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Group cognitive behavioral therapy with interoceptive exposure for drug-refractory irritable bowel syndrome: a randomized controlled trial

Shino Kikuchi*[1,6] MD, Yuki Oe[2,8] MA, Yuri Ito[3] MA, Takashi Sozu[4] PhD, Yohei Sasaki[5] MA, Masatsugu Sakata[6] MA, Yan Luo[6] MD, Ethan Sahker[6,7] PhD, Masaru Horikoshi[8] PhD, Hiroshi Seno[1] MD PhD, Toshi A Furukawa[6] MD PhD.

[1]*Department of Gastroenterology and Hepatology, Kyoto University Graduate School of Medicine, Kyoto, Japan*

[2]*Department of Neuropsychiatry, School of Medicine, Kyorin University, Tokyo, Japan*

[3]*Department of Psychiatry, Kyoto University Hospital, Kyoto, Japan*

[4]*Department of Information and Computer Technology, Faculty of Engineering, Tokyo University of Science, Tokyo, Japan*

[5]*Department of Clinical Epidemiology, Translational Medical Center, National Center of Neurology and Psychiatry, Tokyo, Japan*

[6]*Department of Health Promotion and Human Behavior, Kyoto University Graduate School of Medicine/School of Public Health, Kyoto, Japan*

[7]*Population Health and Policy Research Unit, Medical Education Center, Kyoto University Graduate School of Medicine, Kyoto, Japan*

[8]*National Center for Cognitive Behavior Therapy and Research, National Center of Neurology and Psychiatry, Tokyo, Japan*

***Corresponding author:** shino_k@kuhp.kyoto-u.ac.jp

Shino Kikuchi, Department of Gastroenterology and Hepatology, Kyoto University Graduate School of Medicine, Kyoto, 606-8507, Japan

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Guarantor of the article: Shino Kikuchi, shino_k@kuhp.kyoto-u.ac.jp

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TS reports personal fees from Ajinomoto, Edwards Lifesciences, and Nippon Kayaku. TA participates in the Data Safety Monitoring Board or Advisory Board of Otsuka Pharmaceutical, EPS International Holdings, and EPS Associates. MH has a patent 2020-548587concerning smartphone CBT apps pending, and intellectual properties for Kokoro-app licensed to Mitsubishi-Tanabe. HS reports grants from Sumitomo-Dainippon Pharma, Zeria, EA Pharma, and Astellas. TAF reports grants and personal fees from Mitsubishi-Tanabe, MSD, Shionogi, and has a patent 2020-548587concerning smartphone CBT apps pending, and intellectual properties for Kokoro-app licensed to Mitsubishi-Tanabe. All other authors declare no competing interests.

Ethics Committee and Clinical Trials:

The study protocol was approved by the Medical Ethics Committee of Kyoto University (C1360) and is registered on UMIN-CTR (https://www.umin.ac.jp/icdr/index.html) and trial identification number is UMIN000031710.

Data availability statement:

All individual participant data collected during the study after de-identification are available to scientific researchers upon reasonable request through the first or last author, from immediately after publication until 10 years later. All data will be kept for 10 years. The study protocol was published in BMC Gastroenterology (DOI: 10.1186/s12876-020-1157-z).

ABSTRACT

OBJECTIVES:

Few people can access psychotherapy for irritable bowel syndrome (IBS). Group cognitive-behavioral therapy (GCBT) may be efficient, but the evidence for its efficacy is weak and limited. We aimed to assess the efficacy and safety of GCBT with interoceptive exposure (GCBT-IE), a novel form of GCBT for drug-refractory IBS.

METHODS:

A single-center, open-label, randomized, controlled trial was conducted in Japan among people aged 18–75 with moderate-to-severe drug-refractory IBS. Participants were stratified by IBS severity and allocated 1:1 to 10-week GCBT-IE or waiting-list (WL) in a block-wise randomization by independent staff. Both arms practiced self-monitoring and received treatment as usual. Multiple primary outcomes were changes from baseline to week 13 in the IBS Symptom Severity Score (IBS-SSS) and the IBS-Quality of Life Measure (IBS-QOL), assessed in the intention-to-treat sample.

RESULTS:

A total of 114 people with drug-refractory IBS were randomized to GCBT-IE (n=54) or WL (n=60). Forty-nine participants (90.7%) in the GCBT-IE arm and 58 (96.7%) in the WL arm

completed the week 13 assessment. Participants in the GCBT-IE arm reported greater improvements in both IBS symptom severity and QoL compared to the WL arm, with −115.8 versus −29.7 on the IBS-SSS (a difference of −86.1, 95% CI −117.3 to −55.0), and 20.1 versus −0.2 on the IBS-QOL (a difference of 20.3, 95% CI 15.2 to 25.3), respectively. Six unexpected serious adverse events were reported but were judged as unrelated to the interventions.

CONCLUSIONS:

GCBT-IE is an efficacious, safe, and efficient treatment option for people with drug-refractory IBS.

Keywords:

Irritable bowel syndrome; Functional gastrointestinal disorders; Cognitive-behavioral therapy; Group treatment.

INTRODUCTION

Irritable bowel syndrome (IBS) is a common functional bowel disorder with prevalence ranging from 3.8 to 11.2%[1,2]. IBS mainly occurs in people under the age of 50 and is characterized by recurrent abdominal pain and abnormal bowel habits[1], which negatively affect peoples' daily lives, social activities, and socioeconomic factors such as healthcare costs[3,4]. However, treatments for IBS, especially non-pharmacological treatments, are limited and many people suffer from ongoing symptoms. Effective treatment is therefore important and may dramatically improve the quality of life (QoL) of people with IBS[5].

Cognitive-behavioral therapy (CBT) is one non-pharmacological treatment for people with IBS who do not respond to usual treatments[6,7]. However, despite its reported effectiveness[8,9], the availability of IBS-specific CBT is limited compared to the demand[10]. Considerable barriers to the widespread use of IBS-specific CBT include the shortage of skilled therapists and the time restrictions associated with individual treatments. Group CBT (GCBT) can increase access to CBT, as several people can receive the treatment simultaneously[11]. Although one systematic review reported the efficacy of GCBT for IBS[12], its conclusions remain equivocal because there were only two small studies included and both were rated at high risk of study bias[13,14]. In the meantime, the techniques of CBT for IBS have seen improvements, with interoceptive exposure to visceral sensations showing potentially higher efficacy than conventional CBT[15].

We therefore designed a randomized controlled trial (RCT) using CBT with interoceptive exposure (CBT-IE). We hypothesized that participants in the group CBT-IE (GCBT-IE) arm would show greater improvement in IBS symptom severity, QoL, and anxiety, including visceral anxiety, compared to the waiting list (WL) control arm. We aimed to evaluate the efficacy and safety of GCBT-IE compared to WL in terms of disease severity and QoL in people with drug-refractory IBS.

METHODS

The study protocol was approved by the Medical Ethics Committee of Kyoto University (C1360) and registered on UMIN-CTR (UMIN000031710). The study was conducted in accordance with the principles of the Declaration of Helsinki of 1975, and with the Medical Research Involving Human Subjects Act.

Study design and participants

Study design. The study was conducted as an open-label, individually randomized, parallel-group, WL-controlled trial at Kyoto University Hospital, Japan. Participants aged 18–75 were recruited by self-referral through advertisements or by referral from 178 primary, 12 secondary, and 2 tertiary care in Kyoto and its vicinity, between May 2018 and December 2020.

The majority of primary care physicians in Japan train at secondary or tertiary hospitals and begin their practice after obtaining their specialist certification. Furthermore, patients are free to be seen at any clinic or hospital of their own choice. Therefore, most of our participants were

self-referred or referred from primary care, but had been diagnosed and treated for IBS by either gastroenterologists or general internal medicine physicians.

Eligibility criteria. Eligible people met Rome □ or □ IBS criteria at study enrollment[16,17], and maintained moderate-to-severe IBS with the IBS Symptom Severity Score (IBS-SSS) of 175 or higher[18], despite at least three months of medications. They had sufficient Japanese proficiency and willingness to participate in group sessions. They were excluded if they had uncontrolled comorbid abdominal disease, abdominal surgery likely related to IBS, unremitted mental illness (e.g., severe depression, or psychosis), suicidal ideation with more than two points on item 9 of the Patient Health Questionnaire-9 (PHQ-9)[19], were unsuitable for group therapy, or were pregnant. We also excluded those who had ever received structured psychotherapies to remove the influence of previous psychotherapeutic experiences as much as possible.

Inclusion procedure. We initially conducted a telephone eligibility check with an "alarm function list"[6], and if serious lesions were suggested, recommended seeing a doctor for further assessment. Age, disease severity, and medication duration were also checked at that time. After meeting the telephone eligibility check, potential participants were seen by a gastroenterologist and completed the remaining eligibility checks. Written informed consent was obtained from all participants. Figure 1 shows this study flowchart.

Randomization and masking. After completing baseline assessments, participants were stratified by baseline IBS severity and individually randomized 1:1 to GCBT-IE or WL. To reduce withdrawals, randomization was done on the same day as the intervention. Because four

participants were required in each group, block-wise randomization in variable block sizes between four and eight was done. Randomization was conducted by two independent staff, using consecutively numbered, sealed, opaque envelopes containing the randomization allocation generated by an independent statistician to ensure concealment of the allocation. Participants and therapists were not masked for treatment assignment, only the statistician responsible for the analysis was masked. Assessments were completed by participants using self-administered assessment forms.

Intervention and control

GCBT-IE was delivered face-to-face, with participants attending ten weekly 90-minute group sessions and one booster session one month after the last session. Participants were given weekly homework tasks. From May 2020, to avoid the spread of coronavirus disease 2019, the sessions were held online, with the time and frequency remaining the same.

The contents of GCBT-IE included: psychoeducation of IBS focusing on brain-gut interaction, attention control for hypersensitivity to visceral sensations, cognitive restructuring for unhelpful thoughts, interoceptive exposure to unpleasant visceral sensations, exposure to fear and avoidance situations, and relapse prevention[20]. In interoceptive exposure to unpleasant visceral sensations, participants learn to feel less anxiety about unpleasant sensations through repeated intentional exposure that cause unpleasant sensations. For example, a person who believes "coldness always causes abdominal pain" is asked to apply ice to their stomach for a short time. Then they experience that "coldness does not always cause abdominal pain." Such challenges to unhelpful beliefs promote cognitive restructuring. Other details of GCBT-IE are described in

Supplemental Table 1. The original program was for individual CBT[15], but with the permission of the original authors, we changed it into a Japanese GCBT program[20].

Regardless of assignment, all participants continued treatment as usual (TAU), received one 30-minute group disease education and completed four one-week diaries for self-monitoring on a 4-item, 5-point scale. TAU was defined as the continuation of current treatment without any psychotherapy. Participants were asked not to change their medication without medical advice during their participation period. Meanwhile, non-pharmacological treatments other than psychotherapies, such as diet and lifestyle changes, were not restricted in this study because they were explained in the disease education and were also difficult to control in the participants' daily lives. Participants allocated to the WL arm were allowed to undergo GCBT-IE after the week 13 assessment.

Therapist. Two therapists with over 10 years of clinical experience conducted CBT. One was a gastroenterologist with IBS treatment experience and the other was a skilled clinical psychologist. Because both providers had little experience with IBS-specific CBT, supervised CBT training was completed prior to study commencement. All sessions followed the treatment manual and were recorded for fidelity checking and supervision purposes. An independent clinical psychologist assessed treatment fidelity in a random sample of 17 out of 170 (10%) using a pre-prepared GCBT-IE fidelity measurement.

Data collection

Outcomes were assessed at baseline, 4, 9, 13, and 27 weeks after randomization, with the primary outcomes measured at all five points and secondary outcomes at four points except at week 27. Assessments were completed on an online platform or by participants posting paper questionnaires. A small incentive (a ¥1000 gift card, about $9.0) was paid for each assessment.

Primary outcomes. The multiple primary outcomes were IBS-SSS and the Irritable Bowel Syndrome-Quality of Life Measure (IBS-QOL) at week 13 after randomization[18,21,22]. The IBS-SSS measures IBS severity on a 5-item scale (score 0–500), rated as mild (75–174), moderate (175–300), or severe (301–500)[18]. IBS-SSS responders were defined as a 50-point or greater reduction from baseline[18]. The IBS-QOL measures IBS-specific QoL on a 34-item, 5-point scale (score 0–100), with scores increasing as QoL improves[21]. IBS-QOL responders were defined as a 14-point or greater increase from baseline[23]. Responders on the IBS-SSS and IBS-QOL represented clinically meaningful improvements and were treated as complementary to the primary outcomes.

Secondary outcomes. The Gastrointestinal Symptom Rating Scale (GSRS) measured common symptoms of gastrointestinal disorders[24]. The Generalized Anxiety Disorder-7 (GAD-7) measured the severity of GAD[25]. PHQ-9 measured the severity of depression[19]. EuroQol-5 Dimension-5Level (EQ-5D-5L) and Visual Analog Scale (VAS) assessed health-related QoL and overall health status, respectively[26]. The Irritable Bowel Syndrome-Global Improvement Scale (IBS-GIS) asked about IBS symptom improvement before and after trial[27]. IBS-GIS was not measured at baseline and responders were defined as having moderate or substantial improvement. The Composite Primary Symptom Reduction (CPSR) score measured IBS

improvement and was calculated from a self-monitoring diary[28]. CPSR responders were defined as 0.5 or greater improvement. Patient-reported adverse events (AEs) were recorded by the therapists and serious AEs (SAEs) were reported to the principal investigator and the medical ethics committee. Treatment and homework adherence and medication changes were also recorded by the therapists at each visit.

Statistical analyses

Sample size. Power analysis based on a t-test required 55 participants per arm to detect an effect size of 0.5 (moderate effect size) with at least of 80% power, a correlation coefficient of 0.4 between multiple primary outcomes, and an α-level of 0.025 (two-sided) with consideration of multiple primary outcomes[29,30]. Assuming up to 30% loss of follow-up, 112 participants were required.

Primary and secondary outcomes were analyzed in accordance with the intention-to-treat principle. Efficacy of GCBT-IE was defined when one or more of the primary outcomes was statistically significant at a pre-specified α-level of 0.025 (two-sided)[29]. The Bonferroni method was used to adjust for the multiplicity of the primary outcomes.

For continuous outcomes, between-group differences of least squares (LS) means changes and their 95% confidence intervals (CIs) were calculated using restricted maximum likelihood-based mixed-effects models for repeated measures (MMRM) for the change from baseline to week 13 . Within MMRM, treatment, time (4, 9, or 13 weeks), and treatment-by-time interaction were used as fixed effects, participants as random effects, and baseline score as a covariate. Missing data

were appropriately handled under a missing at random assumption. For binary outcomes, risk ratios and their 95% CIs were calculated. CPSR was calculated from baseline and week 13 data and analyzed by t-test.

The robustness of the main results was confirmed by analysis of covariance (ANCOVA) using data from "completers" who attended the first five sessions (per-protocol set). Last observation carried forward (LOCF) method was used to impute missing data. We also performed subgroup analyses by MMRM on IBS-SSS and IBS-QOL according to disease duration, IBS subtypes, and implementation format (face-to-face or Internet-based; post-hoc analysis). Follow-up assessment at week 27 was assessed descriptively. Statistical analyses were done with SAS version 9.4.

RESULTS

Participants. Between May 2018 and December 2020, 266 people were referred to our study, including self-referrals, and after eligibility screening, 114 were randomly assigned 54 to GCBT-IE or 60 to WL (Figure 1). In the current sample of participants, 83.3% met both Rome Ⅲ and Ⅳ criteria, while 16.7% met only Rome III criteria. Baseline characteristics were balanced between the two arms (Table 1).

After randomization, five of 54 participants (9.3%) in the GCBT-IE arm and 2/60 (3.3%) in the WL arm withdrew from the study by week 13. For adherence, all participants in the GCBT-IE arm received their first session, and 52/54 (96.3%) completed at least the first five sessions (per-protocol set). In the GCBT-IE arm, 48/54 (88.9%) participants completed the week 27 follow-up assessment by July 2021.

Fidelity. Treatment fidelity by the two therapists was high, with a mean fidelity score of 87.3% (range 78.5–100%, SD 6.0) for randomly selected recordings.

Outcomes

Table 2 shows a descriptive summary of the primary outcomes and a comparison between the two arms in the intention-to-treat analysis. Figure 2 and 3 shows the LS means changes from baseline at each assessment time for IBS-SSS (Figure 2) and IBS-QOL (Figure 3) in both arms. At week 13, IBS-SSS was 86.1 points lower (95% CI 55.0–117.3), and IBS-QOL was 20.3 points higher (15.2–25.3) in the GCBT-IE arm than in the WL arm. The GCBT-IE arm also had 1.9 times (95% CI 1.3–2.7) more IBS-SSS responders (≥ 50 points reduction) and 7.6 times (3.2–17.9) more IBS-QOL responders (≥ 14 points increase) than the WL arm. In the GCBT-IE arm, greater improvement in both IBS symptom severity and QoL was maintained at week 27. Scores of IBS-SSS domains and IBS-QOL subscales are provided in Supplemental Tables 2 and 3, respectively.

Table 3 shows a descriptive summary and comparisons between the two arms for the secondary outcomes. All secondary outcomes at week 13 showed a statistically significant improvement in GCBT-IE compared to WL. Scores of GSRS subscales are provided in Supplemental Table 4.

ANCOVA using the per-protocol set showed that IBS-SSS was 80.2 points lower (95% CI 49.1–112.1) and IBS-QOL was 19.0 points higher (13.8–24.2) in the GCBT-IE arm compared to the WL arm, consistent with the results of the intention-to-treat analysis. In all subgroup analyses,

GCBT-IE showed statistically significant improvements in both IBS-SSS and IBS-QOL compared to WL, consistent with the primary outcomes (Supplemental Tables 5 and 6). The interaction was not significant in any subgroup.

Five participants reported six unexpected SAEs (five in the GCBT-IE arm and one in the WL arm). All events were reported to the medical ethics committee and were determined to be unrelated to the intervention. Another 17 AEs were reported (seven in the GCBT-IE arm and 10 in the WL arm). Due to AEs or SAEs, 4/54 (7.4%) participants in the GCBT-IE arm (cardiac death, depression, neurological disorder, fracture) and 2/60 (3.3%) in the WL arm (panic disorder, gastrointestinal disorder) dropped out.

DISCUSSION

The present study in people with drug-refractory IBS showed that GCBT-IE resulted in statistically significant and clinically meaningful improvements in all outcomes at week 13, compared to the WL control. Regarding safety, six SAEs were reported, none of which were directly related to the intervention. Subgroup analyses confirmed consistent efficacy of GCBT-IE, regardless of disease duration, IBS subtypes, or implementation format.

To the best of our knowledge, this study is the largest RCT of GCBT for IBS. One recent systematic review reported the efficacy of GCBT for IBS[12], but it included only two small RCTs[13,14]. These previous studies were similar to ours in terms of frequency and length of sessions and controls, but the methodologies such as sample size calculation and randomization

were not clear[13,14]. Another difference from previous studies was that we included interoceptive exposure as a GCBT component.

Based on brain-gut interaction, exposure practice, especially interoceptive exposure, is thought to reduce visceral anxiety and avoidance behaviors, and improve QoL[31]. Exposure practices were initiated after the week 4 assessment, and in fact, at the week 9 and subsequent assessments, the GCBT-IE arm had greater improvements in food avoidance, activity with interferences (IBS-QOL subscales), and disease-related QoL (IBS-QOL and IBS-SSS QOL domain) than the WL arm. Similar improvements were also seen in anxiety (GAD-7), depression (PHQ-9), and dysphoria (IBS-QOL subscale).

These results may suggest that exposure practices contributed to the improvement in QoL, anxiety, and depression in the GCBT-IE arm. This aligns with previous RCT using individual CBT-IE which also reported improvements in anxiety[15]. Furthermore, GCBT has advantages including normalization through meeting others with the same illness, surrogate learning effects through other participants' experiences, and providing a safe exposure environment[11]. We believe that these effects might encourage exposure practices and led to the high efficacy of GCBT-IE.

Furthermore, this study shows that GCBT-IE is not only efficacious for people with drug-refractory IBS, but also may contribute to increasing IBS-specific CBT delivery by compensating for the shortage of skilled therapists. First, through the group format, the overall estimated treatment time was reduced from 594 hours (54 people received 11 hour-long sessions including one booster) to 280.5 hours (17 groups received 11 1.5-hour sessions). This may

enable more efficient and cost-effective treatment. Next, the results suggest that therapists who are not familiar with IBS-specific CBT may be able to deliver an efficacious treatment with high-fidelity with minimal training by following manualized treatment. Finally, this study also shows the efficacy of GCBT-IE by Internet-based telemedicine. Subgroup analyses suggests that implementation of GCBT-IE through the Internet may be as efficacious as face-to-face treatment and facilitate IBS-specific CBT in remote areas. However, due to the small sample size, the results of subgroup analyses are limited.

Besides efficacy and dissemination, adherence and long-term follow-up need to be considered for implementing GCBT-IE in clinical practice. Our study showed high adherence, which could be attributed to the timeframe of the sessions and absence management. Because most of our participants were workers, we held the sessions at convenient times, such as evenings and weekends. Additionally, we provided individual follow-up sessions for those who could not attend the first five sessions. In face-to-face CBT, work and childcare are the most common causes of poor adherence and withdrawal[32]. The flexibility of timeframes and absence management may therefore have led to high adherence in this study, but it needs to be balanced with the feasibility in clinical practice.

Regarding the long-term follow-up of this study, although the results were descriptive, the beneficial results were maintained through week 27. Another study that followed participants receiving IBS-specific GCBT for an average of 2.5 years reported a 50% reduction in gastrointestinal symptom complaints compared to pre-treatment[33]. However, as both studies lacked comparative controls, we cannot rule out the possibility of spontaneous IBS improvement.

The present study has some limitations that should be noted. First, using the WL condition while on TAU in this study may have potentially overestimated the treatment effect[34,35]. However, setting up the placebo control condition similar to the pill placebo, the gold standard in pharmacotherapy RCTs, is extremely difficult in psychotherapy RCTs. Hence, psychotherapy controls need to be designed with the specific clinical question they intend to answer in mind, while also paying due attention to participant needs, available resources, ethics, and acceptability. This study is intended to answer the clinical question of whether the addition of the CBT-IE program to TAU is meaningful over TAU alone. However, participants in the WL arm were potentially disrupted in their spontaneous recovery during the waiting period[36]. To minimize this effect, both arms received group disease education and self-monitoring in addition to TAU, and the pre-planned 14-week waiting period was adhered to as much as possible. Furthermore, we believe the WL control while receiving TAU was acceptable and ethical for this study in terms of participant needs and available resources, as access to IBS-specific psychotherapy is incredibly limited in Japan. In fact, 55 (91.7%) participants in the WL arm opted to undergo GCBT-IE after their wait period, and 51 (85.0%) completed the sessions. Admittedly, our WL-controlled design was unable to control for the effects of therapists "spending more time" and "paying more attention" in the CBT-IE arm. To estimate the CBT-specific effects over and above such non-specific factors, future studies should provide equivalent time and attention controls, such as supportive group sessions which last the same length, but which completely exclude CBT-specific factors.

Second, because this was an open-label, patient-reported study, treatment assignments potentially led to detection bias in the outcomes and AEs[36]. To minimize these effects, both arms were assessed with the same methods and timing, using reliable and validated measures. It should also be pointed out that for functional disorders such as IBS, patient-reported outcomes represent the best results of interventions[37]. Finally, this study was conducted in only one Japanese hospital, potentially limiting its generalizability. Given the limitations, we adopted a comprehensive recruitment strategy from primary, secondary, tertiary care, and the general public, which may have improved representation of Japanese people with IBS seeking psychotherapy.

Strengths of this study include a broad target population and a rigorously conducted, high adherence RCT. Therapists received supervised training in IBS-specific CBT and delivered high fidelity GCBT-IE based on a detailed treatment manual. While we reported some promising findings of GCBT-IE for IBS, we believe that future studies should consider telemedicine's effectiveness, cost-effectiveness, clinical adherence, and long-term effects to promote its widespread use and implementation in clinical practice.

Conclusion. The present study shows that GCBT-IE may be an efficacious, safe, and efficient treatment for people with drug-refractory IBS. Our results provide a meaningful rationale for considering GCBT-IE for people with drug-refractory IBS while strengthening and complementing the evidence of a systematic review based on two RCTs demonstrating the efficacy of GCBT for IBS.

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Supplemental-http://links.lww.com/AJG/C436

Visual Abstract-http://links.lww.com/AJG/C437

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FIGURE LEGENDS

FIGURE 1

Consolidated Standards of Reporting Trials (CONSORT) flow-chart. COVID-19, coronavirus disease 2019; GCBT-IE, group cognitive-behavioral therapy with interoceptive exposure; IBS, irritable bowel syndrome; TAU, treatment as usual.

FIGURE 2

LS means changes in IBS-SSS up to week 13 in the GCBT-IE and WL arms. CI, confidence interval; GCBT-IE, group cognitive-behavioral therapy with interoceptive exposure; IBS-SSS, the Irritable Bowel Syndrome Symptom Severity Score; LS, Least squares; WL, waiting list.

FIGURE 3

LS means changes in IBS-QOL up to week 13 in the GCBT-IE and WL arms. CI, confidence interval; GCBT-IE, group cognitive-behavioral therapy with interoceptive exposure; IBS-QOL, the Irritable Bowel Syndrome-Quality of Life Measure; LS, Least squares; WL, waiting list.

Study Highlights:

WHAT IS CURRENT KNOWLEDGE

- Irritable bowel syndrome (IBS) negatively affects both individual's daily lives and socioeconomics.
- IBS-specific cognitive-behavioral therapy (CBT) is effective but is scarcely available.
- Current evidence on the efficacy of group CBT (GCBT) for IBS is weak and limited.

WHAT IS NEW HERE

- GCBT with interoceptive exposure (GCBT-IE) is a novel and efficacious treatment for drug-refractory IBS.
- GCBT-IE reduced total treatment time, streamlined therapist education, and provided opportunities for Internet-based telemedicine.
- GCBT-IE may streamline IBS treatment and facilitate the dissemination and implementation of IBS-specific CBT.

Table 1: Baseline characteristics of participants in the intention-to-treat population

	GCBT-IE (n = 54)	Waiting list (n = 60)
Age, years	41.9 (14.3)	37.4 (14.7)
Sex		
Women	35 (64.8%)	37 (61.7%)
Men	19 (35.2%)	23 (38.3%)
Marital status		
Single	25 (46.3%)	30 (50.0%)
Married	23 (42.6%)	25 (41.7%)
Separate	2 (3.7%)	1 (1.7%)
Divorced	3 (5.6%)	2 (3.3%)
Widowed	1 (1.9%)	2 (3.3%)
Educational level		
Primary and secondary	2 (3.7%)	4 (6.7%)
High school/A level	24 (44.4%)	29 (48.3%)
University	24 (44.4%)	23 (38.3%)
Graduate school	4 (7.4%)	4 (6.7%)
Employment status		
Full-time	27 (50.0%)	30 (50.0%)
Part-time	13 (24.1%)	14 (6.7%)
Retirement	3 (5.6%)	5 (8.3%)
In education	4 (7.4%)	7 (11.7%)
Unemployed	7 (13.0%)	4 (6.7%)
Family income[a]		
< $27,300	15 (27.8%)	12 (20.0%)
$27,300–54,600	16 (29.6%)	23 (38.3%)
$54,600–90,900	12 (22.2%)	14 (23.3%)
$90,900–181,800	10 (18.5%)	11 (18.3%)
≥ $181,800	1 (1.9%)	0 (0.0%)
Duration of IBS		
0.5–2 years	7 (13.0%)	4 (6.7%)
2–5 years	10 (18.5%)	7 (11.7%)
5–10 years	13 (24.1%)	12 (20.0%)
≥ 10 years	24 (44.4%)	37 (61.7%)
IBS-SSS score, range 0–500	302.7 (70.6)	301.8 (66.3)
IBS-QOL total score, range 0–100	56.5 (18.6)	53.9 (20.3)
IBS subtype		
IBS diarrhea	33 (61.1%)	34 (56.7%)
IBS constipation	2 (3.7%)	3 (5.0%)
IBS alternating	9 (16.7%)	10 (16.7%)
IBS unclassified	10 (18.5%)	13 (21.7%)
Comorbid mental disorders	25 (46.3%)	33 (55.0%)
Psychotropic medications[b]	23 (42.6%)	32 (53.3%)
Smoking		
never	39 (72.2%)	50 (83.3%)
past-smoker	12 (22.2%)	6 (10.0%)
current-smoker	3 (5.6%)	4 (6.7%)
Drinking habits		
non-drinker	13 (24.1%)	23 (38.3%)
social drinker	30 (55.6%)	33 (55.0%)
habitual drinker	11 (20.4%)	4 (6.7%)
Medications for IBS[c]		
Probiotics	34 (63.0%)	38 (63.3%)
Polycarbophil calcium	15 (27.8%)	23 (38.3%)
Ramosetron	23 (42.6%)	24 (40.0%)
Laxatives	6 (11.1%)	13 (21.7%)
Antidiarrheal agents	9 (16.7%)	6 (10.0%)
Others[d]	19 (35.2%)	20 (33.3%)

Data are mean (SD), or n (%).
[a]One United States dollar is equivalent to about 110 Japanese yen.
[b]Psychotropic medications include medications such as antidepressants, anxiolytics, stabilizers, antipsychotics, and sleeping pills.
[c]Medications for IBS include all current and past prescriptions for IBS, and some people have multiple medications.
[d]Others include medicines such as linaclotide, scopolamine butylbromide, trimebutine maleate, and herbal medicines (Kampo).
GCBT-IE, group cognitive-behavioral therapy with interoceptive exposure; IBS-QOL, the Irritable Bowel Syndrome-Quality of Life; IBS-SSS, IBS Symptom Severity Score.

Table 2 Descriptive summary and comparisons between GCBT-IE and Waiting List for primary outcomes

	GCBT-IE			Waiting list			GCBT-IE versus Waiting list	
	n	Mean (SD)	LS means changes[a] (95% CI)	n	Mean (SD)	LS means changes[a] (95% CI)	Difference in LS means changes[b] (95% CI)	*P* value
IBS-SSS, score 0-500								
baseline	54	302.7 (70.6)	..	60	301.8 (66.3)	..	..	..
4 weeks	52	261.8 (80.7)	−43.1 (−64.3 to −21.8)	59	269.5 (90.9)	−33.3 (−53.3 to −13.4)	−9.7 (−38.8 to 19.4)	0.51
9 weeks	49	226.1 (82.9)	−77.1 (−100.8 to −53.4)	58	266.7 (97.9)	−36.4 (−58.4 to −14.4)	−40.7 (−73.0 to −8.4)	0.014
13 weeks	49	187.6 (85.1)	−115.8 (−138.7 to −93.0)	58	273.5 (96.8)	−29.7 (−50.8 to −8.5)	−86.1 (−117.3 to −55.0)	<0.0001
27 weeks	48	185.4 (90.5)	..	..	..	..	..	..
IBS-QOL, score 0–100								
baseline	54	56.5 (18.6)	..	60	53·9 (20·3)	..	..	..
4 weeks	52	59.2 (18.4)	3.4 (0.0 to 6.7)	59	54.5 (21.6)	0.1 (−3.1 to 3.2)	3.3 (−1.3 to 7.9)	0.16
9 weeks	49	70.6 (17.3)	14.2 (10.6 to 17.7)	58	55.6 (22.0)	0.8 (−2.5 to 4.2)	13.3 (8.4 to 18.2)	< 0.0001
13 weeks	49	76.6 (16.4)	20.1 (16.4 to 23.8)	58	54.5 (23.0)	−0.2 (−3.7 to 3.2)	20.3 (15.2 to 25.3)	<0.0001
27 weeks	48	72.7 (17.7)	..	..	..	..	..	..
	n	responder (%)		n	responder (%)		Risk ratio (95% CI)	*P* value
IBS-SSS responders[c]								
4 weeks	52	22 (42.3)		59	24 (40.7)		1.0 (0.67 to 1.6)	1.00
9 weeks	49	30 (61.2)		58	29 (50.0)		1.2 (0.87 to 1.7)	0.33
13 weeks	49	36 (73.5)		58	23 (39.7)		1.9 (1.3 to 2.7)	0.0008
27 weeks	48	38 (79.2)		..	..		..	..
IBS-QOL responders[d]								
4 weeks	52	13 (25.0)		59	5 (8.5)		3.0 (1.1 to 7.7)	0.022
9 weeks	49	25 (51.0)		58	5 (8.6)		5.9 (2.5 to 14.3)	<0.0001
13 weeks	49	32 (65.3)		58	5 (8.6)		7.6 (3.2 to 17.9)	<0.0001
27 weeks	48	25 (52.1)		..	..		..	..

Data are mean (SD) or n (%) unless otherwise specified.

[a]LS means of changes from baseline to each assessment point are from restricted maximum likelihood-based mixed-model repeated measures.

[b]Between-group differences in LS means, *P* value < 0.025 (two-sided).

[c]IBS-SSS responders are defined as participants who had a clinically meaningful change in IBS-SSS (≥ 50 points) from baseline to 13 weeks.

[d]IBS-QOL responders are defined as participants who had a clinically meaningful change in IBS-QOL (≥ 14 points) from baseline to 13 weeks.

GCBT-IE, group cognitive-behavioral therapy with interoceptive exposure; IBS-QOL, the Irritable Bowel Syndrome-Quality of Life Measure; IBS-SSS, IBS Symptom Severity Score; LS, least squares.

	GCBT-IE		Waiting list		GCBT-IE versus Waiting list	
	n	Mean (SD)	n	Mean (SD)	Differences in LS means[a] or Risk ratio[b](95% CI)	*P* value
GSRS, score 1–7						
Baseline	54	2.7 (1.0)	60	2.7 (0.9)	..	..
4 weeks	52	2.6 (0.9)	59	2.7 (0.9)	−0.11 (−0.35 to 0.14)	0.39
9 weeks	49	2.3 (0.9)	58	2.8 (0.9)	−0.53 (−0.79 to −0.27)	0.0001
13 weeks	49	2.0 (0.7)	58	2.8 (1.0)	−0.75 (−1.02 to −0.48)	<0.0001
GAD-7, score 0–21						
baseline	54	8.5 (4.8)	60	9.4 (5.6)	..	..
4 weeks	52	8.7 (4.3)	59	9.5 (5.7)	−0.44 (−1.8 to 0.90)	0.52
9 weeks	49	6.5 (4.3)	58	8.8 (5.3)	−1.9 (−3.4 to −0.48)	0.0093
13 weeks	49	5.1 (3.8)	58	9.6 (6.1)	−4.1 (−5.6 to −2.6)	<0.0001
PHQ-9, score 0–27						
baseline	54	9.2 (5.1)	60	9.8 (6.0)	..	..
4 weeks	52	9.1 (5.8)	59	9.8 (6.7)	−0.37 (−2.0 to 1.3)	0.66
9 weeks	49	7.3 (5.3)	58	9.5 (6.1)	−1.9 (−3.6 to −0.29)	0.021
13 weeks	49	5.8 (4.9)	58	10.6 (7.2)	−4.5 (−6.5 to −2.6)	<0.0001
EQ-5D-5L, range −0·025 to 1·000						
baseline	54	0.70 (0.15)	60	0.70 (0.18)	..	..
4 weeks	52	0.64 (0.17)	59	0.63 (0.19)	0.01 (−0.04 to 0.07)	0.65
9 weeks	49	0.69 (0.20)	58	0.67 (0.19)	0.02 (−0.05 to 0.08)	0.59
13 weeks	49	0.76 (0.17)	58	0.62 (0.20)	0.14 (0.08 to 0.20)	<0.0001
EQ-VAS, score 0–100						
baseline	54	56.6 (19.1)	60	57.2 (19.4)	..	..
4 weeks	52	55.7 (21.2)	59	52.4 (22.4)	3.6 (−4.2 to 11.4)	0.36
9 weeks	49	61.8 (20.9)	58	55.3 (19.2)	6.7 (−0.68 to 14.0)	0.075
13 weeks	49	63.5 (21.5)	58	48.9 (22.6)	14.7 (6.5 to 22.9)	0.0006
IBS-GIS[c], range 1–7						
4 weeks	52	3.2 (0.9)	59	3.7 (0.8)	−0.54 (−0.85 to −0.22)	0.0011
9 weeks	49	2.6 (1.4)	58	3.8 (1.0)	−1.1 (−1.6 to −0.67)	<0.0001
13 weeks	49	2.1 (0.9)	58	4.1 (1.0)	−1.9 (−2.3 to −1.6)	<0.0001
CPSR, range −1 to 1						
13 weeks	49	0.26 (0.45)	58	0.07 (0.42)	0.19 (0.02 to 0.36)	0.024
	n	responder (%)	n	responder (%)	Risk ratio (95% CI)	*P* value
IBS-GIS responders[c,d]						
4 weeks	52	10 (19.2)	59	3 (5.1)	3.8 (1.2 to 17.2)	0.035
9 weeks	49	25 (51.0)	58	9 (15.5)	3.3 (1.7 to 6.4)	0.0001
13 weeks	49	33 (67.3)	58	3 (5.2)	13.0 (4.3 to 39.9)	<0.0001
CPSR responders[e]						
13 weeks	48	19 (39.6)	57	11 (19.3)	2.1 (1.1 to 3.9)	0.030

Data are mean (SD) or n (%) unless otherwise specified.

[a]Between-group differences in LS means of changes from baseline to each assessment point are from restricted maximum likelihood-based mixed-model repeated measures, *P* value < 0.05 (two-sided).

[b]Risk ratio is presented only for CPSR, and risk ratio and its *P* value are calculated from t-test, *P* value < 0.05 (two-sided).

[c]IBS-GIS was not recorded at baseline.

[d]IBS-GIS responders were defined as participants who had a clinically meaningful change in IBS-GIS (moderate or significant improvement) from baseline to 13 weeks.

[e]CPSR responders were defined as participants who had a clinically meaningful change in CPSR (≥ 0.5) from baseline to 13 weeks.

CPSR, the Composite Primary Symptom Reduction; EQ-5D-5L, EuroQol-5 Dimension-5Level; GAD-7, the Generalized Anxiety Disorder-7; GCBT-IE, group cognitive-behavioral therapy with interoceptive exposure; GSRS, the Gastrointestinal Symptom Rating Scale; IBS-GIS, the Irritable Bowel Syndrome-Global Improvement Scale; LS, least squares. PHQ-9, the Patient Health Questionnaire-9. VAS, visual analogue scale.

Table 3 Descriptive summary and comparisons between GCBT-IE and Waiting List for secondary outcomes