Randomized controlled trial of cognitive behavioural therapy for depressive and anxiety symptoms in Chinese women with breast cancer

Wenwei Ren[a,1], Huihua Qiu[a,1], Yanjie Yang[c], Xiongzhao Zhu[d], Chunyan Zhu[e], Guangyun Mao[f], Shanping Mao[g], Yan Lin[h], Shanshan Shen[i], Changjin Li[j], Xiaodan Xie[j], Hongying Shi[f], Suo Jiang[j], Ke Zhao[j], Li Chen[j], Jingjing He[k], Liuxiu Xu[l], Ye Fu[m], Xiaoqu Hu[n], Yiqun Yu[n], Yingying Gu[a], Kai Wang[e], Xiuchan Guo[b,**], Jincai He[a,j,*]

[a] Department of Neurology, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou 325000, China
[b] Key Laboratory of Laboratory Medicine, School of Laboratory Medicine and Life Science, Wenzhou Medical University, Wenzhou 325000, China
[c] Department of Medical Psychology, Public Health Institute of Harbin Medical University, Harbin 150081, China
[d] Medical Psychological Institute, Second Xiangya Hospital, Central South University, Changsha 410012, China
[e] Department of Psychiatry, the First Affiliated Hospital of Anhui Medical University, Hefei 230601, China
[f] Department of Preventive Medicine, Wenzhou Medical University, Wenzhou 325000, China
[g] Department of Neurology, Renmin Hospital of Wuhan University, Wuhan 430000, China
[h] Department of Neurology, the Second Affiliated Hospital of Wenzhou Medical University, Wenzhou 325000, China
[i] Department of Geriatrics, Zhejiang Hospital, Hangzhou 310013, China
[j] Department of Psychology, Wenzhou Medical University, Wenzhou 325000, China
[k] Department of Psychiatry, Tongde Hospital of Zhejiang Province, Hangzhou 310012, China
[l] Department of Psychiatry, Dujiangyan Third People's Hospital, Sichuan 611800, China
[m] Yinzhou Hospital Affiliated To Medical School of Ningbo University, Ningbo 315175, China
[n] Department of Oncology, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou 325000, China

ARTICLE INFO

ABSTRACT

Depressive and anxiety symptoms are frequently observed in breast cancer survivors. To date, few randomized controlled trials have been conducted on the efficacy of cognitive behavioural therapy (CBT) for depressive and anxiety symptoms in Chinese population. This study aims to verify the efficacy of CBT in Chinese breast cancer survivors. Women ($n = 392$) with breast cancer were randomly assigned to 3 groups: CBT ($n = 98$), self-care management (SCM, $n = 98$), and usual care (UC, $n = 196$) using the proportion 1:1:2. Women in the CBT and SCM groups received a series of nine sessions for 12 weeks, while women in the UC group received their usual medical care only. Depressive and anxiety symptoms were assessed using the Hamilton Depression Rating Scale (HAMD) and the Hamilton Anxiety Scale (HAMA) score at baseline, 2, 4, 8, 12, 16, and 24 weeks. A significant intergroup difference was found in the HAMD and HAMA scores. Women in the CBT group showed significantly less depressive and anxiety symptoms compared with women in the SCM and UC groups over time. In conclusion, this study supports the efficacy of CBT for depressive and anxiety symptoms in Chinese breast cancer survivors.

1. Introduction

Breast cancer is currently a worldwide disease and is the most common type of cancer and the primary cause of cancer death in females (DeSantis et al., 2017). Despite the fact that the incidence rate of breast cancer in Asia is currently lower than that in Western countries, Asian countries such as China have witnessed a rapid increase in the incidence of breast cancer in recent years. Breast cancer is currently

the most common cancer in Chinese women; cases in China account for 12.2% of all newly diagnosed breast cancer patients as well as 9.6% of all deaths from breast cancer worldwide (Fan et al., 2014). Earlier diagnosis and advances in adjuvant treatments, such as chemotherapy and endocrine therapy, have resulted in an increasing number of breast cancer survivors who are able to survive five years or more. Unfortunately, long-term side effects of cancer treatments contribute to poor quality of life of breast cancer survivors (Han and Choi, 2018), which might make breast cancer survivors vulnerable to more psychological symptoms (Chang et al., 2015). In China, approximately 42% of breast cancer survivors experience moderate to severe psychological morbidity after surgery (Lam et al., 2005). Additionally, mortality rates were up to 25% higher in patients experiencing depressive symptoms and were up to 39% higher in patients diagnosed with major or minor depression (Satin et al., 2009). In addition, a recent study showed that women with improving depressive symptoms had longer survival times (Giese-Davis et al., 2011). Therefore, it is important to take measures to improve breast cancer patients' mental health.

Pharmacological treatment with antidepressants may improve depressive symptoms and quality of life. However, the evidence for this in breast cancer patients is limited and is inconsistent in different studies (Toftegard Andersen et al., 2013). Some selective serotonin reuptake inhibitors might reduce the effectiveness of endocrine treatments due to the interference with tamoxifen, a drug applied in the treatment of hormone receptor-positive breast cancers (Breitbart, 2011; Kelly et al., 2010). Consequently, there is a growing need to develop an acceptable, effective and safe treatment for breast cancer patients with depression and anxiety. Cognitive behavioural therapy (CBT) has also been previously proven to be an effective psychotherapy for depression and anxiety (Gazal et al., 2013; Iftene et al., 2015; Oei and McAlinden, 2014). However, studies focusing on the impact of CBT on breast cancer patients' depression and anxiety symptoms in the Chinese population are limited. Additionally, according to a multicentre study based on a large population (Sivasubramaniam et al., 2015), compared to American women, Chinese women were diagnosed with breast cancer at younger ages, with higher stages and larger tumours and undergoing more aggressive surgical treatment, which may exert more severe psychosocial impacts on Chinese women and may predispose them to vulnerability to depressive and anxiety symptoms. Besides, in China, compared to Western countries, nonpharmacological management such as psychotherapy is still not widely available, and few people seek psychological help voluntarily to solve their problems, partly due to the differences in culture and in social-economic structures (Furnham and Chan, 2004; Yang et al., 2007).

Self-care management (SCM) can empower cancer survivors, can increase survivor confidence to manage problems associated with cancer and its treatment, and can enhance physical and psychological functioning (Linder et al., 2017; Primeau et al., 2017). However, estimates of the effects of SCM on cancer survivors are inconsistent (Foster et al., 2016). In this study, SCM is designed as an attention control, and the effects of CBT versus SCM on depression and anxiety symptoms are explored.

A well-designed multicentre randomized controlled trial (RCT) was conducted among Chinese women with breast cancer to investigate the efficacy of CBT for breast cancer patients with depression and anxiety symptoms compared with SCM and usual care (UC). We hypothesized that participants in the CBT group would demonstrate greater improvement in depressive and anxiety symptoms compared with those in the SCM group and in the UC group.

2. Methods

2.1. Participants

The participants were screened in outpatient clinics and inpatient departments by physician referrals from six centres: 1. The First

Affiliated Hospital of Wenzhou Medical University ($n = 74$); 2. The Second Affiliated Hospital of Wenzhou Medical University ($n = 40$); 3. The First Affiliated Hospital of Anhui Medical University ($n = 64$); 4. The Second Xiangya Hospital of Central South University ($n = 64$); 5. Harbin Medical University ($n = 94$); 6. Renmin Hospital of Wuhan University ($n = 56$). Before recruitment, the participants were invited to have a clinical interview with their physicians and their clinical data were collected. Afterwards, they were recommended to trained psychiatrists for evaluation of depressive and anxiety symptoms. Participants were recruited if they: (1) were women diagnosed with breast cancer; (2) had symptoms of depression and/or anxiety, as defined by the Chinese version of the 17-item Hamilton Depression Rating Scale (HAMD-17) (Zheng et al., 1988) score ≥ 8, and/or the Chinese version of the 14-item Hamilton anxiety scale (HAMA-14) (Zhang, 1989) score ≥ 8; (3) were 20–65 years old; (4) had undergone a radical mastectomy 1 week to 1 year prior to the study; and (5) were able to read Chinese and were competent to consent to participate in the research. Participants with serious diseases such as cardiovascular, liver or kidney diseases as well as those with severe visual or auditory impairments and active alcohol or drug abuse were excluded. Additionally, participants with suicidal tendencies were excluded. Participants with previous diagnosis of mental disorder or bipolar disorder or who had recently accepted antidepressants or antipsychotics, as well as those who had participated in any psychological treatments or clinical trials within one month before the screening, were also excluded. In addition, participants with a HAMD-17 score ≥ 24 and considered by the researchers to be unfit for the trial were also excluded.

The study was approved by the Human Research and Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University and registered with ClinicalTrials.gov, number NCT01256008. All the participants in the research received and signed an informed consent disclaimer.

2.2. Measures

2.2.1. Depressive symptoms

Depressive symptoms were evaluated by trained psychiatrists at baseline, 2, 4, 8, 12, 16 and 24 weeks using the Chinese version of the 17-item Hamilton Depression Rating Scale (HAMD-17), which has been validated for use in China (Zheng et al., 1988). Participants with a HAMD-17 score of ≥ 8 were considered to have existing depressive symptoms, with higher scores indicating higher symptom levels. Depressive symptom severity was classified using the following severity range for the HAMD score: normal (0–7), mild depression (8–16), moderate depression (17–23), and severe depression (≥ 24) (Zimmerman et al., 2013).

2.2.2. Anxiety symptoms

Anxiety symptoms were evaluated by trained psychiatrists at baseline, 2, 4, 8, 12, 16 and 24 weeks using the Chinese version of the 14-item Hamilton anxiety scale (HAMA-14), which has been validated for use in China (Bai et al., 2016; Zhang, 1989). Participants with a HAMA-14 score of ≥ 8 were considered to have existing anxiety symptoms, with higher scores indicating higher levels. Anxiety symptom severity was classified by the following severity range for the HAMA score: normal (0–7), mild or probable anxiety (8–14), moderate or definite anxiety (15–21), and severe anxiety (≥ 22) (Bai et al., 2016).

2.3. Procedures

Before the intervention, all the evaluators and therapists completed a rigorous unified training to ensure compliance with the Standard Operation Procedure (SOP) to preserve the quality of the study. The randomization was stratified by centre. A monitor was assigned in each sub-centre to check the schedules and the operation procedure monthly.

Two prime monitors were delegated by the principal investigator (PI) to inspect the case report form, the research progress, the operation procedure in the sub-centres, and problems, if any, were fed back to the PI, who then contacted the sub-centre PI to address the problems. Two trained therapists were assigned to each centre to conduct the CBT or SCM separately. The therapists, blind to the outcome data and the study hypotheses, provided the treatment conditions to avoid contamination. To assure protocol adherence, we recorded sessions and scripts. We randomly selected and evaluated the fidelity of 20% of the recordings and gave feedback to the therapists. Power analyses based on the sample size showed that the study retained 90% power to identify the effect sizes, with an α of 0.05.

Demographic data were obtained through the participants' self-reports. The clinical data were abstracted from the medical records, the surgical records and the participants' self-reports. The participants were randomly assigned to 3 different groups: CBT ($n = 98$), SCM ($n = 98$), and UC ($n = 196$) groups with a proportion of 1:1:2. The participants were allocated to CBT, SCM or UC by picking an envelope that contained random numbers corresponding to the assigned group. The primary investigators and evaluators were kept blind to the allocation. It was impossible to blind the participants, but they did not know the group assignments until the first meeting.

CBT was psycho-educational, structured, and interactive, with presentations, group discussions, handouts, and weekly homework assignments. Nine standardized sessions were designed for the participants randomized to CBT, and 6 to 8 participants were included in each session. CBT focused on teaching the participants how to identify, dispute, and replace unhelpful beliefs based on an ABC framework (David et al., 2002), where the event was represented by the letter A (activating event or adversity), the beliefs were represented by the letter B, and the emotions and behaviours were represented by the letter C (consequences). The participants were introduced to the idea that it is not outside events (A) that cause their dysfunctional reactions (C) but their irrational beliefs (B); thus, they are in control of how they respond to negative events because they can have autonomy over their beliefs. According to the manual codified by Aaron T. Beck (Allen, 2002), the sessions were specifically designed according to the psychological characteristics of breast cancer survivors. The therapist taught participants behavioural strategies to manage distress (e.g., meditation, distraction strategies, and activity scheduling). The therapist also taught participants the use of emotional regulation, social skills, and some psychological techniques. During the final session, the therapist worked with participants to review and summarize what had been learned during the intervention and to share individual maintenance plans. The participants who completed the sessions were then invited for follow-up interviews at intervals of 4 and 12 weeks after the final session. In addition, the participants in the CBT group also received their usual medical care throughout the duration of the study.

SCM was designed to control for the effects of treatment expectations and professional attention, notably, the potential effects of simply interacting with the therapist. The protocol was developed and modified based on the one used by the National Institute of Mental Health Treatment of Depression Collaborative Research Program (Fawcett et al., 1987) and the University of Pittsburgh's late-life depression studies (MD. et al., 1998). SCM also contained nine sessions for 12 weeks, and 6–8 participants were included in each session. The therapist did not teach the participants specific cognitive behavioural therapy techniques such as imagery, relaxation, or evaluation of thought processes. The therapist focused only on the SCM structured protocol content in each session, such as the introduction of breast cancer treatments, diet after surgery, the rehabilitation training, and how to address complications. The sessions focused on discussing the participants' reactions and questions. In addition, the therapist asked general questions about the participant's recovery and complications. The participants who completed the sessions were then invited for follow-up interviews at intervals of 4 and 12 weeks after the final

session. The participants in SCM also received their usual medical care throughout the duration of the study.

The participants in the UC group received usual medical care only, carried out by nurses who were professionally trained. UC was designed to evaluate the effect of CBT and SCM.

2.4. Statistical analysis

Categorical variables were compared using the chi-squared test, while one-way ANOVA or the Kruskal–Wallis test were used to compare continuous variables among groups, as appropriate. Fisher's exact test was used for categorical variables in the cases where the assumptions underlying the chi-squared test were not fulfilled. When the ANOVA showed significant differences among the groups, the *post hoc* Tukey test was used to assess differences in two-group comparisons. Bonferroni corrections were applied to each test to adjust for multiple testing. According to the intention-to-treat principle, a full analysis set (FAS) was established to be emphatically analysed, the result of which proved to be consistent with the Per Protocol Set (PPS). Missing data were addressed by using the last-observation-carried-forward (LOCF) approach.

The changes in the HAMD and HAMA scores throughout the 24 weeks were analysed using the repeated measures analysis of variance (RM-ANOVA), with the baseline HAMD and HAMA scores being the covariates. Partial eta squared (ηp^2) was used in the RM-ANOVA to present effect sizes with 0.01–0.06, 0.06–0.14, and 0.14 or higher corresponding to small, moderate, and large effect sizes, respectively (Sockloff, 1978).

The statistical tests were performed in IBM SPSS 19.0. Two-tailed tests were used with alpha set at 0.05.

3. Results

3.1. Enrolment and participant characteristics

Fig. 1 shows the flow of participants throughout the course of the study. A total of 909 individuals were screened and 493 individuals were eligible, with 392 finally enrolled. Thus, the remaining 392 participants were randomly assigned to 3 different groups: CBT ($n = 98$), SCM ($n = 98$), and UC ($n = 196$) with a proportion of 1:1:2.

As shown in Table 1, there were no significant intergroup differences among three groups in terms of baseline characteristics, such as age ($p = 0.93$), time since surgery ($p = 0.11$), cancer stage at diagnosis ($p = 0.09$), hormone therapy ($p = 1.00$), radiation therapy ($p = 0.37$) and chemotherapy ($p = 0.73$). No intergroup differences were found in baseline characteristics, except the baseline HAMD and HAMA scores ($p < 0.01$), for which they were included as the covariates in the following RM-ANOVA. At baseline, the mean HAMA and HAMD scores in each group were beyond the cut-off (a HAMD and/or HAMA score of 8). In addition, CBT participants had higher mean HAMD and HAMA scores than those in the SCM and UC groups at baseline (both $p < 0.01$).

3.2. Effect of CBT and SCM on depressive symptoms

According to the results of RM-ANOVA, after adjustment for the baseline HAMD and HAMA scores, the three groups showed a downward trend over time in terms of the HAMD score (Fig. 2). Besides, the effect of CBT was maintained after its termination (12 weeks). Additionally, as Table 2 demonstrates, a significant intergroup difference in HAMD score was found ($p < 0.01$), with a large effect size ($\eta p^2 = 0.201$). Moreover, the HAMD score in the CBT group was significantly lower compared to that in the SCM and UC groups ($p < 0.01$). In addition, the HAMD score in the SCM group was significantly lower compared to that in the UC group.

A significant main effect of time for change in the HAMD score was also found ($p < 0.001$), with a large effect size ($\eta p^2 = 0.701$). The
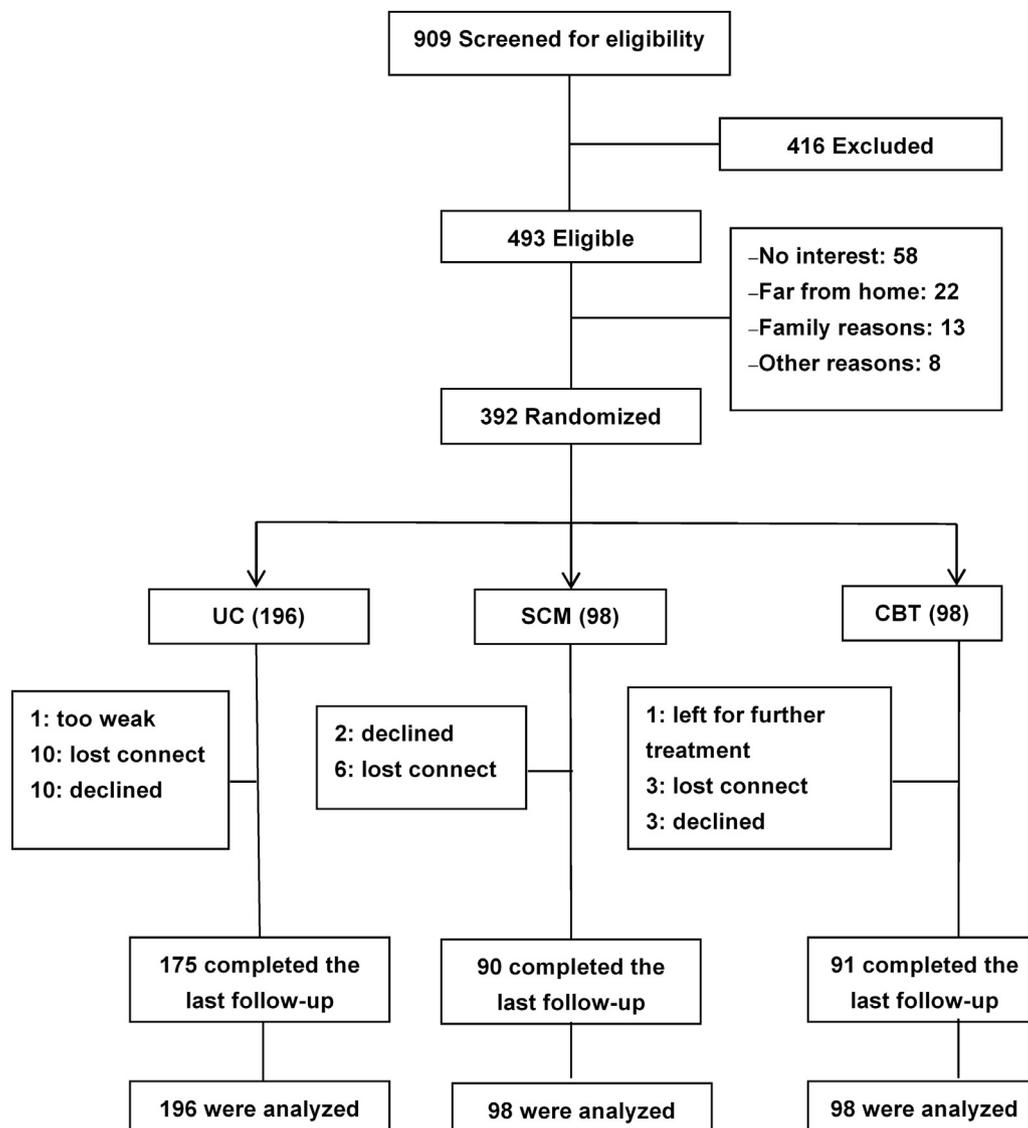
Fig. 1. Flow chart of participants through the randomized trial. CBT (cognitive behavioural therapy), SCM (self-care management), UC (usual care).

group by time interaction was significant for the HAMD score as well ($p < 0.001$), with a large effect size ($\eta p^2 = 0.141$). The group by time interaction was significant for the HAMD score as well ($p < 0.001$), with a large effect size ($\eta p^2 = 0.141$). At the 12-week follow-up (the end of intervention), the mean HAMD score in the CBT group was significantly lower compared to that in the SCM and UC groups (both $p < 0.01$). At the end of the intervention, only the CBT group had mean HAMD scores that were below the cut-off (a HAMD score of 8), while the mean HAMD scores in the SCM and UC groups still approached the cut-off (Table 3). In addition, the decrease in HAMD scores in CBT was faster and larger than those of SCM and UC during the follow-up period (Fig. 2).

3.3. Effect of CBT and SCM on anxiety symptoms

According to the results of RM-ANOVA, after adjustment for the baseline HAMD and HAMA scores, the three groups showed a downward trend over time in the HAMA score (Fig. 3). Meanwhile, the effect of CBT was maintained after its termination. As Table 2 demonstrates, a significant intergroup difference in HAMA score was found ($p < 0.01$), with a large effect size ($\eta p^2 = 0.173$). Moreover, the HAMA score in the CBT group was significantly lower compared to that in the SCM and UC groups ($p < 0.01$). However, although the adjusted mean HAMA score

in the SCM group remained lower than that in the UC group by the last follow-up (Fig. 3), the difference was not statistically significant.

A significant main effect of time for change in the HAMA score was also found ($p < 0.001$), with a large effect size ($\eta p^2 = 0.708$). The group by time interaction was significant for the HAMA score as well ($p < 0.001$), with a moderate effect size ($\eta p^2 = 0.092$). At the end of the intervention, the mean HAMA score in the CBT group was also significantly lower compared to that in the SCM and UC groups (both $p < 0.01$). At the end of the intervention, the mean HAMA score in the CBT group was below the cut-off (a HAMA score of 8), while the mean HAMA scores in the SCM and UC groups still approached the cut-off (Table 3). Besides, the decrease in HAMA scores in the CBT group was faster and larger than that of the SCM and UC groups during the follow-up period (Fig. 3).

4. Discussion

To our knowledge, our results extended previous Western studies by highlighting the efficacy of CBT on breast cancer survivors facing depressive or anxiety symptoms in the Chinese population.

Previous research has proved the efficacy of CBT for the management of depression and anxiety. For example, CBT had been successfully applied in improving depressive and anxiety symptoms

Table 1
Demographic, lifestyle and clinical characteristics at baseline for three groups.

Characteristic	CBT (n = 98)	SCM (n = 98)	UC (n = 196)	p
Age, mean (SD)	46.8 (8.9)	47.3 (8.7)	47.1 (8.3)	0.93
Height, mean, cm	159.9 (5.1)	159.7 (4.7)	160.1 (5.3)	0.81
Weight, mean, kg	58.3 (8.7)	59.8 (7.5)	57.5 (8.4)	0.08
Education, mean (SD), year	9.4 (3.1)	8.97 (4.0)	8.73 (3.4)	0.30
Residence (%)				0.25
urban	73 (74.5)	71 (72.4)	129 (65.8)	
suburban	25 (25.5)	27 (27.6)	67 (34.2)	
Monthly family income (%)				0.36
≤ 1000 RMB	5 (5.1)	10 (10.2)	11 (5.6)	
1001–3000 RMB	35 (35.7)	34 (34.7)	86 (43.9)	
3001–5000 RMB	35 (35.7)	28 (28.6)	61 (31.1)	
5001–10,000 RMB	18 (18.4)	20 (20.4)	35 (17.9)	
> 10,000 RMB	5 (5.1)	6 (6.1)	3 (1.5)	
Marital status (%)				0.62
Single	6 (6.1)	3 (3.1)	10 (5.1)	
Married/partner	92 (93.9)	95 (96.9)	186 (94.9)	
Club (%)				0.94
Attendant	3 (3.1)	4 (4.1)	9 (4.6)	
Non-attendant	93 (96.9)	93 (95.9)	185 (95.4)	
Religion (%)				0.94
Religious	21 (21.4)	21 (21.4)	45 (23)	
Non-religious	77 (78.6)	77 (78.6)	151 (77)	
Sexual life (%)				0.85
Yes	71 (73.2)	74 (76.3)	144 (73.5)	
No	26 (26.8)	23 (23.7)	52 (26.5)	
Smoking (%)				0.15
Smoker	4 (4.1)	2 (2)	14 (7.1)	
Non-smoker	94 (95.9)	96 (98)	182 (92.9)	
Drinking (%)				0.16
Drinker	12 (12.2)	5 (5.1)	23 (11.7)	
Non-drinker	86 (87.8)	93 (94.9)	173 (88.3)	
Time since surgery, median (IQR), months	2.91 (0.33–4.40)	2.88 (0.28–3.75)	3.10 (0.33–5.83)	0.11
Cancer stage at diagnosis (%)				0.09
I	28 (28.6)	20 (20.4)	38 (19.4)	
II	45 (45.9)	61 (62.2)	111 (56.6)	
III	14 (14.3)	10 (10.2)	36 (18.4)	
Unknown	11 (11.2)	7 (7.1)	11 (5.6)	
Receiving hormone therapy (%)				1.00
Yes	7 (7.1)	7 (7.1)	14 (7.1)	
No	91 (92.9)	91 (92.9)	182 (92.9)	
Receiving radiation therapy (%)				0.37
Yes	11 (11.2)	14 (14.3)	34 (17.3)	
No	87 (88.8)	84 (85.7)	162 (82.7)	
Receiving chemotherapy (%)				0.73
Yes	71 (72.4)	75 (76.5)	142 (72.4)	
No	27 (27.6)	23 (23.5)	54 (27.6)	
HAMA score, mean (SD)	13.3 (5.1)[a,b]	11.5 (3.8)	11.0 (3.8)	<0.01
HAMD score, mean (SD)	13.4 (4.9)[a,b]	12.1 (3.2) 11.4 (2.7)		<0.01

Abbreviations: CBT, cognitive behavioural therapy; IQR, interquartile range; SCM, self-care management; UC: usual care; SD, standard deviation; HAMD: Hamilton depression rating scale; HAMA: Hamilton anxiety scale.

[a] p < 0.05 compared SCM
[b] p < 0.05 compared to UC.

accompanying other diseases such as Parkinson's disease and diabetes (Dobkin et al., 2011; Safren et al., 2014). In addition, recent studies focusing on the neural mechanisms of CBT indicated that CBT could affect limbic and prefrontal circuitry thus improving the patients' emotional responses (Rubin-Falcone et al., 2018; Young et al., 2017). In our research, CBT effectively improved breast cancer survivors' depressive and anxiety symptoms by the last follow-up. Before the intervention, both the average levels of the HAMD and HAMA scores in each group approached the cut-off (a score of 8), indicating existing depressive symptoms and anxiety symptoms. Meanwhile, CBT participants were more depressed and anxious than those in the SCM and UC groups at baseline. However, at the end of the intervention, the mean HAMD and HAMA scores in the CBT group were below the cut-off (a score of 8), while the mean HAMD and HAMA scores in the SCM and UC groups still approached the cut-off, which indicated that the decrease in depressive symptoms and anxiety symptoms in CBT happened faster than in SCM and UC during the intervention. Moreover, the decrease in depressive symptoms and anxiety symptoms in CBT was larger compared to that of the SCM and UC groups during the follow-up period. Furthermore, the effect of CBT was maintained after its termination, which was also observed in relevant studies (Mohr et al., 2012; Qiu et al., 2013). Nevertheless, a longer follow-up is still needed to study the long-term efficacy of CBT. In addition, whether less-frequent CBT would be equally effective is not known and deserves further research.

In fact, several previous investigations have showed the advantages of CBT compared to usual care in improving breast cancer survivors' psychological symptoms (Mann et al., 2011; Mann et al., 2012). However, "usual care" cannot exactly exclude the placebo effect of additional clinical monitoring and the support of CBT, which may play an active role in improving patients' depressive or anxiety symptoms. Different types of control conditions are needed to perfect the design. Thus, SCM was cautiously selected as a comparison to CBT in this trial. In this study, SCM participants showed significantly decreased depressive symptoms compared to the UC group, which indicated that the additional clinical supervision and support provided to participants had an impact on depressive symptoms. This result is in line with a recent study, supporting the efficacy of self-care management for breast cancer survivors (Shahsavari et al., 2015). In addition, SCM also demonstrated a greater improvement in anxiety symptoms compared to UC, although the improvement was not statistically significant. However, CBT was superior to SCM in reducing the depressive and anxiety symptoms in this study, which highlighted the efficacy of the CBT protocol when treating breast cancer survivors with depressive and anxiety symptoms.

In addition, we also found a decrease in depressive and anxiety symptoms over time in the UC group, which was also observed in previous studies (Compas et al., 1999; Goldberg et al., 1992). Two assumptions are displayed here: (1) increased social support over time is related to decreasing emotional problems (Clough-Gorr et al., 2007; Gorman et al., 2010); and (2) the stigma associated with breast cancer may have decreased over time and the diagnosis may be less likely to provoke distress (Burgess et al., 2005).

This study is characterized by several strengths. First, six centres across China were selected, and 392 patients were enrolled, which made conclusions of the trial more convincing. Second, the timing of carrying out the intervention was taken into account. Overall, the majority of interventions in previous trials are conducted after the initial diagnosis or treatment. However, as indicated, patients encountered many problems, such as those associated with body image, sexual problems and pain after surgery (Burwell et al., 2006; Fobair et al., 2006; Jung et al., 2003); the risk for depression within the first year is two-fold higher than that in more than one year after surgery (Qiu et al., 2012). Furthermore, a study in China showed that Chinese women experienced considerable psychological morbidity, with 50% experiencing moderate-to-severe distress one month after surgery (Lam et al., 2005). The increased level of depression or anxiety and the lower quality of life after breast cancer surgery highlights the need for psychological support during this time. Therefore, the present intervention was conducted and evaluated primarily on patients who had finished surgery within the preceding year. Finally, this multicentre randomized controlled trial conducted in China extended previous Western studies evaluating the efficacy of CBT on depressive and anxiety symptoms in women with breast cancer.

Admittedly, the present study has its own limitations. In this study, CBT participants were more depressed or anxious than those in the SCM
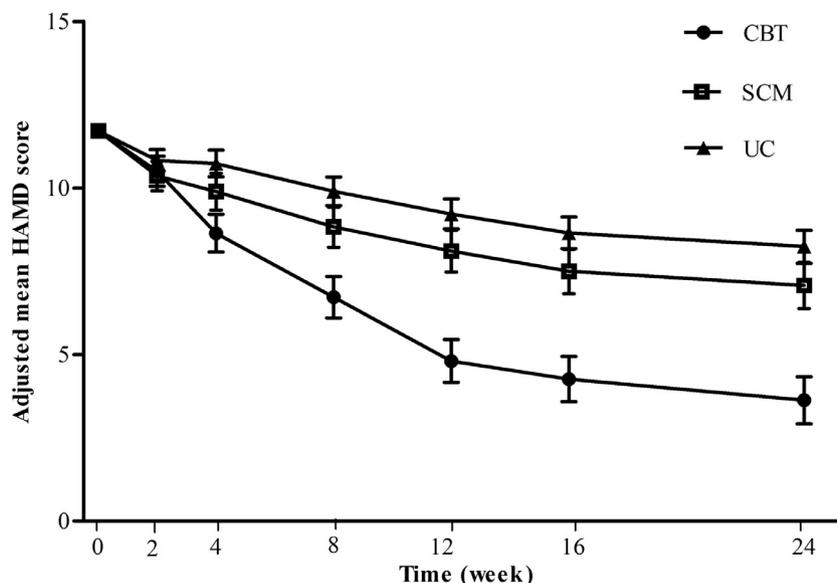
Fig. 2. Adjusted mean score of HAMD at baseline, 2, 4, 8, 12, 16, and 24 weeks. HAMD (Hamilton Depression Rating Scale), CBT (cognitive behavioural therapy), SCM (self-care management), UC (usual care).

Table 2
RM-ANOVA for HAMA, HAMD score among three groups.

	HAMD score Mean (SE)	HAMA score Mean (SE)
Group		
CBT	7.18 (0.22)[a,b]	7.55 (0.22)[a,b]
SCM	9.06 (0.22)[b]	9.52 (0.22)
UC	9.90 (0.16)	10.01 (0.16)
F value	48.82	40.54
p value	<0.001	<0.001
ES	0.201	0.173
Time		
baseline	11.71 (0.00)	12.06 (0.00)
2 weeks	10.56 (0.12)	10.78 (0.13)
4 weeks	9.76 (0.15)	10.02 (0.15)
8 weeks	8.48 (0.16)	8.77 (0.17)
12 weeks	7.37 (0.17)	7.77 (0.18)
16 weeks	6.81 (0.18)	7.08 (0.18)
24 weeks	6.31 (0.19)	6.72 (0.18)
p value	<0.001	<0.001
ES	0.701	0.708
Group × Time		
p value	<0.001	<0.001
ES	0.141	0.092

Abbreviations: RM-ANOVA: repeated measures analysis of variance; HAMD: Hamilton depression rating scale; HAMA: Hamilton anxiety scale; CBT: cognitive behavioural therapy; SCM: self-care management; UC: usual care; SE: standard error; ES: effect size.

[a] *p* < 0.01 compared SCM
[b] *p* < 0.01 compared to UC

and UC groups at baseline. Despite the fact that the baseline scores of the HAMD and HAMA were controlled statistically, we could not rule out the possibility that breast cancer survivors with more depressive or anxiety symptoms would respond better to CBT, thus affecting the results to some extent. Another limitation is that we did not control for all the confounding factors, which could have an effect on the depressive and anxiety symptoms, such as lymphoedema after surgery, and menopausal symptoms secondary to the treatment. In addition, the heterogeneity of the sample with regards to cancer stage and the time since surgery might have an effect on the depressive and anxiety symptoms, which may impose some bias on the results. However, cancer stage and time since surgery did not differ among the three groups in this study, which could reduce the bias to some extent.

Table 3
Depressive and anxiety symptoms measures (means and standard error).

Variables	CBT (n = 98)	SCM (n = 98)	UC (n = 196)	p
HAMD score, mean (SD)				
baseline	13.4 (4.9)[b,c]	12.1 (3.2)	11.4 (2.7)	<0.001
2 weeks	11.7 (5.0)[a,c]	10.2 (3.2)	10.3 (3.5)	0.005
4 weeks	9.7 (4.8)	9.8 (3.1)	10.2 (3.7)	0.468
8 weeks	7.8 (4.4)[c]	8.7 (3.6)	9.4 (4.2)	0.006
12 weeks	5.7 (4.0)[b,c]	8.0 (3.2)	8.8 (4.2)	<0.001
16 weeks	5.1 (4.1)[b,c]	7.4 (3.0)	8.3 (4.3)	<0.001
24 weeks	4.4 (3.9)[b,c]	7.0 (3.3)	7.9 (4.4)	<0.001
HAMA score, mean (SD)				
baseline	13.3 (5.1)[a,c]	11.5 (3.8)	11.0 (3.8)	<0.001
2 weeks	11.3 (4.4)	10.9 (3.4)	10.6 (3.1)	0.278
4 weeks	9.8 (4.0)	10.3 (3.5)	10.4 (3.7)	0.426
8 weeks	8.3 (4.1)	9.2 (3.7)	9.4 (3.8)	0.067
12 weeks	6.3 (3.5)[b,c]	8.6 (3.4)	8.8 (4.2)	<0.001
16 weeks	5.4 (3.6)[b,c]	7.9 (3.3)	8.3 (4.3)	<0.001
24 weeks	5.0 (3.3)[b,c]	7.6 (3.3)	7.9 (4.3)	<0.001

Abbreviations: CBT, cognitive behavioural therapy; SCM, self-care management; UC: usual care; SE, standard error; HAMD: Hamilton depression rating scale; HAMA: Hamilton anxiety scale.

[a] *p* < 0.05 compared to SCM.
[b] *p* < 0.01 compared to SCM.
[c] *p* < 0.01 compared to UC.

In summary, this 24-week follow-up of a multicentre randomized controlled trial shows that CBT participants had significantly decreased depressive and anxiety symptoms during the intervention period compared to those in the SCM and UC groups. This study highlights the importance of providing CBT to Chinese breast cancer survivors with depressive and anxiety symptoms. Therefore, CBT is considered a necessity for patients with breast cancer in China. In addition, SCM also significantly decreased depressive symptoms during the intervention period compared to UC. Therefore, SCM might be considered a convenient treatment option for Chinese breast cancer survivors when CBT is not available. Further investigation may focus on (1) exploring whether a combination of CBT and medication will perform better in improving breast cancer survivors' depressive and anxiety symptoms as well as the long-term survival rate, (2) investigating whether less-
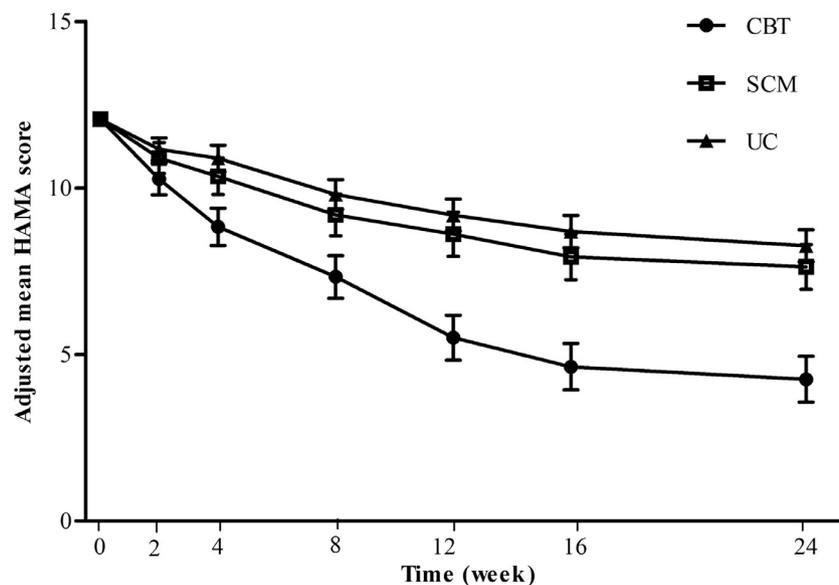
Fig. 3. Adjusted mean score of HAMA at baseline, 2, 4, 8, 12, 16, and 24 weeks. HAMA (Hamilton Anxiety Scale), CBT (cognitive behavioural therapy), SCM (self-care management), UC (usual care).

frequent CBT would be equally effective for depressive and anxiety symptoms, (3) testing the long-term efficacy of CBT in a longer follow-up, and (4) reducing the heterogeneity of the sample with regards to the stage of breast cancer, time since diagnosis, etc.

References

Allen, N.B., 2002. Cognitive therapy of depression. Aaron T Beck, A John Rush, Brian F Shaw, Gary Emery. New York: Guilford Press, 1979. Aust. N. Z. J. Psychiatry 36, 275–278.

Bai, R., Liu, S., Zhao, Y., Cheng, Y., Li, S., Lai, A., et al., 2016. Depressive and anxiety disorders in systemic lupus erythematosus patients without major neuropsychiatric manifestations. J. Immunol. Res. 2016, 2829018.

Breitbart, W., 2011. Do antidepressants reduce the effectiveness of tamoxifen. Psychooncology 20, 1–4.

Burgess, C., Cornelius, V., Love, S., Graham, J., Richards, M., Ramirez, A., 2005. Depression and anxiety in women with early breast cancer: five year observational cohort study. BMJ 330, 702.

Burwell, S.R., Case, L.D., Kaelin, C., Avis, N.E., 2006. Sexual problems in younger women after breast cancer surgery. J. Clin. Oncol. 24, 2815–2821.

Chang, C.H., Chen, S.J., Liu, C.Y., 2015. Adjuvant treatments of breast cancer increase the risk of depressive disorders: a population-based study. J. Affect. Disord. 182, 44–49.

Clough-Gorr, K.M., Ganz, P.A., Silliman, R.A., 2007. Older breast cancer survivors: factors associated with change in emotional well-being. J. Clin. Oncol. 25, 1334–1340.

Compas, B.E., Stoll, M.F., Thomsen, A.H., Oppedisano, G., Epping-Jordan, J.E., Krag, D.N., 1999. Adjustment to breast cancer: age-related differences in coping and emotional distress. Breast Cancer Res. Treat 54, 195–203.

David, D., Schnur, J., Belloiu, A., 2002. Another search for the "hot" cognitions: appraisal, irrational beliefs, attributions, and their relation to emotion. J. Ration. Emot. Cogn. Behav. Ther. 20, 93–131.

DeSantis, C., Ma, J., Goding Sauer, A., Newman, L., Jemal, A., 2017. Breast cancer statistics, 2017, racial disparity in mortality by state. CA Cancer J. Clin. 67, 439–448.

Dobkin, R.D., Menza, M., Allen, L.A., Gara, M.A., Mark, M.H., Tiu, J., et al., 2011. Cognitive-behavioral therapy for depression in Parkinson's disease: a randomized, controlled trial. Am. J. Psychiatry 168, 1066–1074.

Fan, L., Strasser-Weippl, K., Li, J.-J., St Louis, J., Finkelstein, D.M., Yu, K.-D., et al., 2014. Breast cancer in China. Lancet Oncol. 15, e279–e289.

Fawcett, J., Epstein, P., Fiester, S.J., Elkin, I., Autry, J.H., 1987. Clinical management–imipramine/placebo administration manual. NIMH treatment of depression collaborative research program. Psychopharmacol. Bull. 23, 309–324.

Fobair, P., Stewart, S.L., Chang, S., D'Onofrio, C., Banks, P.J., Bloom, J.R., 2006. Body image and sexual problems in young women with breast cancer. Psychooncology 15, 579–594.

Foster, C., Grimmett, C., May, C.M., Ewings, S., Myall, M., Hulme, C., et al., 2016. A web-based intervention (RESTORE) to support self-management of cancer-related fatigue following primary cancer treatment: a multi-centre proof of concept randomised controlled trial. Support Care Cancer 24, 2445–2453.

Furnham, A., Chan, E., 2004. Lay theories of schizophrenia. a cross-cultural comparison of British and Hong Kong Chinese attitudes, attributions and beliefs. Soc. Psychiatry Psychiatr. Epidemiol. 39, 543–552.

Gazal, M., Souza, L.D., Fucolo, B.A., Wiener, C.D., Silva, R.A., Pinheiro, R.T., et al., 2013. The impact of cognitive behavioral therapy on IL-6 levels in unmedicated women experiencing the first episode of depression: a pilot study. Psychiatry Res. 209, 742–745.

Giese-Davis, J., Collie, K., Rancourt, K.M., Neri, E., Kraemer, H.C., Spiegel, D., 2011. Decrease in depression symptoms is associated with longer survival in patients with metastatic breast cancer: a secondary analysis. J. Clin. Oncol. 29, 413–420.

Goldberg, J.A., Scott, R.N., Davidson, P.M., Murray, G.D., Stallard, S., George, W.D., et al., 1992. Psychological morbidity in the first year after breast surgery. Eur. J. Surg. Oncol. 18, 327–331.

Gorman, J.R., Malcarne, V.L., Roesch, S.C., Madlensky, L., Pierce, J.P., 2010. Depressive symptoms among young breast cancer survivors: the importance of reproductive concerns. Breast Cancer Res. Treat 123, 477–485.

Han, J.A., Choi, S.Y., 2018. Effects of menopausal symptoms and depression on the quality of life of premenopausal women with breast cancer in Korea. 1043659618771475.

Iftene, F., Predescu, E., Stefan, S., David, D., 2015. Rational-emotive and cognitive-behavior therapy (REBT/CBT) versus pharmacotherapy versus REBT/CBT plus pharmacotherapy in the treatment of major depressive disorder in youth; a randomized clinical trial. Psychiatry Res. 225, 687–694.

Jung, B.F., Ahrendt, G.M., Oaklander, A.L., Dworkin, R.H., 2003. Neuropathic pain following breast cancer surgery: proposed classification and research update. Pain 104, 1–13.

Kelly, C.M., Juurlink, D.N., Gomes, T., Duong-Hua, M., Pritchard, K.I., Austin, P.C., et al., 2010. Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: a population based cohort study. BMJ 340, c693.

Lam, W.W., Fielding, R., Ho, E.Y., 2005. Predicting psychological morbidity in Chinese women after surgery for breast carcinoma. Cancer 103, 637–646.

Linder, L.A., Erickson, J.M., Stegenga, K., Macpherson, C.F., Wawrzynski, S., Wilson, C., et al., 2017. Symptom self-management strategies reported by adolescents and young adults with cancer receiving chemotherapy. Support Care Cancer 25, 3793–3806.

Mann, E., Smith, M., Hellier, J., Hunter, M.S., 2011. A randomised controlled trial of a cognitive behavioural intervention for women who have menopausal symptoms following breast cancer treatment (MENOS 1): trial protocol. BMC Cancer 11, 44.

Mann, E., Smith, M.J., Hellier, J., Balabanovic, J.A., Hamed, H., Grunfeld, E.A., et al., 2012. Cognitive behavioural treatment for women who have menopausal symptoms after breast cancer treatment (MENOS 1): a randomised controlled trial. Lancet Oncol. 13, 309–318.

MD., M., BP., P., III., R.C., 1998. Medication Clinic Training Procedures and Treatment Manual. University of Pittsburgh, Pa.

Mohr, D.C., Ho, J., Duffecy, J., Reifler, D., Sokol, L., Burns, M.N., et al., 2012. Effect of telephone-administered vs face-to-face cognitive behavioral therapy on adherence to therapy and depression outcomes among primary care patients: a randomized trial. JAMA 307, 2278–2285.

Oei, T.P., McAlinden, N.M., 2014. Changes in quality of life following group CBT for anxiety and depression in a psychiatric outpatient clinic. Psychiatry Res. 220, 1012–1018.

Primeau, C., Paterson, C., Nabi, G., 2017. A qualitative study exploring models of supportive care in men and their partners/caregivers affected by metastatic prostate cancer. Oncol. Nurs. Forum 44, E241–E249.

Qiu, J., Chen, W., Gao, X., Xu, Y., Tong, H., Yang, M., et al., 2013. A randomized controlled trial of group cognitive behavioral therapy for Chinese breast cancer patients with major depression. J. Psychosom. Obstet. Gynaecol. 34, 60–67.

Qiu, J., Yang, M., Chen, W., Gao, X., Liu, S., Shi, S., et al., 2012. Prevalence and correlates of major depressive disorder in breast cancer survivors in Shanghai, China. Psychooncology 21, 1331–1337.

Rubin-Falcone, H., Weber, J., Kishon, R., Ochsner, K., Delaparte, L., Dore, B., et al., 2018. Longitudinal effects of cognitive behavioral therapy for depression on the neural correlates of emotion regulation. Psychiatry Res. 271, 82–90.

Safren, S.A., Gonzalez, J.S., Wexler, D.J., Psaros, C., Delahanty, L.M., Blashill, A.J., et al., 2014. A randomized controlled trial of cognitive behavioral therapy for adherence and depression (CBT-AD) in patients with uncontrolled type 2 diabetes. Diabetes Care. 37, 625–633.

Satin, J.R., Linden, W., Phillips, M.J., 2009. Depression as a predictor of disease progression and mortality in cancer patients: a meta-analysis. Cancer 115, 5349–5361.

Shahsavari, H., Matory, P., Zare, Z., Taleghani, F., Kaji, M., 2015. Effect of self-care education on the quality of life in patients with breast cancer. J. Educ. Health Promot. 4, 70.

Sivasubramaniam, P.G., Zhang, B.L., Zhang, Q., Smith, J.S., Zhang, B., Tang, Z.H., et al., 2015. Breast cancer disparities: a multicenter comparison of tumor diagnosis, characteristics, and surgical treatment in China and the U.S. Oncologist 20, 1044–1050.

Sockloff, A.L., 1978. Statistical Power Analysis For the Behavioral sciences: (revised edition), By Jacob Cohen. Academic Press, New York, pp. 249–250 1977, xv + 474 pp., $24.50. Eval Program Plann 1.

Toftegard Andersen, L., Voigt Hansen, M., Rosenberg, J., Gogenur, I., 2013. Pharmacological treatment of depression in women with breast cancer: a systematic review. Breast Cancer Res. Treat 141, 325–330.

Yang, L.H., Kleinman, A., Link, B.G., Phelan, J.C., Lee, S., Good, B., 2007. Culture and stigma: adding moral experience to stigma theory. Soc. Sci. Med. 64, 1524–1535.

Young, K.S., Burklund, L.J., Torre, J.B., Saxbe, D., Lieberman, M.D., Craske, M.G., 2017. Treatment for social anxiety disorder alters functional connectivity in emotion regulation neural circuitry. Psychiatry Res. Neuroimaging 261, 44–51.

Zhang, M.Y., 1989. The diagnosis and phenomenology of neurasthenia. a Shanghai study. Cult. Med. Psychiatry 13, 147–161.

Zheng, Y.P., Zhao, J.P., Phillips, M., Liu, J.B., Cai, M.F., Sun, S.Q., et al., 1988. Validity and reliability of the Chinese Hamilton Depression Rating Scale. Br. J. Psychiatry 152, 660–664.

Zimmerman, M., Martinez, J., Young, D., Chelminski, I., Dalrymple, K., 2013. Severity classification on the Hamilton Depression Rating Scale. J. Affect. Disord. 150, 384–388.