

# Cognitive Behavioral Therapy for Patients with Social Anxiety Disorder Who Remain Symptomatic following Antidepressant Treatment: A Randomized, Assessor-Blinded, Controlled Trial

Naoki Yoshinaga<sup>a,b</sup> Satoshi Matsuki<sup>b</sup> Tomihisa Niitsu<sup>c</sup> Yasunori Sato<sup>e</sup>  
Mari Tanaka<sup>b</sup> Hanae Ibuki<sup>b</sup> Rieko Takanashi<sup>b</sup> Keiko Ohshiro<sup>d</sup>  
Fumiyo Ohshima<sup>b</sup> Kenichi Asano<sup>d</sup> Osamu Kobori<sup>f</sup> Kensuke Yoshimura<sup>c</sup>  
Yoshiyuki Hirano<sup>d</sup> Kyoko Sawaguchi<sup>e</sup> Masaya Koshizaka<sup>e</sup> Hideki Hanaoka<sup>e</sup>  
Akiko Nakagawa<sup>d</sup> Michiko Nakazato<sup>d</sup> Masaomi Iyo<sup>c</sup> Eiji Shimizu<sup>b,d</sup>

<sup>a</sup>Organization for Promotion of Tenure Track, University of Miyazaki, Miyazaki, Departments of <sup>b</sup>Cognitive Behavioral Physiology and <sup>c</sup>Psychiatry, Graduate School of Medicine, and <sup>d</sup>Research Center for Child Mental Development, Chiba University, and <sup>e</sup>Clinical Research Center, Chiba University Hospital, Chiba, Japan;

<sup>f</sup>Department of Psychology, Swansea University, Swansea, UK

## Key Words

Social anxiety · Social phobia · Antidepressant · Residual symptoms · Cognitive behavioral therapy · Cognitive therapy · Randomized controlled trial

## Abstract

**Background:** Although antidepressants are still a commonly used treatment for social anxiety disorder (SAD), a significant proportion of patients fail to remit following antidepressants. However, no standard approach has been established for managing such patients. This study aimed to examine the effectiveness of cognitive behavioral therapy (CBT) as an adjunct to usual care (UC) compared with UC alone in SAD patients who remain symptomatic following antidepressant treatment. **Methods:** This was a prospective randomized open-blinded end-point study with two parallel groups (CBT + UC, and UC alone, both for 16 weeks) conducted from

June 2012 to March 2014. SAD patients who remain symptomatic following antidepressant treatment were recruited, and a total sample size of 42 was set based on pilot results. **Results:** Patients were randomly allocated to CBT + UC (n = 21) or UC alone (n = 21). After 16 weeks, adjusted mean reduction in the Liebowitz Social Anxiety Scale from baseline for CBT + UC and UC alone was –40.87 and 0.68, respectively; the between-group difference was –41.55 (–53.68 to –29.42, p < 0.0001). Response rates were 85.7 and 10.0% for CBT + UC and UC alone, respectively (p < 0.0001). The corresponding remission rates were 47.6 and 0.0%, respectively (p = 0.0005). Significant differences were also found in favor of CBT + UC for social anxiety symptoms, depressive symptoms, and functional impairment. **Conclusions:** Our results suggest that in SAD patients who have been ineffectively treated with antidepressants, CBT is an effective treatment adjunct to UC over 16 weeks in reducing social anxiety and related symptoms.

© 2016 The Author(s)  
Published by S. Karger AG, Basel

KARGER

E-Mail karger@karger.com  
www.karger.com/ppp

© 2016 The Author(s)  
Published by S. Karger AG, Basel  
0033–3190/16/0854–0208\$39.50/0

Karger  
Open access

This article is licensed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (CC BY-NC-ND) (<http://www.karger.com/Services/OpenAccessLicense>). Usage and distribution for commercial purposes as well as any distribution of modified material requires written permission.

Naoki Yoshinaga, PhD  
Organization for Promotion of Tenure Track, University of Miyazaki  
General Education and Research Building (G704), 5200 Kihara  
Kiyotake, Miyazaki 889-1692 (Japan)  
E-Mail naoki-y@med.miyazaki-u.ac.jp

## Introduction

Social anxiety disorder (SAD) is a highly prevalent psychiatric disorder associated with considerable vocational and psychosocial handicaps and an increased risk for complications such as depression and suicidality [1]. SAD has a low natural recovery rate (only 37% over 12 years) compared with major depressive disorder and other anxiety disorders [2]. Thus, effective and accessible treatments for SAD are in high demand by both patients and health care organizations.

The treatment options for SAD are psychotherapy and pharmacotherapy. With regard to pharmacotherapy, antidepressants have been recommended as the first-line treatment for SAD [3–5]. However, a significant proportion of patients with SAD fail to respond to antidepressants (40–60% are nonresponders over 12–20 weeks of treatment) [6, 7]. Although the inappropriateness of antidepressants due to their low response rates and adverse effects should be discussed, antidepressants are still commonly used as a first-choice treatment for SAD [8]. Some reviews have advocated augmentation with other pharmacological agents or switching to another antidepressant; however, the evidence for such treatment is limited [5]. While some reports have been published on the effectiveness of pharmacotherapy combined with cognitive behavioral therapy (CBT) [9], no data are available on the effectiveness of a combined therapy targeting patients who remain symptomatic despite adequate antidepressant trials.

Clearly, much more work needs to be done to garner evidence and then establish a treatment guideline for patients with SAD who have been ineffectively treated with antidepressants. In the depression literature, a large-scale randomized controlled trial has recently demonstrated the effectiveness of augmenting pharmacotherapy with CBT in treatment-resistant depression [10], marking a milestone in the use of CBT for managing patients who remain symptomatic despite adequate antidepressants; however, a systematic review has revealed no such studies in the literature on SAD [11]. Some studies of individual CBT (e.g. Clark et al. [12] in 2006) and our preliminary study [13] have included a subset of patients who have been ineffectively treated with antidepressants. These studies have reported a subanalysis, which showed that they do not differ in their response to individual CBT. These findings suggest that CBT for SAD is an effective treatment option, even in patients who failed to remit after receiving antidepressants; however, the sample size for this comparison was very small in the subanalysis, so

the absence of a significant difference is not informative. What is really needed is an effectiveness trial of CBT as a next-step treatment in this population.

Here, we conducted a randomized controlled trial to examine the effectiveness of CBT as an adjunct to usual care (UC) compared with that of UC alone, specifically targeting cases who remain symptomatic despite treatment with selective serotonin reuptake inhibitors (SSRIs). We hypothesized that among SAD patients who remain symptomatic following antidepressants, the augmentation with CBT would be superior to UC alone in reducing the severity of social anxiety and depressive symptoms and improving functioning or quality of life.

## Methods

### *Study Design and Participants*

The study protocol has been published elsewhere [14] and, therefore, it is only summarized here. This was a prospective randomized open-blinded end-point single-center trial conducted at the psychiatric outpatient section of Chiba University Hospital between June 2012 and March 2014. Participants were recruited through posters and leaflets placed at medical institutions in Chiba Prefecture and through web-based and newspaper advertisements. The primary inclusion criterion was patients with SAD who remain symptomatic despite treatment with SSRI. Both arms of the trial received active interventions for 16 weeks: one group received CBT combined with UC (CBT + UC group) and another received UC alone (UC group). UC included pharmacotherapy provided by a primary psychiatrist.

Prospective patients were included according to the following criteria: a primary diagnosis of SAD according to the DSM-IV criteria (no restriction on subtype); age 18–65 years; symptomatic status of at least a moderate level of severity (Liebowitz Social Anxiety Scale, LSAS score  $\geq 50$  [15, 16]), and having received adequate treatment with at least one SSRI at maximum-dose treatment for at least 12 weeks, or intolerance to at least one SSRI. Comorbid diagnoses were permitted if they were clearly secondary. Exclusion criteria included psychosis, pervasive developmental disorder/mental retardation, autism spectrum disorders, current high risk of suicide, substance abuse/dependence within the 6 months prior to enrolment, antisocial personality disorder, any unstable medical condition, pregnancy, or lactation. Patients were also excluded if they reported ‘much’ to ‘very much’ improvement in the Clinical Global Impression (CGI) scale [17] following any type of treatment (e.g. medication, psychotherapy, or both) in the 12 weeks prior to the study.

Written informed consent was obtained from all patients after the procedures had been fully explained. Ethical approval was obtained from the Institutional Review Board of Chiba University Hospital (G23075), and the trial was registered as UMIN000007552.

### *Randomization and Masking*

At the end of baseline assessment, eligible patients were randomly assigned to the CBT + UC or UC group in a 1:1 ratio using the minimization method with biased-coin assignment balancing

on primary outcome score (LSAS 50–70 or  $\geq 70$ ) [15], sex, and presence or absence of current treatment with SSRIs. For details of the study management, see online supplementary appendix 1 (see [www.karger.com/doi/10.1159/000444221](http://www.karger.com/doi/10.1159/000444221) for all online suppl. material).

To ensure blinding, the independent assessors had no other contact with the patients. Success of blinding was assessed at weeks 8 and 16 based on Bang's method [18] by asking 'Which type of treatment do you think the patient received during the trial?' with possible responses being 'CBT + UC', 'UC alone', or 'don't know'.

#### Procedures

Primary psychiatrists referred patients to the trial, but continued to provide UC to the patients in both groups. They had no restrictions placed on UC available to them, and medication change was allowed. However, the initiation of a strictly structured CBT program was banned in the UC group in order to properly assess the effectiveness of CBT. All treatment changes, with the reasons for these changes, were recorded throughout the study.

Our CBT program was based on the model of Clark and Wells [19] and conducted over 16 weekly individual sessions. Most sessions lasted for 50 min; however, the treatment manual allowed therapists to extend up to 6 sessions to a maximum of 90 min each to facilitate behavioral experiments. The main treatment steps are presented in online supplementary appendix 2.

#### CBT Therapist and Quality Control

CBT was delivered by seven therapists experienced in the use of CBT for patients with SAD (four clinical psychologists, one psychiatrist, one nurse, and one psychiatric social worker). Four of the seven therapists had experience providing CBT in our preliminary study [13]. All therapists had completed a CBT training course (Chiba Improving Access to Psychological Therapies project: Chiba-IAPT) [20] and received an additional 14-hour special workshop about CBT for SAD. Online supplementary appendix 3 provides more details of therapist training. Five of the seven therapists were female, aged 36.5 years (standard deviation, SD = 5.1), with 6.7 years of clinical experience (SD = 3.9) and 3.5 years of experience as a CBT therapist (SD = 2.7) at the beginning of the study. To assist with session planning, all therapists attended weekly group and individual supervision sessions with a senior supervisor (E.S.). Therapist competence was assessed with a random sample of recordings by raters from the Chiba-IAPT with the Revised Cognitive Therapy Scale (CTS-R) [21].

#### Outcomes

Assessments were conducted at weeks 0 (baseline), 8 (mid-intervention), and 16 (postintervention). The primary outcome was independent assessor-determined symptoms of social anxiety, as measured by the total LSAS score [15]. Treatment response was defined as a 31% or greater reduction in the total LSAS score, and remission was defined as having a final LSAS score of  $\leq 36$  and no longer meeting the diagnostic criteria for SAD (DSM-IV-TR). Secondary outcomes were self-reported using the Social Phobia and Anxiety Inventory (SPAI) [22], the Beck Depression Inventory-II (BDI-II) [23], the Sheehan Disability Scale (SDS) [24], the WHO Quality of Life-26 item version (WHOQOL-26) [25], and the EuroQol-5 Dimensions (EQ-5D) [26]. The CGI-Severity/Improvement (CGI-S/I) [17] was evaluated by independent assessors.

#### Statistical Analysis

Sample size was based on our pilot results, which indicated an estimated group difference in LSAS scores of 30 points (SD = 30), requiring 18 patients per arm to provide >80% power to detect a difference between the two groups over 16 weeks, using a two-sided, two-sample t test at a 5% significance level. Thus, allowing for a 20% dropout rate, 21 patients were required per group.

Statistical analysis and reporting were conducted in accordance with Consolidated Standards of Reporting Trials (CONSORT) guidelines, with the primary analyses based on the intent-to-treat principle without inputting missing observations. Descriptive statistics of patient characteristics were provided using frequencies and proportions for categorical data and means and SD for continuous variables. The baseline variables were compared using Fisher's exact test for categorical outcomes and unpaired t tests for continuous variables, as appropriate.

The primary outcome of change in LSAS from baseline at week 16 was analyzed by analysis of covariance (ANCOVA), with treatment as the fixed effect and the baseline LSAS score (LSAS 50–70 or  $\geq 70$ ), sex, and current treatment with SSRIs as covariates. Adjusted mean differences are provided with 95% confidence intervals (CIs).

For sensitivity analysis, linear mixed-effects models were used for dimensional outcomes to determine the means at each assessment point (weeks 8 and 16) and to test the between-group differences at week 16. Time and treatment were included as fixed effects, and intercept and linear slope terms were included as random effects. An unstructured covariance was used to account for within-subject correlation over time. Secondary analyses were performed similarly to the primary analysis. The success of blinding was measured using Bang's blinding index in a  $2 \times 5$  format [18].

All comparisons were planned. Two-sided p values <0.05 were considered statistically significant. Statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, N.C., USA) and Stata/IC 11.2 (StataCorp, College Station, Tex., USA) with the 'blinding' module written by Jiefeng Chan of the Texas A&M University.

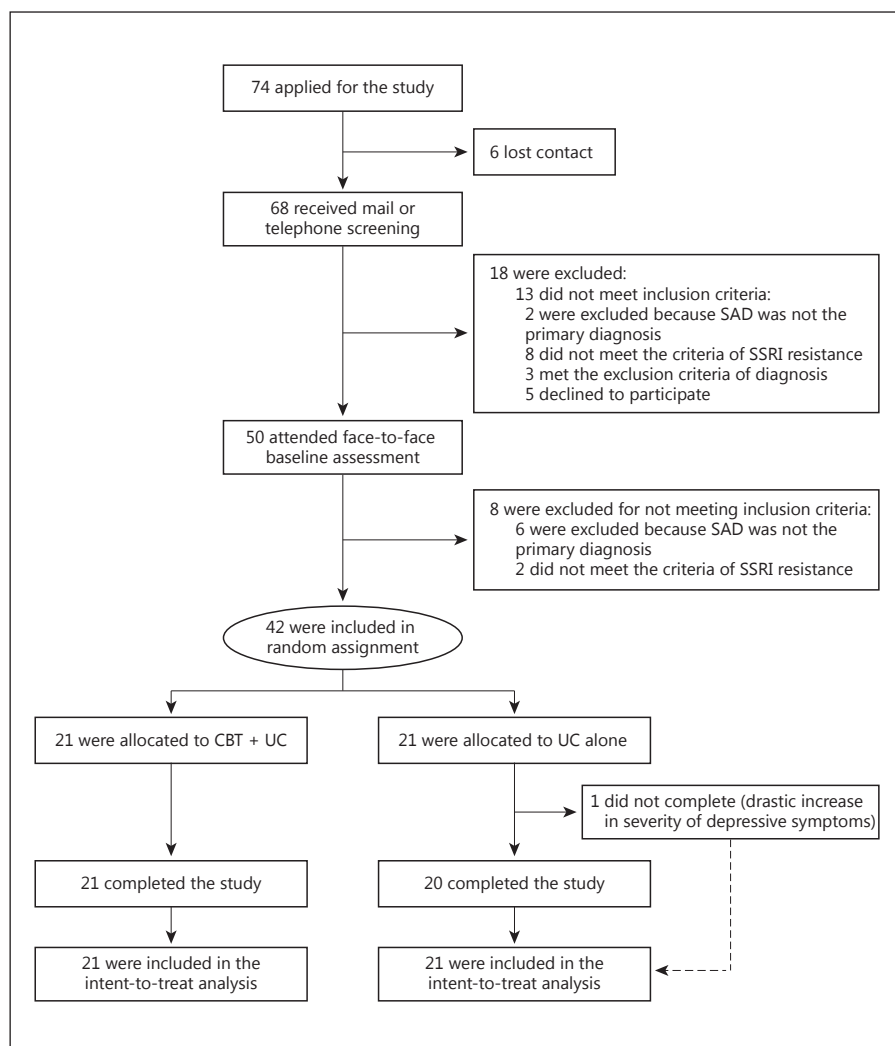
## Results

#### Recruitment

Figure 1 shows the patient flow. Of the 74 patients who applied to participate through our website, 50 attended the face-to-face baseline assessment; 42 were enrolled the study. We randomly assigned 21 patients each to the CBT + UC and UC groups. One patient dropped out from the study in the UC group before the assessment at week 8 because the severity of depression markedly increased. The outcome data for this dropout was included in the intent-to-treat analysis by multiple imputation (data analysis was based on all patients).

#### Demographics and Clinical Characteristics

Table 1 summarizes the baseline demographic and clinical characteristics, demonstrating no significant dif-



**Fig. 1.** CONSORT flow diagram for the trial.

ferences between the study groups. With regard to clinical characteristics, 37 patients (88.1%) had a generalized subtype, 14 (33.3%) had an additional axis I diagnosis, and the mean total LSAS score at baseline was 82.3 (SD = 18.8).

#### Treatment

No significant differences were noted between the groups in antidepressant (imipramine-equivalent) dose or anxiolytic (diazepam-equivalent) dose throughout the study (see online suppl. table 1 for more details). Two patients started another antidepressant during the trial (1 in each group). In the CBT + UC group, the patient restarted escitalopram. In the UC group, the patient started trazodone. Other antidepressant changes are as follows: increased: CBT + UC (n = 2), UC (n = 1); decreased:

CBT + UC (n = 1), UC (n = 1); stopped: CBT + UC (n = 1), UC (n = 2), and other (stopped one of two antidepressants, and increased the other): CBT + UC (n = 1). Online supplementary table 2 describes more details.

With regard to CBT, on average, 15.8 sessions (SD = 0.6) were completed over 19.7 weeks (SD = 4.2). The total mean CTS-R rating was 43.4 (SD = 1.4) for 21 (6.3%) randomly selected sessions from all 331 sessions (1 session from each case), which was over the competence threshold (>36) expected in UK-CBT training programs [21].

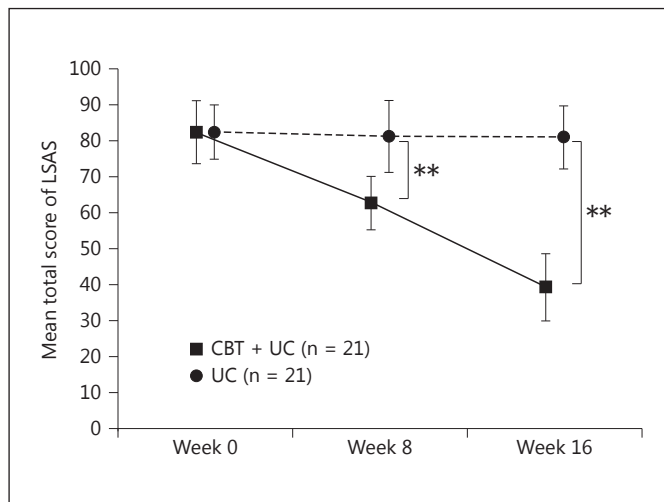
#### Primary Outcomes

Changes in LSAS scores are shown in figure 2. At week 8, mean reductions in LSAS from baseline were -19.67 (95% CI: -27.08 to -12.26) and -0.95 (95% CI:

**Table 1.** Baseline characteristics

Variable	CBT + UC (n = 21)	UC (n = 21)
Male sex	13 (61.9)	12 (57.1)
Age, years	32.5±8.2	31.6±9.2
Length of education, years	14.8±1.7	14.1±1.7
Marital status (married or living as married)	4 (19.1)	3 (14.3)
Employment status (in paid employment, full or part-time)	7 (33.3)	8 (38.1)
Financial status (no financial difficulty)	8 (38.1)	10 (47.6)
Subtype of SAD (generalized)	19 (90.5)	18 (85.7)
Age at onset of SAD, years	18.1±8.0	19.0±6.5
Severity of SAD (LSAS total score)	82.2±20.4	82.4±17.5
Additional axis I diagnosis		
No comorbid condition (SAD only)	12 (57.1)	16 (76.2)
Major depressive disorder	5 (23.8)	4 (19.1)
Others	4 (19.1)	1 (4.8)
Number of past SSRI trials	1.7±0.8	1.5±0.7
Baseline antidepressant (imipramine equivalent dose), mg/day	70.5±62.2	84.5±98.9
Baseline anxiolytics (diazepam equivalent dose), mg/day	3.5±4.3	6.7±10.6

Values are n (%) or means ± SD, as appropriate. There were no group differences on any variables.



**Fig. 2.** Changes in primary outcome (LSAS; see online suppl. table 3 for raw data). Bars indicate 95% CI.

–8.20 to 6.30) for the CBT + UC and UC groups, respectively. As with primary analysis, adjusted mean reductions were –40.87 (95% CI: –50.05 to –31.68) and 0.68 (95% CI: –8.49 to 9.85), respectively. The group difference was –41.55 (95% CI: –53.68 to –29.42,  $p < 0.0001$ ). Combination therapy (CBT + UC) was therefore superior to UC alone. According to the primary outcome

measure (LSAS), a significantly greater proportion of patients in the CBT + UC group achieved response (85.7%) and remission (47.6%) after intervention compared with the UC group (10% and 0%, respectively;  $p < 0.0001$  and  $p = 0.0005$ ).

#### Secondary Outcomes

Results for secondary outcome measures are presented in table 2. At week 8, compared with the UC group, significant improvements were observed in the CBT + UC group in the SPAI, CGI-S, and CGI-I scores (all  $p < 0.05$ ). At week 16, compared with the UC group, significant improvements were observed in all secondary outcomes in the CBT + UC group (all  $p < 0.05$ ). This result shows that, compared with the UC group, measures of social phobia, depression, and functioning or quality of life improved by week 16 in the CBT + UC group.

#### Blinding

At week 8, blinding indices in the CBT + UC and UC groups were –0.01 (95% CI: –0.13 to 0.15) and 0.11 (95% CI: –0.04 to 0.26), respectively. At week 16, the respective values were 0.19 (95% CI: 0.11 to 0.37) and –0.25 (95% CI: –0.20 to 0.15). These results suggested that blinding was unsuccessful in the CBT + UC group at the postintervention assessment ( $p = 0.04$ ; see online suppl. tables 4 and 5 for more details).

**Table 2.** Changes in secondary outcomes

Measures and time points	CBT + UC (n = 21)		UC (n = 21)		p value
	mean ± SD	95% CI	mean ± SD	95% CI	
SPAI (range: 0–144)					
Week 0	110.0±24.6	99.4–120.5	115.1±22.0	105.7–124.6	0.399
Week 8	97.7±24.1	87.4–108.0	114.4±22.7	104.6–124.1	0.038*
Week 16	81.8±31.6	68.3–95.3	115.4±23.0	105.5–125.2	0.0011**
BDI-II (range: 0–63)					
Week 0	22.3±11.6	17.4–27.3	18.4±10.5	13.9–22.9	0.232
Week 8	14.8±7.7	11.5–18.1	18.4±11.5	13.4–23.3	0.447
Week 16	10.9±10.4	6.5–15.3	19.4±11.2	14.6–24.1	0.0094**
SDS (range: 0–30)					
Week 0	16.6±5.8	14.1–19.0	14.7±5.5	12.3–17.1	0.313
Week 8	11.4±5.9	8.9–14.0	14.4±6.8	11.4–17.3	0.143
Week 16	10.4±7.5	7.2–13.6	14.9±6.1	12.2–17.6	0.022*
WHOQOL-26 (range: 26–130)					
Week 0	68.3±13.7	62.5–74.2	71.8±12.0	66.5–77.1	0.339
Week 8	72.8±10.9	68.1–77.5	73.2±12.5	67.7–78.6	0.906
Week 16	79.9±18.1	72.1–87.6	71.7±9.4	67.5–75.8	0.022*
EQ-5D (range: –0.111 to 1.000)					
Week 0	0.7±0.1	0.6–0.7	0.7±0.1	0.7–0.8	0.129
Week 8	0.7±0.2	0.6–0.8	0.7±0.1	0.7–0.8	0.989
Week 16	0.8±0.2	0.7–0.9	0.7±0.2	0.7–0.8	0.0086**
CGI-S (range: 0–7)					
Week 0	5.1±1.0	4.7–5.5	5.0±0.7	4.7–5.2	0.447
Week 8	4.0±1.1	3.5–4.4	4.6±0.9	4.2–5.0	0.028*
Week 16	2.6±1.3	2.0–3.1	4.8±1.1	4.3–5.2	<0.0001**
CGI-I (range: 0–7) <sup>a</sup>					
Week 8	3.1±0.8	2.7–3.4	3.9±0.3	3.8–4.0	<0.0001**
Week 16	2.1±1.1	1.6–2.6	4.1±0.8	3.7–4.4	<0.0001**

Intention-to-treat sample. Measures: higher scores on the WHOQOL-26 and EQ-5D indicate better QOL, and those on the other measurements indicate greater pathology or severity. \* p < 0.05, \*\* p < 0.01.

<sup>a</sup> Compared with baseline assessment (week 0).

## Discussion

This is the first randomized controlled trial that has examined the effectiveness of CBT as a next-step treatment for patients with SAD who remain symptomatic despite SSRI treatment. Over 16 weeks, CBT was effective as an adjunct to UC in reducing the severity of social anxiety symptoms, depressive symptoms, and functional disability.

Baseline clinical characteristics of our recruited patients in Japan were different from those of epidemiological data in Western countries (e.g. low comorbid depression, a high number of single and unemployed partici-

pants, and a high rate of financial problems). It is difficult to explain the reason for this, though a possible factor is culturally different backgrounds [27, 28]. For example, epidemiological data in the USA revealed that 34% of SAD patients have comorbidity of depression [28], whereas in Japanese clinical settings, only 21% of patients have comorbid depression (25.7% in severe cases, LSAS >90) [29]. Therefore, our study population seems to reflect routine clinical practice in Japan; future study should replicate our findings with larger samples.

A report comparing CBT + UC with UC alone for the management of treatment-refractory depression reported that 15% of patients met the remission criteria in the

UC group compared with 28% in the CBT + UC group at the 6-month follow-up [10]. In our study, none of the patients receiving UC alone met the remission criteria at week 16, while 47.6% met the criteria in the CBT + UC group. This indicates that simple continuation of UC on the basis of the judgment of the primary psychiatrists was largely ineffective for our population of patients with SAD and that clinicians should consider providing CBT or referring patients to a CBT therapist if SSRI treatment is not sufficiently effective.

Obviously, a standardized operational definition for describing the phenomenon of 'patients who remain symptomatic following antidepressant treatment' in SAD is necessary to improve the ecological validity of future results in this field. It should be discussed in order to define antidepressant treatment-resistant SAD in terms of the differentiation between nonresponse, loss of efficacy, and resistance [8]. There is a wide variety of terminology (and its use) for this phenomenon, with the use of such different words as 'refractory', 'nonresponsive', 'incompletely responsive', and 'nonremitter' [11]. Therefore, we needed to describe the phenomenon of 'patients who remain symptomatic following antidepressant treatment' in this study because no agreed-upon definition existed. This was particularly relevant given that our sample had more severe symptoms (mean LSAS >80) than those in most previous trials [9, 30, 31]. Some drug-switching trials have targeted more restricted SSRI nonresponders, but patients in those studies had less severe SAD symptoms (mean LSAS <80) than those in our study [16, 32]. We therefore think that our results are more representative of patients with severe SAD symptoms that have been insufficiently treated with antidepressant treatment.

Several trials have assessed medication augmentation/switching strategies for SAD patients who have not been effectively treated with antidepressants. For example, van Ameringen et al. [33] evaluated the efficacy of buspirone augmentation of SSRIs for SAD patients, obtaining only a partial response to an adequate SSRI trial in a small sample ( $n = 10$ ). They reported that 7 patients (70%) achieved 'responder' status ('very' or 'very much' improved in the CGI-I) over the 8-week treatment. Similarly, Pallanti and Quercioli [32] investigated the efficacy of escitalopram in 29 patients with SAD who did not respond to an adequate trial of paroxetine. After treatment for 12 weeks, 48.3% of their patients were considered responders ('much' or 'very much' improved in CGI-I, and LSAS reduction of >35% compared with baseline). Only one randomized controlled trial was identified [16]. In this trial, patients with SAD who were still symptomatic after sertraline

treatment for 10 weeks received either add-on clonazepam, add-on placebo, or a switch to venlafaxine. After further 12 weeks of treatment, 27% of the patients receiving sertraline and clonazepam achieved remission (LSAS  $\leq 30$ ). In contrast, 17% achieved remission with sertraline plus placebo and 19% achieved remission with a switch to venlafaxine. However, none of these differences reached statistical significance. Our result that 85.7 and 40% of patients in our study responded to treatment and achieved remission after adjunctive CBT, respectively, was therefore a remarkable finding. However, accurate assessment of the effectiveness of next-step treatment options has been precluded by diverse definitions of resistance and outcome measures. Therefore, further controlled trials should compare these treatment options for treatment-resistant SAD.

Individual CBT led to considerable improvements in our population; however, CBT therapists had limited experience compared with those in previous studies [34–36]. We should also consider the results of the Cognitive Therapy Competence Scale (CTCS) against other studies, given that evidence suggests that competence predicts outcome in CBT for SAD [37]. Although we did not evaluate the CTCS, when we calculated the pre-post effect size of the CBT arm by the same formula [ $(M_{\text{pre-CBT}} - M_{\text{post-CBT}})/SD_{\text{pooled}}$ ] using raw data from each study, our effect size of 2.00 for the LSAS was comparable to those in previous studies on individual-based CBT using the model of Clark and Wells [19] (1.22–2.17) [12, 30, 31, 35]. We should also take into consideration the time of each session across different studies. There are now seven published randomized controlled trials of individual CBT based on the model of Clark and Wells [19], and the absolute magnitude of the within-treatment change in social anxiety varies as a function of session duration. Trials which used longer sessions (up to 90 min) and involved an extensive number of behavioral experiments obtained improvements on the LSAS of almost 45 points [12, 30]. By contrast, trials that only used sessions of 50 min and appear to have involved very few behavioral experiments reported improvements on the LSAS of only 30 points [31, 36]. Although our protocol involved up to 16 weekly sessions, most of which lasted 50 min, and up to 6 sessions (minimum 3 sessions) lasting 90 min to facilitate behavioral experiments, our observed improvements (40 points) after receiving CBT are closer to the trials with longer sessions.

Our individual CBT achieved a large treatment effect despite having CBT therapists with limited experience and targeting severe cases; four possible reasons may ac-

count for this. First, our CBT therapists received sufficient training before the trial (see online suppl. appendix 3 and our published paper [20] for more details). All of the therapists had a structured CBT training experience to provide high-intensity therapy as a Chiba-IAPT trainee (more than 400 h over 2 years, similar to UK-IAPT). In addition to this basic training, they received an additional 14-hour special workshop about CBT for SAD. Second, there are possible nontreatment-specific effects. Patients' preferences, motivation, and patient-doctor interaction are examples of what may affect treatment outcome in therapeutic trials [38, 39]. In Japan, the effectiveness of CBT has recently become known, not only among professionals but also in the general public; however, there are few competent CBT therapists, and patients' access to CBT is extremely limited [40]. Thus, patients who received CBT may have had high expectations, preferences, motivation, and allegiance to CBT during the trial. Third, our sample size was relatively small. A recent meta-epidemiological study found that small-to-moderately sized trials had significantly larger estimates of treatment effects than large-sized trials (>1,000 patients) [41]. Finally, high baseline severity on primary outcome might contribute to a larger treatment effect.

Assessor blinding was broken in the CBT + UC group at the end of the trial, mainly because LSAS showed considerable improvement only in the group receiving adjunctive CBT. At week 16, the assessors correctly guessed that patients were receiving CBT + UC in 13 cases (61.9%), giving the reasons 'intuition' (n = 7), 'LSAS test result' (n = 5), and 'informed by the patient' (n = 1). Thus, most correct guesses were determined by intuition or after rating the LSAS score, suggesting that unblinding had a minimal impact on primary outcome ratings.

This study has several limitations. First, most patients were recruited from outside our hospital, but CBT was delivered in our single-center facility; the quality of CBT therapists was somewhat different from that observed in routine clinical practice. Second, we did not set psychological placebo-controlled conditions; it is unclear whether factors unrelated to the treatment-specific effects might have contributed to the large effects of the psychological treatment. Third, the lack of follow-up data limits the generalizability of our conclusions to longer-term outcomes. Studies using longer-term CBT may affect relapse rates and cost-effectiveness, and data of long-term effectiveness will be analyzed and reported elsewhere. Fourth, although the sample size had adequate power, it was relatively small; future study should therefore attempt to rep-

licate our findings with larger samples. Finally, two independent assessors have the same professional license and received the same rater training, but lack of interrater reliability for LSAS and CGI limits the quality of these assessor-administered outcomes.

Although this study targeted patients who remain symptomatic following antidepressant treatment, we need to rethink the first-choice treatment for SAD; benzodiazepine is an alternative first-choice pharmacological approach. There has been a progressive shift in prescribing patterns from benzodiazepine to second-generation antidepressants in anxiety disorders [42]. However, recent systematic reviews have revealed that there is no consistent evidence supporting the advantages of using antidepressants over benzodiazepine in treating anxiety disorders, and benzodiazepine showed fewer treatment withdrawals and adverse events than antidepressants [43, 44]. Further, a recent trial reported the inappropriateness of first-line sertraline for 297 patients with SAD due to its very low rates of response (32%) and remission (13%), which are very unlikely to be better than those of a placebo [16]. Based on this evidence, Fava [8] recently suggested that the utilization of antidepressants in anxiety disorders should be reduced unless a comorbid major depression is present, benzodiazepine fails to provide adequate relief, or psychotherapeutic alternatives are not available.

CBT still remains an important first-line treatment option for SAD. CBT has a number of advantages over pharmacotherapy: larger and longer effects, fewer adverse effects, smaller relapse rates, and greater acceptability [45–47]. Further, patients often prefer psychotherapeutic intervention (this is better known in the depression literature) [48]. Taking these factors into account, the National Institute for Health and Care Excellence (NICE) recently concluded that individual CBT should be offered as the first-choice treatment for SAD [49]. However, patient access to psychotherapy is limited in many countries because it is more difficult to increase its provision than that of pharmacotherapy. As of 2015, Japanese national health insurance covers only pharmacotherapy, but not CBT, for anxiety disorders. The UK and Australia have introduced initiatives to increase access, provided supervised training, and set minimum competency standards to ensure a consistent standard of psychotherapy. Worldwide, including Japan, such initiatives are rare, and more investment is urgently required to improve patients' access to CBT.

In conclusion, our results suggest that in patients with SAD who remain symptomatic following treatment with



antidepressants, CBT is an effective treatment adjunct to UC over 16 weeks in reducing the severity of social anxiety symptoms, depressive symptoms, and functional disability.

## Acknowledgments

This study was supported by the Grant-in-Aid for the Japan Society for the Promotion of Science (JSPS) Fellows from the JSPS (grant 13J00177 to N.Y.), part of the Grant for Scientific Research on Priority Areas from the University of Miyazaki (to N.Y.), the Grant-in-Aid for Scientific Research from the Japanese Ministry of Health, Labor and Welfare (grant 22SE1P0051 to E.S.), and part of the Special Budget for Project from the Japanese Ministry of Education, Culture, Sports, Science and Technology (to E.S.). The funding sources had no role in any of the following: design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript, and decision to submit the manuscript for publication.

## Disclosure Statement

N.Y. has received speaking honorarium from the Japanese Psychiatric Nurses Association and writing honoraria from Igaku-Shoin, Nihon-Hyouronsha, and Sogensha. T.N. has received a

grant from the SENSHIN Medical Research Foundation. Y.S. has received speaking honoraria from Elekta and Siemens, royalties from the University of Tokyo Press, Medical View, Kanehara-Shuppan, and Igaku-Shoin, advisory board or consulting fees from Pfizer, Japan Medical Association, and Japan Association for Diabetes Education and Care, and grants from Kowa Pharmaceutical Company. K.Y. has received speaking honoraria from Eli Lilly, Sumitomo Dainippon Pharma, Otsuka, and MSD. Y.H. has received speaking honorarium from the Japanese Association for Cognitive Therapy, royalties from Igaku-Shoin and Sentan-Igaku-sha, and a grant from the Mental Health Okamoto Memorial Foundation. M.K. has received speaking honoraria from Kyowa Kirin and Kowa Souyaku, and writing honoraria from Medical View, Igaku-Shuppan, and Life Science. A.N. has received speaking honoraria from Otsuka Pharmaceutical Company, Kawasaki Medical College, Kobe University, and Kyoto Counseling Center of Cognitive Behavior Therapy, and has writing honoraria or royalties from Iwasaki-Gakujutu-Shuppansha, Nakayama-Shoten, Seronjihou, Seiwa-Shoten, and Kongo-Shuppan, Nanzando. M.I. has received speaking honoraria from Janssen, Eli Lilly, Otsuka, Meiji Seika, Astellas, Dainippon Sumitomo, Ono, GlaxoSmith-Kline, Takeda, Mochida, Kyowa Hakko, MSD, Eisai, Daiichi-Sankyo, Novartis, Teijin, Shionogi, Hisamitsu, and Asahi Kasei, as well as writing honorarium from Eli Lilly, royalties from Seiwa-Shoten and Zihousya, and consultant fees from Eli Lilly, Dainippon Sumitomo, Pfizer, and Abbott. E.S. has received speaking honoraria from Astellas, Eisai, Eli Lilly, GlaxoSmithKline, Janssen, Meiji Seika, Mochida, MSD, Otsuka, Pfizer, and Yoshitomi, and royalties from Igaku-Shoin, Seiwa-Shoten, Koudan-Sha, and Nanzan-Dou.

## References

- 1 Ruscio AM, Brown TA, Chiu WT, Sareen J, Stein MB, Kessler RC: Social fears and social phobia in the USA: results from the National Comorbidity Survey Replication. *Psychol Med* 2008;38:15–28.
- 2 Bruce SE, Yonkers KA, Otto MW, Eisen JL, Weisberg RB, Pagano M, Shea MT, Keller MB: Influence of psychiatric comorbidity on recovery and recurrence in generalized anxiety disorder, social phobia, and panic disorder: a 12-year prospective study. *Am J Psychiatry* 2005;162:1179–1187.
- 3 Bandelow B, Zohar J, Hollander E, Kasper S, Möller HJ, Zohar J, Hollander E, Kasper S, Möller HJ, Bandelow B, Allgulander C, Ayuso-Gutierrez J, Baldwin DS, Buenvicium R, Cassano G, Fineberg N, Gabriels L, Hindmarch I, Kaiya H, Klein DF, Lader M, Lecrubier Y, Lépine JP, Liebowitz MR, Lopez-Ibor JJ, Marazziti D, Miguel EC, Oh KS, Preter M, Rupprecht R, Sato M, Starcevic V, Stein DJ, van Ameringen M, Vega J: World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders – first revision. *World J Biol Psychiatry* 2008;9:248–312.
- 4 Stein DJ, Baldwin DS, Bandelow B, Blanco C, Fontenelle LF, Lee S, Matsunaga H, Osser D, Stein MB, van Ameringen M: A 2010 evidence-based algorithm for the pharmacotherapy of social anxiety disorder. *Curr Psychiatry Rep* 2010;12:471–477.
- 5 Blanco C, Bragdon LB, Schneier FR, Liebowitz MR: The evidence-based pharmacotherapy of social anxiety disorder. *Int J Neuropsychopharmacol* 2013;16:235–249.
- 6 Van Ameringen MA, Lane RM, Walker JR, Bowen RC, Chokka PR, Goldner EM, Johnston DG, Lavalley YJ, Nandy S, Pecknold JC, Hadrava V, Swinson RP: Sertraline treatment of generalized social phobia: a 20-week, double-blind, placebo-controlled study. *Am J Psychiatry* 2001;158:275–281.
- 7 Liebowitz MR, Gelenberg AJ, Munjack D: Venlafaxine extended release vs placebo and paroxetine in social anxiety disorder. *Arch Gen Psychiatry* 2005;62:190–198.
- 8 Fava GA: Rational use of antidepressant drugs. *Psychother Psychosom* 2014;83:197–204.
- 9 Blanco C, Heimberg RG, Schneier FR, Fresco DM, Chen H, Turk CL, Vermes D, Erwin BA, Schmidt AB, Juster HR, Campeas R, Liebowitz MR: A placebo-controlled trial of phenelzine, cognitive behavioral group therapy, and their combination for social anxiety disorder. *Arch Gen Psychiatry* 2010;67:286–295.
- 10 Wiles N, Thomas L, Abel A, Ridgway N, Turner N, Campbell J, Garland A, Hollinghurst S, Jerrom B, Kessler D, Kuyken W, Morrison J, Turner K, Williams C, Peters T, Lewis G: Cognitive behavioural therapy as an adjunct to pharmacotherapy for primary care based patients with treatment resistant depression: results of the CoBaT randomised controlled trial. *Lancet* 2013;381:375–384.
- 11 Rodrigues H, Figueira I, Gonçalves R, Mendlowicz M, Macedo T, Ventura P: CBT for pharmacotherapy non-remitters – a systematic review of a next-step strategy. *J Affect Disord* 2011;129:219–228.
- 12 Clark DM, Ehlers A, Hackmann A, McManus F, Fennell M, Grey N, Waddington L, Wild J: Cognitive therapy versus exposure and applied relaxation in social phobia: a randomized controlled trial. *J Consult Clin Psychol* 2006;74:568–578.
- 13 Yoshinaga N, Ohshima F, Matsuki S, Tanaka M, Kobayashi T, Ibuki H, Asano K, Kobori O, Shiraishi T, Ito E, Nakazato M, Nakagawa A, Iyo M, Shimizu E: A preliminary study of individual cognitive behavior therapy for social anxiety disorder in Japanese clinical settings: a single-arm, uncontrolled trial. *BMC Res Notes* 2013;6:74.

- 14 Yoshinaga N, Niitsu T, Hanaoka H, Sato Y, Ohshima F, Matsuki S, Kobori O, Nakazato M, Nakagawa A, Iyo M, Shimizu E: Strategy for treating selective serotonin reuptake inhibitor-resistant social anxiety disorder in the clinical setting: a randomised controlled trial protocol of cognitive behavioural therapy in combination with conventional treatment. *BMJ Open* 2013;3:e002242.
- 15 Liebowitz MR: Social phobia. *Mod Probl Pharmacopsychiatry* 1987;22:141–173.
- 16 Pollack MH, Van Ameringen M, Simon NM, Worthington JW, Hoge EA, Keshaviah A, Stein MB: A double-blind randomized controlled trial of augmentation and switch strategies for refractory social anxiety disorder. *Am J Psychiatry* 2014;171:44–53.
- 17 Guy W: *The ECDEU Assessment Manual for Psychopharmacology*, rev ed. Rockville, National Institute of Mental Health, 1976.
- 18 Bang H, Ni L, Davis CE: Assessment of blinding in clinical trials. *Control Clin Trials* 2004; 25:143–156.
- 19 Clark D, Wells A: A cognitive model of social phobia; in Heimberg RG, Liebowitz MR, Hope DA, Schneier FR (eds): *Social Phobia: Diagnosis, Assessment, and Treatment*. New York, Guilford Press, 1995, pp 69–93.
- 20 Kobori O, Nakazato M, Yoshinaga N, Shirashi T, Takaoka K, Nakagawa A, Iyo M, Shimizu E: Transporting cognitive behavioral therapy (CBT) and the Improving Access to Psychological Therapies (IAPT) project to Japan: preliminary observations and service evaluation in Chiba. *J Ment Health Train Educ Pract* 2014;9:155–166.
- 21 Blackburn IM, James IA, Milne DL, Baker C, Standart S, Garland A, Reichelt FK: The revised Cognitive Therapy Scale (CTS-R): psychometric properties. *Behav Cogn Psychother* 2001;29:431–446.
- 22 Turner SM, Beidel DC, Dancu CV, Stanley MA: An empirically derived inventory to measure social fears and anxiety: The Social Phobia and Anxiety Inventory. *Psychol Assess J Consult Clin Psychol* 1989;1:35–40.
- 23 Beck A, Steer R, Brown G: *BDI-II: Beck Depression Inventory Manual*, ed 2. San Antonio, Psychological Corporation, 1997.
- 24 Sheehan DV, Harnett-Sheehan K, Raj BA: The measurement of disability. *Int Clin Psychopharmacol* 1996;11(suppl 3):89–95.
- 25 Skevington SM, Lotfy M, O’Connell KA; WHOQOL Group: The World Health Organization’s WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group. *Qual Life Res* 2004;13:299–310.
- 26 Tsuchiya A, Ikeda S, Ikegami N, Nishimura S, Sakai I, Fukuda T, Hamashima C, Hisashige A, Tamura M: Estimating an EQ-5D population value set: the case of Japan. *Health Econ* 2002;11:341–353.
- 27 Hofmann SG, Asnaani A, Hinton DE: Cultural aspects in social anxiety and social anxiety disorder. *Depress Anxiety* 2010;27:1117–1127.
- 28 Grant BF, Hasin DS, Blanco C, Stinson FS, Chou SP, Goldstein RB, Dawson DA, Smith S, Saha TD, Huang B: The epidemiology of social anxiety disorder in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry* 2005;66:1351–1361.
- 29 Asakura S, Koyama T, Hosokai T, Kawano H, Kajii Y: Post-marketing surveillance of fluvoxamine maleate used long-term in patients with social anxiety disorder in Japan. *Drugs Real World Outcomes* 2014;1:7–19.
- 30 Clark DM, Ehlers A, McManus F, Hackmann A, Fennell M, Campbell H, Flower T, Davenport C, Louis B: Cognitive therapy versus fluoxetine in generalized social phobia: a randomized placebo-controlled trial. *J Consult Clin Psychol* 2003;71:1058–1067.
- 31 Stangier U, Schramm E, Heidenreich T, Berger M, Clark DM: Cognitive therapy vs interpersonal psychotherapy in social anxiety disorder: a randomized controlled trial. *Arch Gen Psychiatry* 2011;68:692–700.
- 32 Pallanti S, Quercioli L: Resistant social anxiety disorder response to escitalopram. *Clin Pract Epidemiol Ment Health* 2006;2:35.
- 33 Van Ameringen M, Mancini C, Wilson C: Buspirone augmentation of selective serotonin reuptake inhibitors (SSRIs) in social phobia. *J Affect Disord* 1996;39:115–121.
- 34 Stangier U, Heidenreich T, Peitz M, Lauterbach W, Clark DM: Cognitive therapy for social phobia: individual versus group treatment. *Behav Res Ther* 2003;41:991–1007.
- 35 Mörtberg E, Clark DM, Sundin O, Aberg Wistedt A: Intensive group cognitive treatment and individual cognitive therapy vs. treatment as usual in social phobia: a randomized controlled trial. *Acta Psychiatr Scand* 2007;115:142–154.
- 36 Leichsenring F, Salzer S, Beutel ME, Herpertz S, Hiller W, Hoyer J, Huesing J, Joraschky P, Nolting B, Poehlmann K, Ritter V, Stangier U, Strauss B, Stuhldreher N, Tefikow S, Teismann T, Willutzki U, Wiltink J, Leibing E: Psychodynamic therapy and cognitive-behavioral therapy in social anxiety disorder: a multicenter randomized controlled trial. *Am J Psychiatry* 2013;170:759–767.
- 37 Ginzburg DM, Bohn C, Höfling V, Weck F, Clark DM, Stangier U: Treatment specific competence predicts outcome in cognitive therapy for social anxiety disorder. *Behav Res Ther* 2012;50:747–752.
- 38 Fava GA, Guidi J, Rafanelli C, Sonino N: The clinical inadequacy of evidence-based medicine and the need for a conceptual framework based on clinical judgment. *Psychother Psychosom* 2015;84:1–3.
- 39 Fava GA, Tomba E, Tossani E: Innovative trends in the design of therapeutic trials in psychopharmacology and psychotherapy. *Prog Neuropsychopharmacol Biol Psychiatry* 2013;40:306–311.
- 40 Ono Y: Cognitive therapy/cognitive behavioral therapy in Japan: past, present, future (in Japanese). *Jpn J Cogn Ther* 2011;4:1–7.
- 41 Dechartres A, Trinquart L, Boutron I, Ravaud P: Influence of trial sample size on treatment effect estimates: meta-epidemiological study. *BMJ* 2013;346:f2304.
- 42 Baldwin DS, Allgulander C, Bandelow B, Ferre F, Pallanti S: An international survey of reported prescribing practice in the treatment of patients with generalised anxiety disorder. *World J Biol Psychiatry* 2012;13:510–516.
- 43 Offidani E, Guidi J, Tomba E, Fava GA: Efficacy and tolerability of benzodiazepines versus antidepressants in anxiety disorders: a systematic review and meta-analysis. *Psychother Psychosom* 2013;82:355–362.
- 44 Fava GA, Gatti A, Belaise C, Guidi J, Offidani E: Withdrawal symptoms after selective serotonin reuptake inhibitor discontinuation: a systematic review. *Psychother Psychosom* 2015;84:72–81.
- 45 Mayo-Wilson E, Dias S, Mavranzeouli I, Kew K, Clark DM, Ades AE, Pilling S: Psychological and pharmacological interventions for social anxiety disorder in adults: a systematic review and network meta-analysis. *Lancet Psychiatry* 2014;1:368–376.
- 46 Gelernter CS, Uhde TW, Cimboric P, Arnkoff DB, Vittone BJ, Tancer ME, Bartko JJ: Cognitive-behavioral and pharmacological treatments of social phobia: a controlled study. *Arch Gen Psychiatry* 1991;48:938–945.
- 47 Heimberg RG, Liebowitz MR, Hope DA, Schneier FR, Holt CS, Welkowitz LA, Juster HR, Campeas R, Bruch MA, Cloitre M, Fallon B, Klein DF: Cognitive behavioral group therapy vs phenelzine therapy for social phobia: 12-week outcome. *Arch Gen Psychiatry* 1998; 55:1133–1141.
- 48 Dwight-Johnson M, Sherbourne CD, Liao D, Wells KB: Treatment preferences among depressed primary care patients. *J Gen Intern Med* 2000;15:527–534.
- 49 Pilling S, Mayo-Wilson E, Mavranzeouli I, Kew K, Taylor C, Clark DM; Guideline Development Group: Recognition, assessment and treatment of social anxiety disorder: summary of NICE guidance. *BMJ* 2013;346:f2541.