Insomnia early	1.4 ± 0.2	0.7 ± 0.1*	1.7 ± 0.3	1.0 ± 0.3*
Insomnia middle	1.6 ± 0.4	0.7 ± 0.2*	1.4 ± 0.3	1.3 ± 0.2
Insomnia late	1.4 ± 0.6	1.3 ± 0.5	1.5 ± 0.5	1.3 ± 0.3
Work and activities	3.4 ± 1.1	3.1 ± 1.0	3.7 ± 1.2	2.8 ± 0.9*
Retardation: Psychomotor	3.0 ± 1.2	2.8 ± 0.7	3.2 ± 1.2	3.1 ± 0.7
Agitation	3.8 ± 1.2	3.5 ± 1.2	3.9 ± 1.5	3.2 ± 0.9*
Anxiety (Psychological)	3.3 ± 1.3	2.3 ± 0.5*	3.2 ± 0.7	2.5 ± 0.5*
Anxiety (Somatic)	3.9 ± 0.9	3.3 ± 0.6*	3.7 ± 1.0	3.5 ± 0.5
Gastrointestinal symptoms	1.9 ± 0.5	1.7 ± 0.3	1.8 ± 0.4	1.7 ± 0.4

\**p* < 0.05, compared with baseline in the same group.

groups ( $p > 0.05$ ) (Table 2). Among the twelve leading items in the HAMD, depressed mood, feelings of guilt, suicide, anxiety (psychological), and insomnia early were significantly relieved in both groups after treatment (Table 3). The symptoms of insomnia middle and anxiety (somatic) were significantly relieved only in the GNL group while, in the comparison group, work and activities and agitation were improved significantly.

#### *Serum levels of FSH, LH, and E<sub>2</sub>*

There were no significant differences between the two groups in the serum levels of FSH, LH, and E<sub>2</sub> at baseline. After treatment, the levels of FSH decreased significantly and the levels of E<sub>2</sub> increased significantly in both groups ( $p < 0.05$ ). The serum levels of FSH, LH, and E<sub>2</sub> changed more in the comparison group than in the GNL group ( $p < 0.05$ ).

#### *Adverse effects*

No side effects were reported in either group during the period of the research.

#### **Discussion**

The perimenopausal period is one of the most important stages in the female life cycle. Physical and mental symptoms are common in this stage due to the metabolic disturbance of hormones.<sup>48</sup> Mood changes make women seek medical care during the menopausal transition and over a third of women with depression experience their first episode of depression during the perimenopausal period.<sup>72</sup> Among women attending community or university menopause clinics, two-thirds of those at a London site and three-quarters of those at a San Diego site met criteria for recurrent major depression (beginning prior to perimenopause) when evaluated by a psychiatric interview.<sup>73</sup>

Transition to menopause and its changing hormonal milieu are strongly associated with new onset of low mood among women with no history of depression.<sup>9</sup> An association between estrogen activity and mood disturbance in women has been well established.<sup>74</sup> The effect of estrogen on mood is partly mediated by the hypothalamus.<sup>75</sup> Changes in estrogen levels have been found to affect the levels of dopamine and serotonin, which are both important mood-stabilizing neurotransmitters.<sup>64,65</sup> Estrogen affects the serotonin system through increasing the rate of degradation of monoamine oxidase.<sup>76,77</sup> Sudden estrogen withdrawal, fluctuating estrogen, and sustained estrogen deficit may induce mood disorders, including depression, in estrogen-sensitive women.<sup>78</sup> The serotonin-deficit hypothesis is the most prominent biological theory of the etiology of depression.<sup>66</sup> Estrogen has been found to stimulate a significant increase of the density of 5-hydroxytryptamine 3A binding sites in the areas of the brain concerned with the control of mood, mental state, cognition, emotion, and behavior. Estrogen was also found to modulate serotonergic function and thus mood.<sup>78</sup>

As the HPO axis remains intact during the menopausal transition, FSH levels rise in response to ovarian failure and the absence of negative feedback from the ovary.<sup>79</sup> Atresia of the follicular apparatus, in particular the granulosa cells, results in the reduced production of estrogen and inhibin, which leads to elevated FSH levels, a cardinal sign of meno-

pause.<sup>79</sup> Our research showed after twelve weeks of treatment both groups' HAMD scores decreased significantly ( $p < 0.05$ ) with no significant difference between groups ( $p > 0.05$ ). The levels of FSH decreased significantly and the level of E<sub>2</sub> increased significantly in both groups after treatment.

The lowered level of estrogen and the increased levels of FSH and LH are associated with depression during the menopausal transition;<sup>5,6</sup> it may be partly through increasing the level of E<sub>2</sub> and decreasing the levels of FSH that GNL alleviated perimenopausal depression. Further research should be conducted to address whether GNL has an effect on hormonal regulation or potentially addresses other mechanisms of depression. As the subjects were recruited from one hospital, it is unclear how well this relatively small sample represents the population of perimenopausal women with depression living in the region and/or seeking treatment for mood symptoms. Consequently, our results may be somewhat limited. Further research with larger samples from different hospitals should be conducted.

#### **Conclusions**

The Chinese medicinal formula GNL showed promise in relieving perimenopausal depression and merits further study.

#### **Acknowledgments**

The authors wish to thank the patients who participated in the study. Fan Qu was funded by the National Natural Science Foundation of China (No. 30800390), China Postdoctoral Science Foundation (No. 20070421188), Outstanding Young Medical Scientist Foundation of Zhejiang Province (No. 2008QN022), and Zhejiang TCM Foundation (No. 2008YB010).

#### **Disclosure Statement**

No competing financial interests exist.

#### **References**

- Schmidt PJ. Mood, depression, and reproductive hormones in the menopausal transition. *Am J Med* 2005;118:54–58.
- Maartens LW, Leusink GL, Knottnerus JA, et al. Climacteric complaints in the community. *Fam Pract* 2001;18:189–194.
- Avis NE, Brambilla D, McKinlay SM, Vass K. A longitudinal analysis of the association between menopause and depression: Results from the Massachusetts Women's Health Study. *Ann Epidemiol* 1994;4:214–220.
- Zhao G, Bao Y, Qu C. Occurrence of depression symptoms and their influence factors in perimenopausal women [in Chinese]. *Chin J Obstetr Gynec* 1996;31:614–616.
- Schmidt PJ, Haq N, Rubinow DR. A longitudinal evaluation of the relationship between reproductive status and mood in perimenopausal women. *Am J Psychiatry* 2004;161:2238–2244.
- Freeman EW, Sammel MD, Liu L. Hormones and menopausal status as predictors of depression in women in transition to menopause. *Arch Gen Psychiatry* 2004;61:62–70.
- Schmidt PJ, Murphy JH, Haq N, et al. Stressful life events, personal losses, and perimenopause-related depression. *Arch Womens Ment Health* 2004;7:19–26.
- Cohen L, Soares C, Vitonis A, et al. Risk for new onset of depression during the menopausal transition: The Harvard

- study of moods and cycles. *Arch Gen Psychiatry* 2006;63:385–390.
9. Freeman EW, Sammel MD, Lin H, Nelson DB. Associations of hormones and menopausal status with depressed mood in women with no history of depression. *Arch Gen Psychiatry* 2006;63:375–382.
  10. Woods NF, Mariella A, Mitchell ES. Patterns of depressed mood across the menopausal transition: Approaches to studying patterns in longitudinal data. *Acta Obstet Gynecol Scan* 2002;81:623–632.
  11. Cassem NH, Papakostas GI, Fava M, Stern TA. Mood-disordered patients. In: Stern T, Fricchione G, Cassem NH, eds. *Massachusetts General Hospital Handbook of General Hospital Psychiatry*. Philadelphia: Mosby, 2004:69–92.
  12. Joffe H, Soares CN, Cohen LS. Assessment and treatment of hot flushes and menopausal mood disturbance. *Psychiatr Clin North Am* 2003;26:563–580.
  13. Worthington JJ, Peters PM. Treatment of antidepressant-induced sexual dysfunction. *Drugs Today (Barc)* 2003;39:887–896.
  14. Morgan ML, Cook IA, Rapkin AJ, Leuchter AF. Neurophysiologic changes during estrogen augmentation in perimenopausal depression. *Maturitas* 2007;56:54–60.
  15. Morgan ML, Cook IA, Rapkin AJ, Leuchter AF. Estrogen augmentation of antidepressants in perimenopausal depression: A pilot study. *J Clin Psychiatry* 2005;66:774–780.
  16. Rasgon NL, Altshuler LL, Fairbanks LA, et al. Estrogen replacement therapy in the treatment of major depressive disorder in perimenopausal women. *J Clin Psychiatry* 2002;63:45–48.
  17. Soares CN, Poitras JR, Prouty J, et al. Efficacy of citalopram as a monotherapy or as an adjunctive treatment to estrogen therapy for perimenopausal and postmenopausal women with depression and vasomotor symptoms. *J Clin Psychiatry* 2003;64:473–479.
  18. Joffe H, Groninger H, Soares CN, et al. An open trial of mirtazapine in menopausal women with depression unresponsive to estrogen replacement therapy. *J Womens Health Gend Based Med*. 2001;10:999–1004.
  19. Amsterdam J, Garcia-Espana F, Fawcett J, et al. Fluoxetine efficacy in menopausal women with and without estrogen replacement. *J Affect Disord* 1999;55:11–17.
  20. Nagata H, Nozaki M, Nakano H. Short-term combinational therapy of low-dose estrogen with selective serotonin re-uptake inhibitor (fluvoxamine) for oophorectomized women with hot flashes and depressive tendencies. *J Obstet Gynaecol Res* 2005;31:107–114.
  21. Murakami S, Shirota T, Hayashi S, Ishizuka B. Aromatherapy for outpatients with menopausal symptoms in obstetrics and gynecology. *J Altern Complement Med* 2005;11:491–494.
  22. Lai JN, Hwang JS, Chen HJ, Wang JD. Finished herbal product as an alternative treatment for menopausal symptoms in climacteric women. *J Altern Complement Med* 2005;11:1075–1084.
  23. Smolinski D, Wollner D, Orłowski J, et al. A pilot study to examine a combination botanical for the treatment of menopausal symptoms. *J Altern Complement Med* 2005;11:483–489.
  24. Yao SA. Review on the research and development of Chinese medicine in menopausal syndrome [in Chinese]. *J Tradit Chin Med* 1994;35:112–114.
  25. Kronenberg F, Fugh-Berman A. Complementary and alternative medicine for menopausal symptoms: A review of randomized, controlled trials. *Ann Intern Med* 2002;137:805–813.
  26. Wiseman N, ed. *English-Chinese Chinese-English Dictionary of Chinese Medicine*. Changsha: Hunan Science and Technology Press, 2006.
  27. Notelovitz M. Postmenopausal tibolone therapy: Biologic principles and applied clinical practice. *MedGenMed* 2007;9:2. Online document at [www.medscape.com/viewarticle/548593](http://www.medscape.com/viewarticle/548593) Accessed November 8, 2008.
  28. Robb-Nicholson C. What's the latest on tibolone, the estrogen alternative? Online document at [www.health.harvard.edu/newsweek/Whats\\_the\\_latest\\_on\\_tibolone.htm](http://www.health.harvard.edu/newsweek/Whats_the_latest_on_tibolone.htm) Accessed November 7, 2008.
  29. Baksu A, Ayas B, Citak S, et al. Efficacy of tibolone and transdermal estrogen therapy on psychological symptoms in women following surgical menopause. *Int J Gynaecol Obstet* 2005;91:58–62.
  30. Kloosterboer HJ. Tibolone: A steroid with a tissue-specific mode of action. *J Steroid Biochem Mol Biol* 2001;76:231–238.
  31. Davis SR. The effects of tibolone on mood and libido. *Menopause* 2002;9:162–170.
  32. Genazzani AR, Petraglia F, Facchinetti F, et al. Effects of Org OD 14 on pituitary and peripheral endorphin in castrated rats and in postmenopausal women. *Maturitas* 1987;1:35–48.
  33. Kenemans P, Speroff L, International Tibolone Consensus Group. Tibolone: Clinical recommendations and practical guidelines. A report of the International Tibolone Consensus Group. *Maturitas* 2005;51:21–28.
  34. Egarter C, Huber J, Leikermoser R, et al. Tibolone versus conjugated estrogens and sequential progestogen in the treatment of climacteric complaints. *Maturitas* 1996;23:55–62.
  35. Huber J, Palacios S, Berglund L, et al. The effect of tibolone compared with conjugated equine oestrogens continuously combined with medroxyprogesterone acetate on bleeding rates, quality of life and tolerability in postmenopausal women. *Br J Obstet Gynaecol* 2002;109:886–893.
  36. Roux C, Pelissier C, Fechtenbaum J, et al. Randomized, double-blind, 2-year comparison of tibolone with 17-estradiol and norethindrone acetate in preventing postmenopausal bone loss. *Osteoporosis Int* 2002;13:241–248.
  37. Lundström E, Christow A, Svane G, et al. Effects of tibolone and a continuous combined HRT regimen on mammographic breast density. *Am J Obstet Gynecol* 2002;186:717–722.
  38. Valdivia I, Campodonico I, Tapia A, et al. Effects of tibolone and continuous combined hormone therapy on mammographic breast density and breast histochemical markers in postmenopausal women. *Fertil Steril* 2004;81:617–623.
  39. Conner P, Christow A, Kersemaekerc W. A comparative study of breast cell proliferation during hormone replacement therapy: Effect of tibolone and continuous combined estrogen progestogen therapy. *Climacteric* 2004;7:50–58.
  40. Dören M, Rübiger A, Coelingh Bennink HJT, Holzgreve W. Impact on uterine bleeding and endometrial thickness: Tibolone compared with continuous combined estradiol and norethisterone acetate replacement therapy. *Menopause* 1999;6:299–306.
  41. Völker W, Coelingh Bennink HJT, Helmond FA. Effects of tibolone on the endometrium. *Climacteric* 2001;4:203–208.
  42. Wender MC, Edelweiss MI, Campos LS, et al. Endometrial assessment in women using tibolone or placebo: 1-year randomized trial and 2-year observational study. *Menopause* 2004;11:423–429.

43. Haenggi W, Bersinger N, Altermatt HJ, Birkhäuser MH. Comparison of transvaginal ultrasonography and endometrial biopsy in endometrial surveillance in postmenopausal hormone replacement therapy users. *Maturitas* 1997;27:133–143.
44. Fedele L, Bianchi S, Raffaelli R, Zanconato G. A randomized study of the effects of tibolone and transdermal estrogen replacement therapy in postmenopausal women with uterine myomas. *Eur J Obstet Gynecol Reprod Biol* 2000;88:91–94.
45. Egarter C, Sator M, Berghammer P, Huber J. Efficacy, tolerability, and rare side effects of tibolone treatment in postmenopausal women. *Int J Gynaecol Obstet* 1999;64:281–286.
46. Haenggi W, Lippuner K, Jaeger P, et al. Differential impact of conventional oral or transdermal hormone replacement therapy or tibolone on body composition in postmenopausal women. *Clin Endocrinol* 1998;48:691–699.
47. Meeuwssen IB, Samson MM, Duursma SA, Verhaar HJ. The effect of tibolone on fat mass, fat-free mass, and total body water in postmenopausal women. *Endocrinology* 2001;142:4813–4817.
48. Katz VL, Lentz GM, Lobo RA, Gershenson DM, eds. *Comprehensive Gynecology*. Philadelphia: Mosby Elsevier, 2007.
49. Cummings SR, Ettinger B, Delmas PD, et al. The effects of tibolone in older postmenopausal women. *N Engl J Med* 2008;359:697–708.
50. Kuhl H, Wiegatz I. Can 19-nortestosterone derivatives be aromatized in the liver of adult humans? Are there clinical implications? *Climacteric* 2007;10:344–353.
51. Sundar SS, Gornall RJ, Kerr-Wilson R, et al. A case report of recurrent endometriosis following tibolone hormone replacement therapy. *J Obstet Gynaecol* 2007;27:433–434.
52. Beral V, Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2003;362:419–427.
53. Cao BZ, ed. *Great Compendium of Chinese Ancient Medical Classics*. Beijing: China Press of Traditional Chinese Medicine, 1997.
54. *Chinese Materia Medica*. Shanghai: Shanghai Press of Science and Technology, 1999.
55. Lei ZQ, ed. *Chinese Herbal Medicine*. Shanghai: Shanghai Press of Science and Technology, 1994.
56. Wang BX, ed. *Modern Pharmacology and Clinical Practice of Chinese Medicine*. Tianjin: Tianjin Company of Scientific and Technologic Translation, 2004.
57. Xiao PG, ed. *Modern Chinese Materia Medica*. Beijing: The Chemical Industry Press, 2007.
58. Saito K, Umeda S, Kawashima K, Kano Y. Effects of Sansohnin-to on pentobarbital sleep in stressed mice. *Bio Pharm Bull* 2000;23:76–79.
59. Shiyi L. Some basic features of the new sleep-aid tea (SAT) for the treatment of insomnia. *Sleep Res Online* 2000;3:49–52.
60. Choi EM, Koo SJ, Hwang JK. Immune cell stimulating activity of mucopolysaccharide isolated from yam (*Dioscorea batatas*). *J Ethnopharmacol* 2004;91:1–6.
61. Wang XM, Fu H, Liu GX. Effect of Wuzi Yanzong pill and its disassembled prescription on mitochondrial DNA deletion, respiratory chain complexes and ATP synthesis in aged rats [in Chinese]. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 2001;21:437–440.
62. Zhang H, Han T, Zhang L, et al. Effects of tenuifolin extracted from radix polygalae on learning and memory: A behavioral and biochemical study on aged and amnesic mice. *Phytomedicine* 2008;15:587–594.
63. Hao SC, Bi P, Yu K, et al. Electron microscopic studies on the effect of *Frutus Ligustri Lucidi* on the corticotrophs of rat hypophyses [in Chinese]. *J Tianjin Normal University* 1997;17:4952.
64. Peng N, Clark JT, Wei CC, Wyss JM. Estrogen depletion increases blood pressure and hypothalamic norepinephrine in middle-aged spontaneously hypertensive rats. *Hypertension* 2003;41:1164–1167.
65. Moses EL, Drevets WC, Smith C, et al. Effects of estradiol and progesterone administration on human serotonin 2A receptor binding: A PET study. *Biol Psychiatry* 2000;48:854–860.
66. Sherwin BB. Estrogen function in women. *Endocr Rev* 2003;24:133–151.
67. Wissink S, van der Burg B, Katzenellenbogen NB, van der Saag PT. Synergistic activation of the serotonin-1A receptor by nuclear factor-kappa B and estrogen. *Mol Endocrinol* 2001;15:543–552.
68. Sun QX. The effects of Chinese medicinal herbs on the hypothalamic-pituitary-ovarian axis: A review [in Chinese]. *Li Shizhen Med Mater Med Res* 2005;16:1297–1298.
69. He JQ, Tang XW, Chen HX, Xing ZQ. Study on treatment of climacteric depression with bushen tiaogan qingxin recipe [in Chinese]. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 2004;24:889–892.
70. Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol* 1967;6:278–296.
71. Mulsant BH, Sweet RA, Rifai AH, et al. The use of the Hamilton Rating Scale for Depression in elderly patients with cognitive impairment and physical illness. *Am J Geriatr Psychiatry* 1994;2:220–229.
72. Kornstein SG, Clayton AH, eds. *Women's Mental Health: A Comprehensive Textbook*. New York: Guilford, 2002.
73. Tam LW, Stucky V, Hanson RE, Parry BL. Prevalence of depression in menopause: A pilot study. *Arch Womens Ment Health* 1999;2:175–181.
74. Douma SL, Husband C, O'Donnell ME, et al. Estrogen-related mood disorders: Reproductive life cycle factors. *ANS Adv Nurs Sci* 2005;28:364–375.
75. Ostland H, Keller E, Hurd YL. Estrogen receptor gene expression in relation to neuropsychiatric disorders. *Ann N Y Acad Sci* 2003;1007:54–63.
76. Luin VN, Khlicheoskaya RI, Mcewen BS. Effects of gonadal steroids on activities of monamine oxidase and choline acetylase in rat brains. *Brain Res* 1975;86:273–306.
77. Lindsay R, Dempster DW, Jordan VC, eds. *Estrogens and Antiestrogens*. Philadelphia: Lippincott-Raven, 1997.
78. Arpels JC. The female brain hypoestrogenic continuum from the premenstrual syndrome to menopause: A hypothesis and review of supporting data. *J Reprod Med* 1996;41:633–639.
79. Berek JS, ed. *Berek & Novak's Gynecology*. Philadelphia: Lippincott Williams & Wilkins, 2007.

Address reprint requests to:

Hefeng Huang, M.D.

Women's Hospital, School of Medicine

Zhejiang University

No. 2 on Xueshi Road

Hangzhou, Zhejiang 310006

China

E-mail: huanghefg@hotmail.com