Acknowledgements

We thank all of the volunteers for their participation and H. Tanaka for extracting RNA from whole blood.

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LETTER

Tipepidine in adolescent patients with depression: a 4 week, open-label, preliminary study

Tsuyoshi Sasaki[1,2]
Kenji Hashimoto[3]
Masumi Tachibana[1]
Tsutomu Kurata[1]
Hiroshi Kimura[2]
Hideki Komatsu[2]
Masatomo Ishikawa[2]
Tadashi Hasegawa[2]
Akihiro Shiina[1]
Tasuku Hashimoto[2]
Nobuhisa Kanahara[4]
Tetsuya Shiraishi[2]
Masaomi Iyo[1–4]

[1]Department of Child Psychiatry, Chiba University Hospital, [2]Department of Psychiatry, Chiba University Graduate School of Medicine, [3]Division of Clinical Neuroscience, Chiba University Center for Forensic Mental Health, [4]Division of Medical Treatment and Rehabilitation, Chiba University Center for Forensic Mental Health, Inohana, Chiba, Japan

Correspondence: Tsuyoshi Sasaki
Department of Child Psychiatry, Chiba University Hospital, Inohana 1-8-1, Chiba, 260-8670, Japan
Tel +81 43 226 2297
Fax +81 43 226 2297
Email sasaki@faculty.chiba-u.jp

Dear editor

Depression in children and adolescents is a common, recurrent, and debilitating condition associated with increased psychosocial, and medical morbidity and mortality.[1]

The global prevalence of depression in children and adolescents is 1%–2% and 3%–8%, respectively.[2] Depressive symptoms are also associated with significant functional impairment in school and the work place (often requiring legal interventions),[1–5] and an increased risk for substance abuse and suicide.[6–9] Clinical guidelines suggest the use of two selective serotonin reuptake inhibitors (SSRI), namely fluoxetine and escitalopram, both of which are effective with generally acceptable safety profiles in the treatment of adolescent depression.[10] Additionally, combination treatment with an SSRI and psychotherapy, typically cognitive behavioral therapy (CBT), has shown benefit in this cohort.[10] However, caution is warranted since antidepressants therapy in children and adolescents is associated with increased rates of suicidal ideation[11–13] and adverse effects, characterized by excessive emotional arousal or behavioral activation.[14] These results highlight the need for new therapies in adolescent patients with depression, particularly therapies with fewer side effects.

Tipepidine (3-[di-2-thienylmethylene]-1-methylpiperidine) has been used as a non-narcotic antitussive in Japan since 1959. The safety of short-term tipepidine use in children and adults has already been established. Furthermore, no suicide related side effects have been documented for tipepidine. It appears to act by inhibiting G-protein-coupled inwardly rectifying potassium (GIRK) channel currents.[15] The activation of the GIRK channels causes membrane hyperpolarization through potassium efflux. This inhibition is thought to modulate monoamine levels in the brain, since GIRK channels are coupled with G-protein-coupled receptors, such as 5-hydroxytryptamine $(5\text{-HT})_{1A}$, adrenaline α_2 and dopamine D_2 receptors.[15] Using in vivo microdialysis, Kawaura et al demonstrated that tipepidine increases levels of 5-HT and catecholamines, including dopamine, in the prefrontal cortex of rats.[16] Furthermore, Kawaura et al[17] showed that tipepidine produces antidepressant-like effects in rats subjected to the forced swimming test (a model of depression), by modulating these monoamine systems. Furthermore, our recent preliminary study suggests that tipepidine therapy may prove to be an effective alternative treatment for pediatric patients with ADHD.[18] Considering these results, we hypothesize that tipepidine can improve adolescent depressive symptoms by modulating monoaminergic neurotransmission, through the inhibition of GIRK channel coupling to monoamine receptors in the brain.

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http://dx.doi.org/10.2147/NDT.S63075

We report six cases where tipepidine treatment (30 mg/day) proved effective in treating the symptoms of adolescent depression. The ethics committee of Chiba University Graduate School of Medicine approved the study protocol (G24062), which was performed in accordance with the Declaration of Helsinki II. All subjects and their parents provided written informed consent for study participation, after receiving a full explanation of the study, as well as any potential risks and benefits. This trial was registered on the official database of clinical research (Clinical Trials.gov), on April 17, 2013.[19] Statistical analyses were performed using the software package SPSS Version 21.0, for Macintosh (SPSS Statistics Desktop; IBM Corporation, Armonk, NY, US).

We recruited a total of ten outpatients from Chiba University Hospital, who were diagnosed according to the ICD-10 criteria for depressive episodes.[20] However, four subjects dropped out of the trial, because of feelings of mild irritation (n=2) and mild skin eruptions (n=2) less than 2 weeks into the study. These symptoms disappeared several days after the discontinuation of tipepidine. Overall, six subjects received tipepidine hibenzate tablets (Asverin; Mitsubishi Tanabe Pharma Corporation, Osaka, Japan), taken orally at 30 mg/day (10 mg after breakfast, 10 mg after lunch, and 10 mg after supper), for 4 weeks. Six adolescent subjects with depression (66% female, mean age 15.7 years, standard deviation (SD) ±2.2 years; mild depressive episode subtype, n=1; moderate depressive episode subtype, n=1; severe depressive episode subtype, n=4) were studied. The six subjects were Japanese adolescents. The mean height (cm), weight (kg), and tipepidine hibenzate dosage (mg/kg/day) of the six subjects were 158.2 cm±9.3; 57.3 kg±4.9; and 0.527 mg/kg/day ±0.044 mg, respectively. Four subjects were receiving drug treatment before entry into this trial, namely, quetiapine (25 mg/day, 500 mg/day, n=2), milnacipran (100 mg/day, n=1), and a combination of lamotrigine and blonanserin (400 mg/day and 4 mg/day, respectively, n=1), while two subjects were drug-naïve. These treatment regimes were stable for at least 4 weeks prior to enrollment and remained stable through the duration of the trial.

The Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID)[21] was conducted to document any current or past, personal or familial history of mental illness. One subject had a family history of depression in their mother, one subject had a family history of bipolar disorder in their mother, while four subjects had no family history of psychiatric disease. The six subjects completed the Children's Depression Rating Scale-Revised (CDRS-R).[22] As a result, no significant changes were revealed in general state, weight, height, blood pressure, or heart rate, during the 4 week follow-up period in the six subjects who completed the trial. In the six subjects who completed the trial, a comparison of baseline and the 4 week endpoint showed that CDRS-R total scores (baseline score, 58.83±10.83; 4 week endpoint score, 38.87±3.33; P=0.003, df=5, t=5.384) and subscores for Difficulty Having Fun (baseline score; 4.33±0.82, 4 week endpoint score; 2.67±0.52; P=0.011, df=5, t=3.953), Social Withdrawal (baseline score; 4.00±0.89, 4 week endpoint score; 2.83±0.75; P=0.013, df=5, t=3.796), Appetite Disturbance (baseline score; 3.00±0.63, 4 week endpoint score; 2.00±0.89; P=0.012, df=5, t=3.873), Physical Complaints (baseline score; 3.67±0.82, 4 week endpoint score; 1.50±0.84; P=0.006, df=5, t=4.540), Excessive Guilt (baseline score; 3.17±0.75, 4 week endpoint score; 1.83±0.75; P=0.010, df=5, t=4.000), Low Self-Esteem (baseline score; 4.00±0.89, 4 week endpoint score; 2.33±1.03; P=0.011, df=5, t=3.953), Depressed Feelings (baseline score; 4.17±1.47, 4 week endpoint score; 2.33±1.21; P=0.038, df=5, t=2.803), Excessive Weeping (baseline score; 3.83±2.40, 4 week endpoint score; 1.67±0.82; P=0.027, df=5, t=3.081); and Depressed Facial Affect (baseline score; 3.83±1.17, 4 week endpoint score; 2.17±0.75; P=0.004, df=5, t=2.524), improved significantly using paired t-test. Wilcoxon signed rank test also detected statistical significance in the CDRS-R total score (P=0.027), as well as subscores for Difficulty Having Fun (P=0.039), Social Withdrawal (P=0.038), Appetite Disturbance (P=0.034), Physical Complaints (P=0.038), Excessive Guilt (P=0.020), Low Self-Esteem (P=0.039), and Depressed Facial Affect (P=0.026). However, a comparison between baseline and the 4 week end-point found subscores for Impaired Schoolwork, Sleep Disturbance, Excessive Fatigue, Irritability, Morbid Ideation, Suicidal Ideation, Listless Speech, and Hypoactivity showed no significant changes. The Wilcoxon signed rank test also failed to detect any statistical significance in subscore changes for Impaired Schoolwork, Sleep Disturbance, Excessive Fatigue, Irritability, Depressed Feelings, Morbid Ideation, Suicidal Ideation, Excessive Weeping, Listless Speech, or Hypoactivity. Tipepidine was well tolerated in the six subjects who completed the trial, with no further dropouts due to side effects. Furthermore, three patients with adolescent depression have been continuing the oral use of tipepidine (30 mg/day) for its efficacy against depressive symptoms for 3 months or more after this trial.

Tipepidine improved symptoms of adolescent depression in the six subjects who completed the trial, as shown by CDRS-R scores. To our knowledge, this is the first report

demonstrating a beneficial effect for tipepidine in adolescent depression. Tipepidine inhibits GIRK channels and is predicted to modulate brain monoamine levels, in a similar manner to SSRIs, serotonin and norepinephrine reuptake inhibitors (SNRIs) and other antidepressants. Four subjects with depression dropped out during the trial due to feelings of mild irritation and mild skin eruptions. One possible reason for having dropout patients is diagnostic error. There is a chance that some of these children with depression may have been suffering from the onset of bipolar disorder or schizophrenia. Therefore, a follow-up check may be required for the dropout patients to examine their progression.

Recent mapping the of c-Fos-like immunoreactivity (FLI) induction in rat brains identified FLI-positive neurons in several brain areas after acute dosing with different classes of antidepressants.[23] Very recently Kawahara et al[24] showed that a single injection of tipepidine (20 mg/kg or 40 mg/kg) in rats, increased FLI-positive neurons in the central nucleus of the amygdala (CeA) in a manner similar to the tested antidepressants, as well as inducing the characteristic increase in FLI-positive neurons in six other brain regions, including the nucleus accumbens (NAcc). This latter effect was not observed with other antidepressants. Therefore, further detailed studies investigating tipepidine induced dopamine activation in the CeA, NAc, and its neural pathways are warranted.

The main limitation of our study is its small sample size (n=6 evaluable subjects). Another is the low proportion of drug naïve subjects. Additional trials are needed to evaluate the efficacy and safety for tipepidine use in adolescent depression. Although tipepidine is widely used, however, there are reports[25–27] indicating a possible toxic effect like agitation, fixed drug eruption and toxic epidermal necrolysis also in pediatric populations. So we must pay attention to the mood symptoms, especially irritability and cutis symptoms, because there were patients for whom a feeling of irritation and a cutis symptom appeared in this tipepidine study. Also, future studies with greater analytical power, using larger sample sizes and more drug naïve subjects will be necessary to determine tipepidines efficacy and safety.

In conclusion, our pilot study suggests that tipepidine therapy may prove to be an effective alternative treatment for adolescent patients with depression. However, the long-term safety of tipepidine still needs to be assessed, as a cough suppressant therapy is usually completed within 1 week. In addition, the side effects detected here need careful evaluation, as part of more detailed randomized, double-blind studies into this encouraging finding for tipepidine in adolescent depression.

Disclosure

The authors report no conflicts of interest in this work.

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Emerald Journal of Mental Health Training, Education and Practice

Transporting Cognitive Behavioral Therapy (CBT) and the Improving Access to Psychological Therapies (IAPT) Project to Japan: Preliminary observations and service evaluation in Chiba

Journal:	*Journal of Mental Health Training, Education and Practice*
Manuscript ID:	JMHTEP-10-2013-0033.R1
Manuscript Type:	Research Paper
Keywords:	Anxiety, Cognitive Behaviour Therapy, Eating Disorders, Psychotherapist Training/Supervision/Development, Outcome Research

Transporting **Cognitive Behavioral Therapy (CBT) and the Improving Access to Psychological Therapies (IAPT) Project** to Japan: Preliminary observations and service evaluation in Chiba

RUNNING HEAD: Transporting CBT/IAPT to Japan

Abstract

Purpose: This paper discusses the implementation and evaluation of a cognitive behavioral therapy (CBT) training course for clinicians in Chiba, the sixth-largest **province** in Japan.

Design/methodology/approach: Individual CBT for obsessive-compulsive disorder, bulimia nervosa, **or** social anxiety disorder was delivered by trainees of the Chiba CBT training course **in** a single study design.

Findings: The results demonstrated that individual CBT delivered by trainees **led** to **statistically** significant reductions in symptom severity **for all** three disorders. **Feedback from the trainees indicated that the training course achieved its aims.**

Implications: Barriers to the dissemination of CBT in Japan **such as opportunities for training** and possible solutions are discussed.

Originality: This paper evaluates the Chiba CBT training course, which is a Japanese adaptation of the UK Improving Access to Psychological Therapies Project and the first post-qualification CBT training course in Japan.

Keywords: anxiety, cognitive behavior therapy, eating disorders, psychotherapist training, psychotherapist supervision, psychologist development, outcome research

Introduction

Barriers to the dissemination of CBT

Among evidence-based treatments, forms of cognitive behavior therapy (CBT) have been consistently shown to be effective across a wide range of disorders. **While some studies have demonstrated the clinical effectiveness of cognitive behavior therapy for adults in routine clinical practice (e.g., Westbrook & Hill, 1998; Westbrook & Kirk, 2005)**, several authors have noted that evidence of the effectiveness of empirically supported treatments in routine practice is rarely available, and often, the evidence may be delivered suboptimally (e.g. Andrews & Titov, 2009; Gunter & Whittal, 2010; Shafran et al., 2009).

Shafran et al. (2009) identified two barriers to the dissemination of CBT. First, commonly held beliefs, such as 'Research trials have limited applicability to clinical practice' and 'Non-specific therapist effects are more important than specific interventions', hamper the availability of CBT. Second, gaps in the current knowledge about training, measuring competence, **key factors in the etiology or maintenance of the treated disorder**, and the minimum dose required for treatment, limit the **widespread** adoption of the protocols to clinical settings (Shafran et al., 2009). Gunter and Whittal (2010) also identified various barriers to the wide-scale dissemination of CBT for anxiety disorders, including those that are applicable to empirically supported treatments in general (e.g. lack of training opportunities, failure to address practitioner concerns), as well as those that may be specific to CBT for anxiety disorders (e.g. practitioner concerns about using exposure interventions). To overcome these barriers, Gunter and Whittal (2010) advise continuing the accumulation of research-based data, advocating and appealing for the required funding and organisational support, and training practitioners to deliver CBT treatments. Advocates of CBT for anxiety disorders will also need to demonstrate that these treatments are cost effective if wide-scale dissemination is to occur.

In order to address the severe under-provision of treatments and the

dissemination of CBT, the UK government has instigated a highly ambitious program, Improving Access to Psychological Therapies (IAPT), by funding the implementation of NICE guidelines for people suffering from depression and anxiety disorders in England. The IAPT program aims to address the under-provision of these treatments by training 3600 new psychological therapists between 2008–2011, which will provide 900,000 people access to treatment, with half of those engaging in treatment moving to recovery, and 25,000 fewer sick pay and medical benefit expenditures by 2010/11. Initial evaluation of two UK demonstration sites, Doncaster and Newham (Clark et al., 2009) has been published, and a two-year prospective cohort study was carried out to assess the impact of implementing empirically supported stepwise psychotherapy programs in routine practice in northern England (Richards & Borglin, 2011).

Status of mental healthcare and CBT in Japan

Awareness of the effectiveness of CBT has spread **in Japan**, not only among professionals and academics but also to the public through media (e.g., books, newspapers, TV). In April 2010, the inclusion of CBT for mood disorders in the national health insurance scheme marked a milestone **for** psychiatric care in Japan, where pharmacotherapy has historically been much more common. The inclusion of CBT in Japan's insurance program is boosting CBT research **through** randomized controlled trials and facilitating training and practice in this field. However, many obstacles **must still be overcome**. For example, CBT for mood disorders is covered by national health insurance only if **it is** provided by medical doctors. Thus, patients bear all costs when other mental health professionals (e.g., clinical psychologists) conduct CBT. In addition, **CBT for other** mental health problems—such as anxiety disorders—are not yet covered by national health insurance. **Most** importantly, there are few competent CBT therapists in Japan, mainly because the opportunities for training are extremely limited **compared to the UK supervision structure in the IAPT services.** There

are workshops during annual conferences, and several institutions, such as the Tokyo CBT Academy and the National Centre for Cognitive Behavior Therapy and Research, regularly provide a series of workshops. **However, only a limited number of clinicians can attend such training because it is primarily in Tokyo. Moreover, the total training time is relatively short (2–50 hours), and supervision is not provided (even when available, it is not provided on a regular basis).**

Chiba University training course

Chiba University was founded in 1949 by uniting several regional national colleges and schools, **including** the Chiba Medical College. The university is located in Chiba **province**, which has a population of approximately **six** million—the sixth largest among the 47 **provinces** in Japan. In 2010, the Graduate School of Medicine at Chiba University set up a CBT training course, the first post-qualification course for CBT in Japan. Trainees who enroll in the course are required to attend a series of workshops **held** over **two** years. **The training day typically consists of a 3-hour workshop in the morning, and a 90-minute clinical case conference, and 60-minute group supervision in the afternoon. In addition, trainees receive 30-minute individual supervision.** The **full course of** training **includes more than** 400 hours. This training course started in April 2010 with **three** supervisors (**two** psychiatrists and **one** psychologist) and 18 trainees; **however, the** numbers of supervisors and trainees are increasing. Most trainees work in Chiba **province** and are psychiatrists, psychologists, psychiatric social workers, nurses, and pharmacologists.

Our training course was inspired and influenced by the IAPT Project in the UK; our project aims to disseminate CBT in Chiba **province** and to increase the number of CBT therapists equivalent to **the** "high-intensity practitioners" in the UK. Similar to the accreditation for high-intensity practitioners, our trainees are required to complete 200 hours of clinical practice, receive 70 hours of supervision, and complete written reports for a

minimum of eight cases. **Along with the written reports, trainees are required to submit audio or a video record of the sessions, and their competence in each session is assessed by supervisors using the Revised Cognitive Therapy Scale (CTS-R: Blackburn et al., 2000).** The major differences between **the** UK IAPT and our course are **the frequency that** trainees come to the university for the course and how this training is funded. Because the trainees do not receive government funding, they attend the course only once per week for **two** years, and their training is funded by their employers. For those with limited opportunity to conduct individual psychotherapy at their own workplaces, the course also provides placement at Chiba University Hospital, where trainees see patients with anxiety disorders or bulimia nervosa (BN). **Furthermore, our course, unlike the UK IAPT, offers follow-up supervision sessions, in which trainees received 30-minute individual supervision once a month for one year after the completion of the course. Moreover, some trainees go on to a PhD course and continue to attend the program.**

Purpose of the present study

The purpose of this study is to report the preliminary outcomes of individual CBT for obsessive–compulsive disorder (OCD), BN, and social anxiety disorder (SAD) delivered by **the** trainees at Chiba University Hospital. To reflect routine clinical practice, we included patients with comorbid mood disorders if OCD, SAD, **or** BN was the principal diagnosis. The outcomes of trainee-delivered CBT **are** used to measure the effectiveness of our training course. We predicted that CBT would be associated with decreased symptom severity. **Additionally, a post-hoc survey was conducted to receive feedback from the trainees who completed the course.**

Methods

Design

Between April 2010 and December 2011, patients were recruited by clinical referrals from both Chiba University Hospital and other local psychiatric hospitals and clinics; **these patients were assessed by the supervisors at Chiba University Hospital** using the Structured Clinical Interview for Axis I Disorders (SCID-I; First & Gibbon, 1997). Written informed consent was obtained from all participants. The criteria for inclusion in this study included a primary diagnosis of OCD, BN, **or** SAD according to the DSM-IV and 18–65 years **of age.** The exclusion criteria were psychosis, mental retardation, current high risk of suicide, substance abuse or dependence in the past **six** months, antisocial personality disorder, unstable medical condition, pregnancy, or lactation.

After enrolling in the study, the patients were placed on a waiting list. The waiting period was not controlled because it was based on the availability of therapy rooms; the wait averaged 140.90 days (SD = 62.18) for OCD, 89.6 days (SD = 84.5) for BN, and 13.26 days (SD = 3.21) for SAD. After the waiting period, the participants received a **50-minute individual** CBT intervention for 12 weeks. Extra sessions were flexibly added, and termination of treatment was determined jointly by the participants and therapists in consultation with the supervisor. The average number of sessions per participant was 16.25 (SD = 3.77) for OCD, 13.75 (SD = 2.87) for BN, and 13.89 (SD = 1.24) for SAD. **Concominant** medications were permitted if the dose remained stable throughout the study. Participants were assessed using the outcome measures at pre- (first session) and post-CBT (final session).

This study was conducted at an outpatient clinic at Chiba University Hospital, which is used by trainees who have limited opportunities to conduct individual psychotherapy at their own workplaces.

Outcome measures

The primary outcome measures were self-reported obsessive–compulsive symptoms, as measured by the Obsessive Compulsive Inventory distress scale (OCI; Foa et al., 1998); self-reported bulimic symptoms, as measured by the Severity Scale of the Bulimic **Investigatory** Test, Edinburgh (BITE-SS; Henderson et al., 1987); and self-reported symptoms of social anxiety, as measured by the Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987).

General severity of mood and anxiety were measured by the standard measures used in the UK IAPT: the 9-item version of the Patient Health Questionnaire (PHQ-9; Kessler et al., 2002), which has scores ranging from 0 to 27 and a recommended cut-off of ≥10 for distinguishing between clinical and non-clinical populations; and the 7-item version of the Generalized Anxiety Disorder scale (GAD-7; Löwe et al., 2008), which was originally developed to screen for GAD, but also has satisfactory sensitivity and specificity for the detection of other anxiety disorders. These scales are outcome measures commonly used in the UK.

Therapists

CBT was delivered by the trainees in the CBT training program. As a course requirement, they attended 30-minute individual supervision sessions **once every two weeks** and 60-minute weekly group supervision sessions, allowing both supervisors and other trainees to give support and assistance in planning future sessions.

Twenty-two therapists participated in the present study (16 women and six men) with a mean age of 42.13 years (SD = 10.99). In this study, the trainees treated an average of 1.86 patients; most therapiss were allocated 1 or 2 patients. In terms of clinical licenses, there were 13 clinical psychologists, three psychiatrists, one general physician, two psychosocial workers, and three nurses. The average number of years in practice as a clinician was 7.00 years (SD = 6.95), and the average number of days of CBT workshop they had attended before enrolling in our course was 7.47 days (SD = 9.61). The clinical or therapeutic orientation they had used

most in their practice included psychodynamic (n = 1), CBT (n = 3), psychiatric (n = 3), counseling/client-centered (n = 6), integrated/eclectic (n = 7), or a combination of these orientations/other (n = 7).

Interventions

The main steps in the CBT treatment for OCD were:

- Provision of psycho-education about the cognitive-behavioral model of OCD
- Goal setting
- Tailored case formulation
- Exposure and response prevention
- Homework
- Relapse prevention

Therapists were also permitted to use other intervention strategies as needed (e.g., Hougton et al., 2010), including behavioral experiments to test the validity of erroneous beliefs, opinion surveys, and ratings of mastery and pleasure.

Our CBT program for BN was based on Maudsley's model, "Getting Better Bite by Bite" (Schmidt & Treasure, 1993). Getting Better Bite by Bite is the only self-help program that has been evaluated in a randomized controlled trial and provides detailed, step-by-step advice for dealing with BN. The main steps in treatment were:

- Guidelines for behavior change
- Discussion of the pros and cons of maladaptive eating behaviors
- Core values and goal setting
- Psycho-education regarding nutrition, food, and weight
- Self-monitoring using a food diary and provision of a structure for eating
- Action plans on how to stop bingeing and purging behaviors
- Identification of automatic thoughts and modification of maladaptive assumptions and

core beliefs

- Behavioral experiments to challenge maladaptive beliefs
- Progressive actions
- Discussion of remaining challenges
- Dealing with interpersonal difficulties
- Relapse prevention.
- Homework assigned after every session

Our CBT program for SAD was based on the model of Clark and Wells (1995). The main steps in treatment were:

- Developing an individualized version of the cognitive behavioral model of SAD
- Conducting role-play–based behavioral experiments with and without safety behaviors
- Restructuring distorted self-imagery using videotape feedback
- Practicing external focus and shifting attention
- Conducting behavioral experiments to test negative beliefs
- Modifying problematic pre- and post-event processing
- Discussing the difference between self-beliefs and other people's beliefs (reflected in survey results)
- Dealing with remaining assumptions (schema work)
- Rescripting early memories linked to negative images in social situations
- Preventing relapse
- Homework assigned after every session

Statistical analysis

The outcomes of the CBT treatment were **examined by the comparison of** pre- and post-CBT scores **of** each scale (OCI, BITE-SS, LSAS, PHQ-9, and GAD-7) using within-group *t*-

tests. Effect sizes **were** determined ($[M_{pre\text{-}CBT} - M_{post\text{-}CBT}]/SD_{re\text{-}baseline}$). According to Cohen (1988), the effect sizes **were** categorized as follows: small (0.20–0.49), medium (0.50–0.79), and large (0.80 and above).

Feedback from trainees

A post-hoc survey via email was conducted with the trainees who took part in this study to obtain their feedback on the training course. They were asked to rate the following questions on a seven-point scale (ranging from very satisfied [7], satisfied [6], slightly satisfied [5], neutral [4], slightly dissatisfied [3], dissatisfied [2] to very dissatisfied [1]):

1. **How satisfied were you with the length (i.e., one day a week for two years) of the training course?**
2. **How satisfied were you with the content and the delivery of the workshops?**
3. **How satisfied were you with the frequency and the duration of the supervision?**

Additionally, they were asked to note the distinctive aspects of our training course compared to the CBT training they had previously and note any difficulties faced during the training.

Results

Results of patients with OCD

Of the 21 patients screened, three were excluded because OCD was not their primary diagnosis (one OCPD, one adjustment disorder, and one hypochondriasis). Eighteen participants satisfied the study criteria and were referred to the study. During the waiting period, four patients declined the treatment without disclosing their reasons. Once the treatment started, the remaining 14 patients completed the study.

Table 1 shows the baseline demographic and clinical variables of the 14 participants (Table 1). Eleven were women (79%), and the participants' mean age was 36.79 years. Five participants (36%) were unemployed, and six (43%) were single. All participants met the principal DSM-IV diagnostic criteria for OCD (mean duration: 5.21 years). Six participants (57%) also met the criteria for major depressive disorder as an additional Axis I diagnosis. Other clinical variables and participants' demographics are shown in Table 1.

Table 1 about here

The primary outcome measure was the severity score of the OCI. The mean OCI score decreased from 64.43 (SD = 3.39) to 32.54 (SD = 17.49) over the course of treatment. The PHQ-9 and GAD-7 scores reduced from 8.57 (SD = 4.09) to 5.07 (SD = 4.29) and from 8.14 (SD = 5.63) to 4.07 (SD = 2.84), respectively. A within-group *t*-test revealed significantly different scores between the pre- and post-CBT scores on the assessed scales: $t(1, 13) = 5.153$, $p < .001$ for the OCI; $t(1, 13) = 2.775$, $p = .015$ for the PHQ-9; and $t(1, 13) = 3.277$, $p = .006$ for the GAD-7. The effect sizes between the pre- and post-CBT were 1.05 (large), .86 (large), and .72 (medium) for the OCI, PHQ-9, and GAD-7, respectively.

Results for patients with BN

Of the 11 subjects screened, one was excluded from the study because her primary diagnosis was not BN (anorexia nervosa binge-eating/purging type). After enrolling in the study, no patients dropped out, but assessment data were not obtained from two patients. As a result, the data of eight patients were subject to analysis.

Table 2 shows the baseline demographic information and clinical variables of the eight patients whose data were analyzed. All of the participants were female, and their mean age was 31.3 years. One patient was employed, three were students, and four were single. Four patients had comorbid psychiatric disorders: two had additional Axis I diagnoses of major depressive disorder, one had bipolar disorder, and one had SAD. Other clinical variables and

participants' demographics are shown in Table 2.

Table 2 about here

The primary outcome measure was the severity score on the BITE-SS. The average BITE-SS score decreased from 9.75 (SD = 4.28) to 4.00 (SD = 4.34) over the course of the study. The PHQ-9 and GAD-7 scores reduced from 12.12 (SD = 7.70) to 8.13 (SD = 7.42) and from 9.38 (SD = 6.12) to 6.25 (SD = 6.67), respectively. A within-group *t*-test revealed significant differences between pre- and post-CBT in BITE-SS, $t(1, 7) = 2.803$, $p = .026$, and GAD-7 scores, $t(1, 7) = 2.739$, $p = .028$. However, there was no significant difference in the PHQ-9 scores over the course of the study, $t(1, 7) = 1.782$, $p = .117$. The effect sizes between pre- and post-CBT were 1.348 (large), .516 (medium), and .508 (medium) for the BITE-SS, PHQ-9, and GAD-7, respectively.

Results for patients with SAD

Of the 23 subjects screened, four were excluded: two had high risk of suicide, and the primary diagnoses of the other two were not SAD (autism spectrum disorders). As a result, 19 patients met the enrolment criteria and were referred to the study. All patients completed the study.

Table 3 shows the baseline clinical variables and demographics of the 19 patients who enrolled in this study (Table 3). Fourteen of the participants were women (74%), and the patients' mean age was 32.3 years. Four patients (21%) were unemployed and 12 (63%) were single. All participants met the principal DSM-IV diagnostic criteria for SAD (mean duration: 14.3 years). Patients with additional Axis I diagnoses included five (26%) who met the criteria for major depressive disorder, two (13%) for bipolar disorder type II, and one (5%) for panic disorder with agoraphobia.

Table 3 about here

The primary outcome measure was the severity score of the LSAS. The average LSAS