Kokoro-App No specific adverse events are presumed in participants who use the Kokoro-App. However, using the Kokoro-App might lead to psychological distress in some participants depending on their psychological state.

Compensation insurance

Because all the protocol antidepressant interventions are administered within the approved regulations in Japan, any health hazards shall be covered by the National Health Insurance. However, because the trial involves random allocation, we have contracted a private health insurance (Tokio Marine and Nichido Fire Insurance Co., Ltd.) to compensate for health hazards that have arisen due to this trial.

Data monitoring

The trial will be supervised by the Data and Safety Monitoring Board (DSMB). The board consists of three independent experts in psychiatry and clinical trial methodology. The members of the committee are independent from the present study: Dr Teruhiko Higuchi (Chair of the DSMB, Psychiatrist, National Center for Neurology and Psychiatry), Professor Yoshio Hirayasu (Psychiatrist, Yokohama City University) and Dr Akiko Kada (Biostatistician, National Hospital Organization Nagoya Medical Center). The purpose of DSMB is to check the data monitoring reports prepared by the data center and make recommendations to the principal investigator, where necessary.

Ethical issues

The present study is subject to the ethical guidelines for clinical studies published by the Japanese Ministry of Health, Labor and Welfare, as well as the ethical principles established for research on human beings as stipulated in the *Declaration of Helsinki* and further amendments thereto.

The protocol has been approved by the institutional review boards of Kyoto University Medical School on 12 June 2014 (ID: C842), of Nagoya City University on 11 August 2014 (ID: 45-14-0009) and of Kochi Medical School on 10 September 2014 (ID: ERB-100826). If important protocol modifications such as changes to eligibility criteria, outcomes, or analyses are needed, the investigators will discuss them and report to the review boards for approval.

Written informed consent will be obtained from all participants included in this study. Data of each participant will be handled with sequentially allocated numbers to maintain participant confidentiality.

Data analysis

Details of the planned analyses for the trial will be given in the Statistical Analysis Plan, to be drafted by the trial statistician. The analyses will be conducted according to the plan.

Primary analyses

The primary outcome will be analyzed using a mixed model with repeated measures to examine treatment effect parameters of all the eligible subjects in the primary comparison set according the ITT principle. Allocation group (intervention) and stratification variables used in randomization will be incorporated into the model. A regression coefficient (beta), its 95 % CIs, and a 2-side P value will be calculated. The statistical significance is set at 0.05 (2-sided). If the changes are not linear, an appropriate model will be applied.

Secondary analyses

We will perform secondary analyses to supplement our primary analysis and to obtain finer understanding of our clinical questions. The secondary analyses will use models similar to those of the primary analysis, will analyze data from both the primary and secondary comparison sets as well as from the per protocol set, and will also examine data for the secondary outcome measures. These analyses will be conducted for exploratory purposes. We will not use adjustment for multiple tests. We will report the effect sizes and their 95 % CIs. The methods for these secondary analyses will be stated in detail in the Statistical Analysis Plan.

Interim analyses

We will not perform interim analyses.

Sample size

Sample size was based on a power analysis with 0.8 power to detect an effect size of 0.5 between the groups at $P = 0.05$ (2-sided). It was calculated that 63 patients would be required for each of the two arms for the primary comparison set. Assuming that 30 % of the initial entries would drop out or otherwise be classified into the secondary comparison set at week 1, 164 participants would need to be recruited into the trial.

The effect size of the Kokoro-App was estimated at 0.5 because we anticipated a medium effect size [33] compared with the wait-list control group. In fact, an effect size of 0.69 was observed when we conducted a clinical trial of a 1-to-1 telephone-based CBT program, which formed the prototype of the Kokoro-App, in comparison with a wait-list control [11]. Systematic reviews of clinical trials on the efficacy of computer or Internet-based CBT showed 0.49 [8] and 0.78 [7] in the acute-phase treatment. We therefore calculate that we could anticipate an effect size of approximately 0.5 for the Kokoro-App.

The primary outcome of the present trial is the change in the PHQ-9 through weeks 0, 1, 5 and 9. Taking account of the sample size calculation for repeated measures [34], a sample size per group will not exceed 63 even when we consider associations of 4 time points. However, this is derived from presumption that the treatment effect is stable between any two time points. If there is a large difference between time points, statistical power would decrease. If this does occur, we will recalculate and examine the achieved statistical power post hoc.

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Publication policy

The results from the study will be submitted to peer-reviewed journals. The collaborating researchers have the right to be named as the first author of these papers in the order of their number of recruitment. TAF will be the corresponding author for all the papers.

Trial principal physicians, trial participating physicians and other members of the Steering Committee, if they do not appear as co-author, will be listed at the end of the article. Such authors may be counted as co-authors in some journals but not in others.

Study period

The study period of this trial will be between September 2014 and March 2017, with the participant entry period between June 2014 and October 2016.

Discussion

To our knowledge, the present study represents the first trial investigating the efficacy of smartphone-based CBT in clinical settings, especially for patients still suffering from depression after an adequate trial of antidepressant treatment. Considering the high dropout rate of computer-based CBT [8], smartphone-based CBT may offer a more accessible option because patients can access it anywhere and anytime they have a chance and are willing to do so. Only fewer than 50 % of patients receiving acute-phase antidepressant treatment can achieve remission [4], so that easily accessible CBT may offer some additional benefits in the treatment of depression. The present study focuses on patients with antidepressant-resistant depression, so that targeted population may be those in most need. If the efficacy of a smartphone-based CBT program in this population is confirmed, applicability of the program in real clinical settings is quite promising.

The present study is, however, not without some methodological limitations. First of all, not all patients who are interested in and willing to do the Kokoro-App have a smartphone. This may undermine the applicability of the results from this trial to all patients with antidepressant-resistant depression. Especially, the results might not be applicable to patients in developing countries and to patients with poor ICT literacy.

Second, we selected a wait-list control as the comparator due to the feasibility and ethical considerations, but the nocebo effects of the latter condition can play an important role in the estimation of the efficacy of the smartphone-based CBT. In a network meta-analysis of CBTs, waiting-list controls and no treatment controls, the odds ratio of response for no treatment over waiting-list was statistically significant at 2.9 (95 % CI: 1.3 to 5.7) [35]. However, in the present trial we planned to switch a previous antidepressant treatment to a newer drug for each patient (e.g., sertraline or escitalopram) for all participants at entry to the study, thus raising expectation across the intervention and control arms. This might lead to decreasing nocebo effects of the waiting-list control.

Third, one may consider that results from the primary comparison set are those of an efficacy trial not of an effectiveness trial, because we would only include patients who are able to tolerate the trial antidepressant for 1 week and are accustomed to using a smartphone. This decision was made a priori because the trial is the first one of this kind. However, we will include patients who had failed to meet these conditions in our secondary comparison set, and results from these analyses can be utilized in future effectiveness trials.

Fourth, although the effect size of 0.5 used for calculation of sample sizes was estimated from results of the previous studies on the efficacy of computer or Internet-based CBT [7, 8], one may think that the effect size is too optimistic because the present study focuses on patients with treatment-refractory depression. In addition, a majority of the control conditions used in trials included in previous systematic reviews [7, 8] were waiting-list, which might have led to plausibly large effect sizes. However, our previous clinical trial comparing the efficacy of a telephone-based CBT program added to the employee assistance program with that of the latter alone showed an effect size of 0.69 [11]. The

smartphone-based CBT program in the present study was based on this telephone-based program, and we considered that the estimated effect size of 0.5 in the present study was reasonable.

Trial status

The randomized trial, which commenced in September 2014, is currently in the phase of participant enrollment and follow up.

Abbreviations

BDI-II: Beck Depression Inventory-II; CI: Confidence interval; CRC: Clinical research coordinator; CBT: Cognitive-behavior therapy; DSM: Diagnostic and Statistical Manual of Mental Disorders; DSMB: Data and Safety Monitoring Board; EDC: Electronic data capturing; FIBSER: Frequency, Intensity, and Burden of Side Effects Rating; ICT: Information and communication technology; ITT: Intention-to-treat; PHQ-9: Patient Health Questionnaire-9; PRIME-MD: Primary Care Evaluation of Mental Disorders; QTc: Heart-rate corrected QT interval; RCT: Randomized controlled trial; SIADH: Syndrome of inappropriate anti-diuretic hormone secretion; SSL: Secure Sockets Layer; TAU: Treatment as usual.

Competing interests

The authors have no conflicts of interests to declare that may be affected by the publication of the manuscript.
NW has research funds from the Japanese Ministry of Health, Labor and Welfare and the Japanese Ministry of Education, Science, and Technology. He has also received royalties from Sogensha and Paquet, and speaking fees and research funds from Asahi Kasei, Dai-Nippon Sumitomo, Eli Lilly, Glaxo SmithKline, Janssen, Meiji, MSD, Otsuka and Pfizer.
MH has research funds from the Japanese Ministry of Health, Labor and Welfare and the Japanese Ministry of Education, Science, and Technology. He has received royalties from Igaku Shoin, Shogakukan Shueisha Production, Shindan to Chiryosha, Sogensha, Kangokyokai Shuppan, Kitaoji Shobo and Kongo Shuppan.
MY has research funds from the Japanese Ministry of Health, Labor and Welfare and the Japanese Ministry of Education, Science, and Technology. He has received honoraria for lectures from Meiji Seika Pharma, MSD, Asahi Kasei Pharma, and has contracted research with Nippon Chemiphar. He has received royalties from Igaku Shoin, Seishin Shobou, Koubundou, Sentan Igakusha.
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HI has no conflicts of interest to declare.
AT has received honoraria for speaking at a meeting sponsored by Eli Lilly and Tanabe-Mitsubishi.
YO has received research funds from the Japan Society for the Promotion of Science and speaking fees from Eli Lilly.
NT has no conflicts of interest to declare.
YH has no conflicts of interest to declare.
TAF has received lecture fees from Eli Lilly, Meiji, Mochida, MSD, Otsuka, Pfizer and Tanabe-Mitsubishi, and consultancy fees from Sekisui Chemicals and Takeda Science Foundation. He has received royalties from Igaku-Shoin, Seiwa-Shoten and Nihon Bunka Kagaku-sha publishers. He has received grant or research support from the Japanese Ministry of Education, Science, and Technology, the Japanese Ministry of Health, Labor and Welfare, the Japan Foundation for Neuroscience and Mental Health, Mochida and Tanabe-Mitsubishi. He is a diplomate of the Academy of Cognitive Therapy.

Authors' contributions

All authors contributed to the manuscript as follows: NW designed the study, interpreted the data, and drafted the manuscript. MH designed the study and interpreted the data. MY obtained funding, designed the study, and interpreted the data. SS designed the study, acquired data, and interpreted the data. TA designed the study, acquired data, and interpreted the data. KM designed the study, acquired data, and interpreted the data. MI designed the study, and interpreted the data. NY designed the study, and conducted statistical analysis. HI acquired data, and developed administrative or technical materials. AT acquired data, and developed administrative or technical materials. YO acquired data, and developed administrative or technical materials. NT acquired data. YH acquired data. TAF obtained funding, conceived of and designed the study, acquired data, interpreted the data, developed administrative or technical materials and drafted the manuscript. He has also full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors have revised the important intellectual content critically and have read and approved the final manuscript.

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Regular Article

Cost-effectiveness of cognitive behavioral therapy for insomnia comorbid with depression: Analysis of a randomized controlled trial

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Aim: Although the efficacy of cognitive behavioral therapy for insomnia has been confirmed, dissemination depends on the balance of benefits and costs. This study aimed to examine the cost-effectiveness of cognitive behavioral therapy for insomnia consisting of four weekly individual sessions.

Methods: We conducted a 4-week randomized controlled trial with a 4-week follow up in outpatient clinics in Japan. Thirty-seven patients diagnosed as having major depressive disorder according to DSM-IV and suffering from chronic insomnia were randomized to receive either treatment as usual (TAU) alone or TAU plus cognitive behavioral therapy for insomnia. Effectiveness was evaluated as quality-adjusted life years (QALY) over 8 weeks' time, estimated by bootstrapping of the observed total scores of the Hamilton Depression Rating Scale. Direct medical costs for cognitive behavioral therapy for insomnia and TAU were also evaluated. We calculated the incremental cost-effectiveness ratio.

Results: Over the 8 weeks of the study, the group receiving cognitive behavioral therapy for insomnia plus TAU had significantly higher QALY ($P = 0.002$) than the TAU-alone group with an incremental value of 0.019 (SD 0.006), and had non-significantly higher costs with an incremental value of 254 (SD 203) USD in direct costs. The incremental cost-effectiveness ratio was 13 678 USD (95% confidence interval: −5691 to 71 316). Adding cognitive behavioral therapy for insomnia demonstrated an approximately 95% chance of gaining one more QALY if a decision-maker was willing to pay 60 000 USD, and approximately 90% for 40 000 USD.

Conclusion: Adding cognitive behavioral therapy for insomnia is highly likely to be cost-effective for patients with residual insomnia and concomitant depression.

Key words: behavior therapy, cost–benefit analysis, depressive disorder, resource allocation, sleep initiation and maintenance disorders.

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THE PREVALENCE OF insomnia is very high with a prevalence rate of approximately 5–20% in the general population,[1] which leads to increased use of health-care services and products as well as insomnia-related work absences and reduced productivity. The average annual per-person costs, including direct and indirect costs, have been estimated to be about 5000 USD for individuals with insomnia, and about 1400 USD for those presenting with insomnia symptoms.[2] In addition, insomnia occurs comorbidly with many axis I disorders, especially for depression. The prevalence rates of insomnia are estimated to be as high as 80–90% in untreated depressive patients.[3,4]

Pharmacological and psychological therapies for the treatment of insomnia have been developed and assessed for their efficacy. For psychotherapy, the efficacy of cognitive behavioral therapy for insomnia (CBT-I) has been well investigated. CBT-I is based on a multi-component approach that includes several modules,[5] such as sleep hygiene education, sleep restriction and stimulus control as first-line interventions, and cognitive therapy, relaxation training and sleep compression as adjunctive ones.[6] From results from several randomized controlled trials (RCT), the efficacy of CBT-I has been confirmed for primary insomnia[7,8] as well as insomnia concomitant with depression.[9,10]

In practice, for the purpose of considering a strategy to disseminate an effective treatment to reduce the burden of insomnia, decisions about the value of insomnia treatment should be considered with the cost of the treatment. With regard to CBT for depression, a large number of trials have examined the cost-effectiveness of the psychotherapy in various situations.[11–13] However, to the best of our knowledge, the cost-effectiveness of CBT-I has been investigated in only one cluster trial on hypnotic-dependent people with insomnia.[14]

In the present study, therefore, we aimed to examine the cost-effectiveness of CBT-I consisting of four weekly individual sessions in treatment for patients with residual insomnia and concomitant depression, by using the data from an efficacy trial of CBT-I we previously published.[10]

METHODS

Participants

Patients were recruited from 18 February 2008 to 9 April 2009 at three psychiatric outpatient departments in Japan. The patients were included in the trial if they were currently partially remitted and suffering from mild or moderate major depressive disorder (diagnosed with the DSM-IV), despite having already been on maximum doses of two types of antidepressants for at least 4 weeks for the index episode. In addition to refractory depression, patients were only eligible for the present study if they presented with chronic comorbid insomnia. Inclusion criteria included a score between 8 and 23 on the 17-item GRID-Hamilton Depression Rating Scale (HAMD)[15] and a score of 8 or more on the Insomnia Severity Index (ISI).[5,16,17] Psychotropic medications other than methylphenidate or modafinil, including antidepressants and hypnotics, and prescriptions for medical conditions were allowed and continued.

Study design and interventions

Participants were individually randomized to receive CBT-I plus treatment as usual (TAU) or TAU alone.

An independent statistician generated the random allocation sequences by the computer, using variable blocks and stratified by the severity of depression and by study sites. Allocation sequences were kept centrally, and the allocation was provided by facsimile to each site upon notification of a patient's enrolment.

The psychotherapy consisted of four weekly individual sessions, each lasting approximately 50 min, developed based on a published treatment manual for CBT-I.[6] The treatment regimen was highly structured, including modules of sleep hygiene education, introduction of the behavioral model of insomnia, sleep restriction, stimulus control, sleep titration, and relapse prevention.[10] The regimen was provided to therapists in Japanese as a written manual. Therapists for the psychotherapy were five psychiatrists and a psychiatric nurse. They participated in a 2-day intensive training course on the psychotherapy before the study commencement, and received ongoing supervision monthly thereafter. Patients allocated to the combination group were asked to self-administer these skills after the termination of the intervention sessions at 4 weeks until the final assessment at 8 weeks.

In TAU sessions, a patient met a physician (psychiatrist, none of the psychiatrists who conducted CBT-I) biweekly during which time they discussed their depression symptoms and insomnia and obtained medication. Each session typically lasted

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10 min. Changing types and doses of medication were not allowed in the first 4 weeks of the study unless rapid exacerbation of depression occurred. Physicians were allowed to discuss sleep hygiene but not sleep restriction or stimulus control for insomnia.

Assessment measures

Utility measures

Patients were assessed at baseline, at 4 (post-treatment) and at 8 weeks (1-month follow up). Patients who dropped out of the intervention were still asked to complete the assessments. Depression was assessed using the GRID-HAMD[15] through a face-to-face semi-structured interview by blinded raters at each assessment.[18] Patients were deemed as remitters for depression if their 17-item HAMD score was 7 or less, and as severely depressed if their HAMD score was 27 or more. This scale has been validated in Japan.[19]

In the primary analysis, the data from the HAMD were used to construct an outcome measure called depression-free days (DFD), as used in previous studies.[20,21] In brief, if patients had an HAMD score of 27 or higher, they were assumed to be lacking a DFD; when scoring 7 or lower, they were assumed to have a full DFD; if they scored between 7 and 27, the day was weighted proportionally. To determine the number of DFD over the study period, the scores for the baseline and 4 weeks, and those for 4 weeks and 8 weeks were added and divided by 2, and then multiplied by the number of days between assessments. The sums were totaled.

To compare the cost-effectiveness of the two arms, DFD were transformed into quality-adjusted days by using utility weights assigned to depression based on previous studies.[20,21] The transformation assumes that a non-depressed person has a utility score of 1 (healthy) while a person meeting criteria for major depression has a utility score of 0.59. The utility scores were then transformed into quality-adjusted life years (QALY),[22] which are a measure of disease burden, including both the quality and the quantity of life lived. The QALY is based on the number of years of life, and each year in perfect health is assigned the value of 1 down to a value of 0 for being deceased. As the duration of the present study was 8 weeks, a QALY score for a patient in the present study fell between 0.09 and 0.15.

To confirm the robustness of the results, we planned sensitivity analyses by means of changing the calculation method of QALY to another one focusing on the categorized severity of depression.[23] A QALY score was allocated to a patient according to the severity of depression validated and categorized in Japan based on the total score of the HAMD[19] at each time-point of the assessments (i.e. 0.86 to remission, 0.74 to mild depression, 0.44 to moderate depression, and 0.30 to severe depression). The scores for the baseline and 4 weeks, and those for 4 weeks and 8 weeks were added and divided by 2, and then multiplied by the number of days between assessments. The sums were totaled.

Cost measures

Direct costs, which consisted of the costs for CBT-I, TAU for depression and insomnia, prescribed medications, and hospital inpatient expense if any, were estimated in the present study. From a policy-makers' points of view, indirect costs and educational costs for therapists were not included in the cost measures. In the primary analysis (Approach 1), the cost for each session of the psychotherapy was presumed as the same as that of CBT for depression (Table 1), because CBT-I has not been covered by the insurance system in Japan. Actual costs for medication and hospital inpatient expense, if any, were regrettably not recorded in the study. However, information about a dose transformed to a defined daily dose (DDD) for each class of antidepressants and hypnotics[24] and duration of admission during the study was collected. The costs for these were imputed using costs for a representative drug (e.g. amitriptyline as a representative for tricyclic antidepressants) in each class for medication in Japan, and an estimate from a survey using the national data for inpatient expense,[25] respectively. As a result, tricyclic antidepressant per DDD was estimated at 0.286 USD, selective serotonin reuptake inhibitor at 1.900, serotonin and norepinephrine reuptake inhibitor at 1.245, other antidepressants at 0.947 and hypnotics at 0.810. Consultation fee at the outpatient clinic in the TAU group was estimated at 48.045 USD per session, defined by the national insurance system.

For sensitivity analyses, costs for each session of the psychotherapy were presumed according to different medical systems, and utilized to examine the robustness of the results from the primary analysis (Table 1).

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Table 1 Presumed unit cost of CBT for insomnia and of inpatient care for estimating cost-effectiveness ratios

Approach	Number of patients included	Presumed location and situation to calculate unit cost of CBT for insomnia	Cost per session (USD)	Presumed hospital inpatient expense in Japan per day (USD)
1 (primary)	37	Japan, CBT for depression by a physician	43.210	135.103
2	37	Japan, CBT for depression by a physician	43.210	135.103
3	37	USA, typical face-to-face CBT for depression	100.000	135.103
4	37	Japan, 5 general short appointments at psychiatric clinics (assuming that a physician meets 6 patients per hour)	169.753	135.103
5	35	Japan, CBT for depression by a physician	43.210	NA
6	35	Japan, CBT for depression by a physician	43.210	NA
7	35	USA, typical face-to-face CBT for depression	100.000	NA
8	35	Japan, 5 general short appointments at psychiatric clinics (assuming that a physician meets 6 patients per hour)	169.753	NA

In Approaches 5, 6, 7 and 8, participants who admitted to hospital during the study were excluded for sensitivity analyses.
Costs were calculated using an exchange rate on 25 June 2013: 1 USD equaled 97.2000 JPY, 0.6476 GBP, 0.7624 EUR, 1.0477 CAD, 1.0803 AUD and 0.9353 CHF.
CBT, cognitive behavioral therapy; NA, not applicable.

Data management and analysis

The number of patients who should be included in the study was calculated prior to study commencement, based on a power analysis conducted for the ISI scores.[10]

For the primary analysis named as Approach 1 (Table 1), we included QALY calculated using DFD[21] as the effectiveness, and costs for the psychotherapy presumed as the same as those for CBT for depression, TAU, medication and inpatient expense. For the sensitivity analyses, QALY calculated using the severity of depression[23] were employed in Approaches 2 and 5. Costs of the psychotherapy presumed based on different medical systems were entered in Approaches 3, 4, 7 and 8. Hospital inpatient expenses, if any occurred, were considered as an important outcome but could be outliers and highly likely to bias the results to a large extent due to the small sample size in the present study. For sensitivity analyses, we planned to exclude participants who admitted to hospital during the study in Approaches 5, 6, 7 and 8.

Cost-effectiveness was evaluated by relating the differential cost per patient receiving either the psychotherapy plus TAU or TAU alone to the differential effectiveness of each treatment in terms of QALY. The incremental cost-effectiveness ratio (ICER) was calculated as the difference in the cost divided by the difference in QALY.

Sampling uncertainty of the incremental cost per QALY was investigated by estimating a cost-effectiveness acceptability curve (CEAC). A CEAC can show the probability that an intervention is cost-effective compared with the alternative for a range of monetary values that a decision-maker may be willing to pay for a particular unit change in outcome.[26] Both the ICER and the CEAC are derived from the joint distribution of incremental costs and incremental effectiveness, as estimated by 1000 non-parametric bootstrapping replicates of the observed data. The bootstrap re-sampling and inferential t-tests at a significant level of 0.05 for estimated costs and effectiveness between the groups were performed with Microsoft EXCEL 2010.

The protocol was approved by the Nagoya City University Institutional Review Board and the Ethical Review Board of Kochi Medical School. Atago Hospital was approved to participate in the study by the latter review board, and the president of the hospital approved the protocol and study procedures. Thus, the study was approved by all the recruiting centers. With regard to participants, before enrolment in the study, interested individuals were contacted by study

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Table 2 Clinical characteristics of participants at baseline

Characteristic	CBT-I + TAU ($n = 20$)	TAU alone ($n = 17$)	All patients ($n = 37$)
Age, mean (SD), years	52.9 (11.6)	47.8 (10.1)	50.5 (11.1)
Sex, *n* (%)			
Female	15 (75.0)	8 (47.1)	23 (62.2)
Male	5 (25.0)	9 (52.9)	14 (37.8)
Duration of treatment for index episode, mean (SD), months	18.1 (11.1)	27.8 (46.5)	22.5 (32.4)
Hamilton Depression Rating Scale, mean (SD)	15.0 (3.6)	16.8 (4.2)	15.8 (3.9)
Insomnia Severity Index, mean (SD)	15.3 (4.7)	17.4 (3.3)	16.3 (4.2)
Total antidepressant usage, mean (SD), DDD	1.7 (0.9)	1.5 (0.9)	1.6 (0.9)
Hypnotic usage, mean (SD), DDD	0.7 (0.9)	1.1 (0.7)	0.9 (0.8)

CBT-I, cognitive behavioral therapy for insomnia; DDD, defined daily dose; TAU, treatment as usual.

staff in a single room at hospital to maintain confidentiality. Study staff explained the purposes, procedures and potential risks or discomforts of the study to those who satisfied the eligibility criteria using the standard informed consent form, which emphasized that all potential participants who declined to participate or otherwise did not participate were eligible for usual treatment and were not disadvantaged in any other way by not participating in the study. Following these instructions, written informed consent was obtained from all the participants included in the study.

RESULTS

Thirty-seven patients satisfied the eligibility criteria, with 20 participants randomly assigned to receive combined treatment with CBT-I and TAU and 17 to receive TAU alone. Table 2 summarizes the clinical characteristics at baseline. During the study, antidepressant dosage was changed for two participants each in the two groups. Hypnotic dosage was changed for two participants in the combination group and for none of the participants in the TAU-alone group. In the CBT-I-plus-TAU group, one patient discontinued the psychotherapy after reporting that it was too difficult to comply with the prescribed sleep schedule. Beyond this reason, one subject in the intervention (received inpatient care for 25 days) and one in the control (for 18 days) groups were admitted to hospital due to exacerbation of depression. All the patients nevertheless completed all the study assessments at 8 weeks, thus no missing data were observed.

Figure 1 shows the incremental cost-effectiveness planes, which are scatter plots of the bootstrapped incremental costs and effectiveness pairs for all Approaches between the CBT-I-plus-TAU and the TAU-alone groups. A majority of plots were located in the upper right quadrant, which represented the position where adding CBT-I was more effective and more costly than TAU alone.

Effectiveness outcomes

QALY was statistically significantly higher ($P = 0.002$) in the CBT-I-plus-TAU group than in the TAU-alone group, at the incremental value of 0.019 (SD 0.006) for the primary analysis, Approach 1 (Table 3). In all the other analyses, QALY were also significantly higher in the intervention than those in the comparator. Incremental QALY appeared to be higher in Approaches 2 and 6, where those were estimated using the categorized severity of depression.

Cost outcomes

In the primary analysis (Approach 1), the total direct medical costs were not statistically significant ($P = 0.404$) but appeared to be higher in the CBT-I-plus-TAU group than in the TAU-alone group, at the incremental cost of 254 USD (SD 203) (Table 3). An incremental cost was the highest at 783 USD in Approach 4, where one session of CBT-I was presumed for around 170 USD and inpatient expenses were included. Costs for the intervention group were significantly higher than the alternative, after

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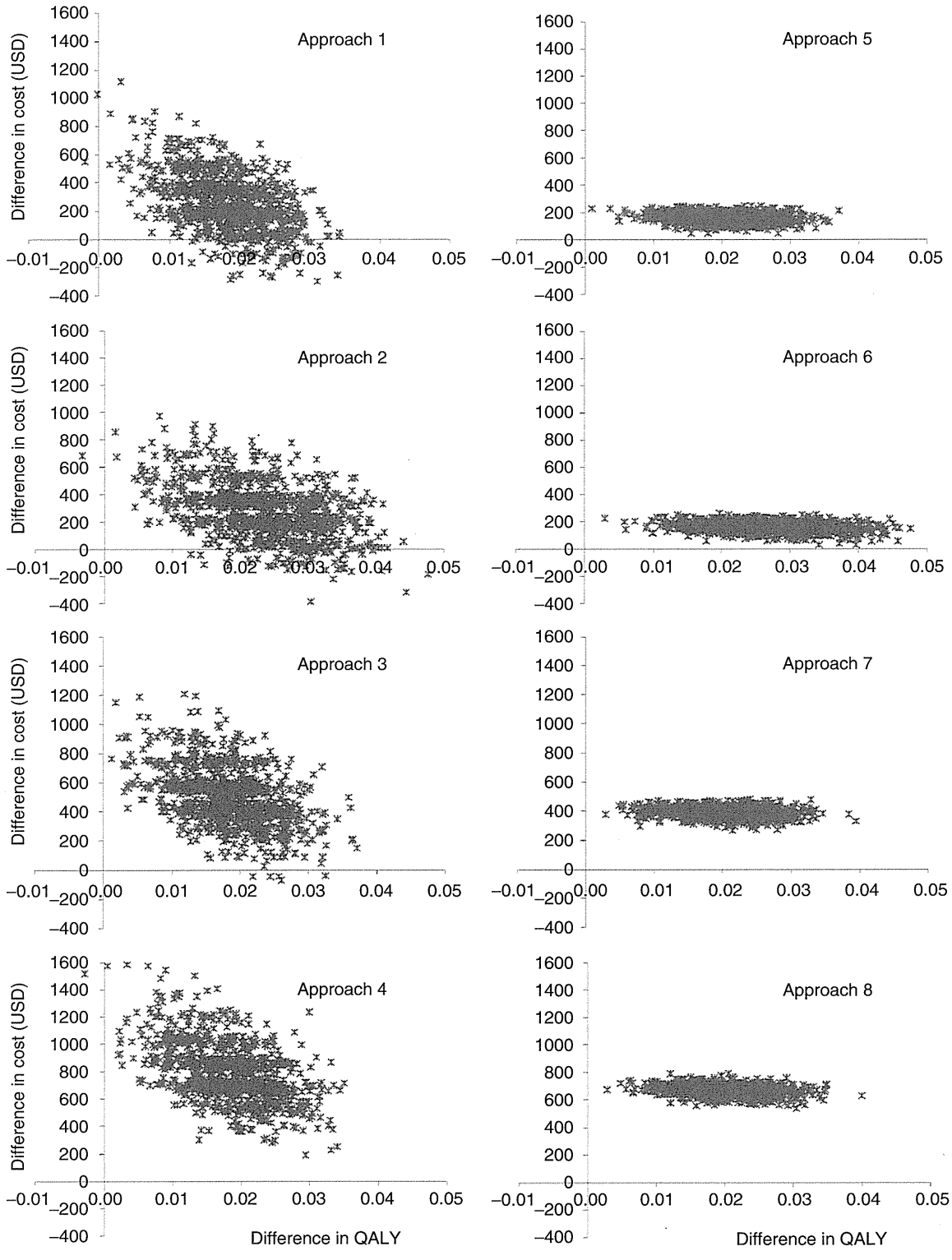

Figure 1 Estimated incremental differences in costs and in effectiveness. Values were estimated from the trial data using 1000 bootstrap replicates. QALY, quality-adjusted life year.

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Table 3 Costs, effectiveness and ICER, estimated using bootstrapping of the observed data

Approach	Effectiveness (QALY), mean (SD)			Cost (USD), mean (SD)			ICER (USD/QALY), mean (95%CI)
	CBT-I + TAU	TAU	Incremental	CBT-I + TAU	TAU	Incremental	
1	0.139 (0.004)	0.120 (0.004)	0.019 (0.006)*	702 (175)	448 (115)	254 (203)	13 678 (−5691 to 71 316)
2	0.108 (0.005)	0.084 (0.006)	0.024 (0.008)*	711 (170)	444 (108)	266 (201)	11 152 (−4108 to 65 443)
3	0.138 (0.004)	0.120 (0.005)	0.018 (0.006)*	937 (165)	435 (101)	501 (199)	27 252 (5220 to 128 572)
4	0.139 (0.004)	0.120 (0.005)	0.018 (0.006)*	1223 (181)	440 (109)	783 (213)*	42 929 (16 994 to 163 146)
5	0.141 (0.003)	0.120 (0.005)	0.020 (0.005)*	531 (17)	371 (32)	160 (36)*	7 828 (3527 to 18 613)
6	0.111 (0.004)	0.084 (0.006)	0.027 (0.007)*	531 (18)	372 (33)	159 (38)*	5 900 (2485 to 14 958)
7	0.141 (0.003)	0.121 (0.005)	0.020 (0.006)*	758 (18)	372 (33	387 (37)*	18 927 (11 586 to 44 439)
8	0.141 (0.003)	0.121 (0.005)	0.020 (0.005)*	1037 (18)	372 (34)	665 (38)*	32 780 (20 617 to 70 249)

*$P < 0.05$.
The results are different from those of original data because the values here are based on the bootstrap calculation.
CBT-I, cognitive behavioral therapy for insomnia; CI, confidence interval; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years; TAU, treatment as usual.

excluding participants who admitted to hospital during the study period (Approaches 5–8).

Cost-effectiveness outcomes

The ICER for the primary analysis (Approach 1) was 13 678 (95% confidence interval: −5691 to 71 316) USD/QALY (Table 3). Figures 2 and 3 show the CEAC of the primary (Approach 1) and the other sensitivity analyses (Approaches 2–8), which represent the probability for the addition of the psychotherapy to be cost-effective for a range of potential maximum amounts that a decision-maker is willing to pay for one more QALY. For the primary analysis, adding CBT-I demonstrated an approximately 95% chance of being cost-effective when a decision-maker was willing to pay 60 000 USD for one more QALY, around 90% for 40 000 and around 70% for

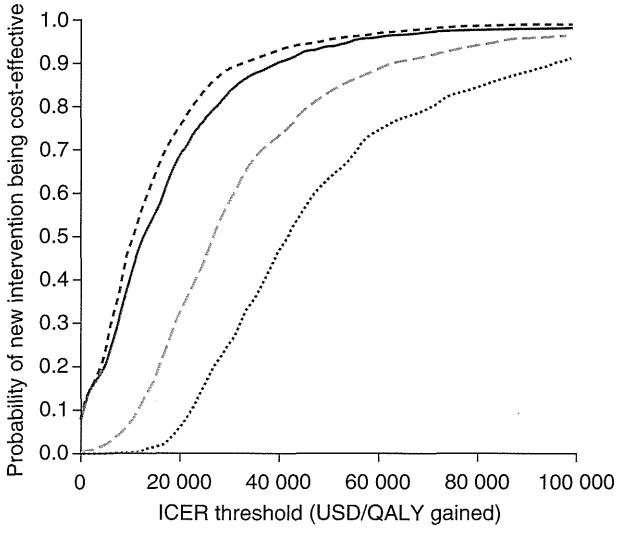

Figure 2 Cost-effectiveness acceptability curves for Approaches 1–4. ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year. ——, Approach 1; - - -, Approach 2; – –, Approach 3; ·····, Approach 4.

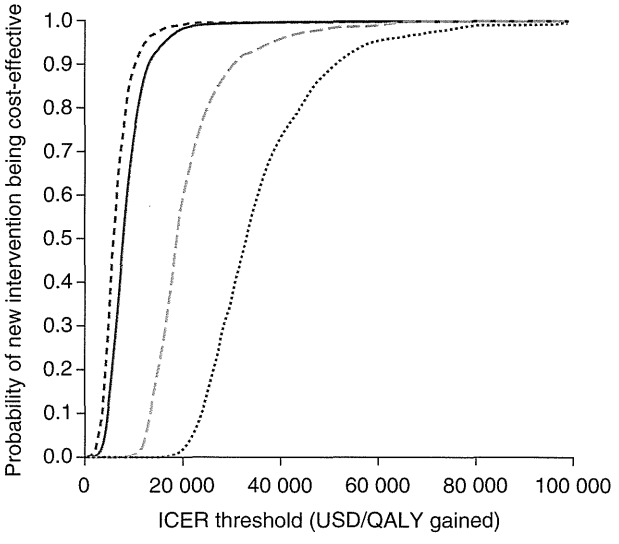

Figure 3 Cost-effectiveness acceptability curves for Approaches 5–8. ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year. ——, Approach 5; - - -, Approach 6; – –, Approach 7; ·····, Approach 8.

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20 000. The probability values were higher in sensitivity analyses, other than Approaches 3, 4, 7 and 8, where more costs for CBT-I were presumed than that in the primary analysis.

DISCUSSION

To our knowledge, this paper represents the first study investigating the cost-effectiveness of CBT-I from results of an RCT of psychotherapy for insomnia with concurrent depression. Adding CBT-I is highly likely to be cost-effective with the point estimate of the ICER of around 14 000 USD even for 8 weeks. Adding CBT-I demonstrated an approximately 95% chance of gaining one more QALY when a decision-maker is willing to pay for 60 000 USD, and around 90% for 40 000. The cost-effectiveness was robust when considering the results from the sensitivity analyses using a worst-case scenario. Given one QALY is often valued at 50 000–70 000 USD,[27] the results reported herein demonstrate that patients with insomnia concurrent with depression benefit even for the 8 weeks up to which we followed the patients. The estimated QALY difference is limited to the trial period and any sustained effect of treatment is not included in the study. Considering that the effectiveness of the psychotherapy is highly unlikely to disappear immediately after the follow-up, monetary value of adding CBT-I appears very promising in terms of treatment for insomnia concurrent with depression.

Comparing our study with the previous cluster trial on CBT-I for hypnotic-dependent people with insomnia,[14] the present trial has several drawbacks, including smaller sample size, shorter duration of follow up, and study sites not being primary care clinics but outpatient clinics at university hospitals and a psychiatric hospital. However, although the previous trial reported a drop-out rate of 34% in patients during six sessions of CBT-I and of 29% at the 3-month follow-up assessment in patients in both the intervention and the control groups,[28] the present study had a drop-out rate of 5% in patients receiving the psychotherapy and no drop-out at all assessment sessions, thus we have no missing data. This was achieved probably because of our enthusiastic follow ups of the patients.

Although the findings seem very promising, one may need to note some methodological limitations of the present study.

First, the sample sizes were small and concerns about the generalizability of the results may be raised. As a matter of fact, the costs were heavily affected by the periods of only two admissions. Moreover, the study evaluated the patients up to 8 weeks only, and the long-term consequences were unclear. A further replication study with a larger sample and a longer period of follow up is needed to evaluate the outcomes with more confidence. Second, we could not determine whether the psychotherapy itself or careful watching of patients resulted in greater cost-effectiveness. We aimed to conduct the study to examine the added value of the psychotherapy to usual clinical care, but not to examine the effectiveness of the psychotherapy itself.

On the other hand, the strengths of our study include our method for calculation of the effectiveness. The cost-effectiveness of CBT-I has not often been investigated to date, probably due to difficulties in measuring the utility in patients with insomnia. In the present study, an objective measure for depression severity, the HAMD, was used to estimate the effectiveness. The HAMD raters in the present study were successfully blinded to the group allocation,[18] although raters in the previous trial were not blinded.

In conclusion, adding CBT-I is highly likely to be cost-effective for patients with residual insomnia and concomitant depression. Once the program and its cost-effectiveness are replicated in more trials with a larger sample and a longer period of follow up, CBT-I should be more widely disseminated to cover more patients in need.

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