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Complete List of Authors:	Nakagawa, Atsuo; Keio University School of Medicine, Center for Clinical Research Sado, Mitsuhiro; Keio University School of Medicine, Department of Neuropsychiatry Mitsuda, Dai; Keio University School of Medicine, Department of Neuropsychiatry Fujisawa, Daisuke; Keio University School of Medicine, Department of Neuropsychiatry Kikuchi, Toshiaki; Kyorin University School of Medicine, Department of Neuropsychiatry Abe, Takayuki; Keio University School of Medicine, Center for Clinical Research Sato, Yuji; Keio University School of Medicine, Center for Clinical Research Iwashita, Satoru; Sakuragaoka Memorial Hospital, Department of Psychiatry Mimura, Masaru; Keio University School of Medicine, Department of Neuropsychiatry Ono, Yutaka; National Center of Neurology and Psychiatry, National Center for Cognitive Behavioral Therapy and Research
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Effectiveness of Cognitive behavioral therapy Augmentation in Major depression treatment (ECAM study): study protocol for a randomised clinical trial

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Atsuo Nakagawa[1,2,4], Mitsuhiro Sado[2], Dai Mitsuda[2,4], Daisuke Fujisawa[2], Toshiaki Kikuchi[3], Takayuki Abe[1], Yuji Sato[1], Satoru Iwashita[4], Masaru Mimura[2], and Yutaka Ono[5]

[1] Center for Clinical Research, Keio University School of Medicine, Tokyo, Japan

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

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

[4] Department of Psychiatry, Sakuragaoka Memorial Hospital, Tokyo, Japan

[5] National Center for Cognitive Behavioral Therapy and Research, National Center of Neurology and Psychiatry, Tokyo, Japan

Corresponding author

Atsuo Nakagawa, MD, PhD

Center for Clinical Research, Keio University School of Medicine

Shinanomachi 35, Shinjuku-ku

Tokyo 160-8582

Tel +81-3-5363-3235, FAX +81-3-5363-3480

e-mail: anakagawa@z2.keio.jp

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Abstract (293 words)

Introduction

Major depression is a serious mental disorder that causes substantial distress and impairment on individual and society. Although antidepressant treatment is the most widely used treatment modality in routine practices, there is little evidence to guide second-line option for patients who have failed to respond to antidepressants. The aim of this paper is to describe the study protocol for a randomized controlled trial that measures the clinical effectiveness of cognitive behavioral therapy (CBT) as an augmentation strategy to treat patients with non-psychotic major depression who were identified as suboptimal responders to usual depression care.

Methods and analysis

The current study is a 16-week assessor-blinded randomised, parallel-groups superiority trial with a 12-month follow-up at an outpatient clinic as part of usual depression care. Patients aged 20-65 years with DSM-IV Major Depressive Disorder who have experienced at least one failed trial of antidepressants as part of usual depression care, will be randomly assigned to receive CBT plus treatment as usual, or treatment as usual alone. The primary outcome is the change in clinician-rated 17-item GRID-HAMD score at 16-weeks, and secondary outcomes include severity and change in scores of subjective depression symptoms, proportion of responders and remitters, safety and quality of life. The primary population will be the intention-to-treat.

Ethics and dissemination

All protocol and Informed Consent Form are compliant with the Ethics Guideline for Clinical Research (Japanese Ministry of Health, Labour and Welfare). Ethical Review Committees at the Keio University School of Medicine and the Sakuragaoka Memorial Hospital approved the study protocol. The results of the study will be disseminated at several research conferences and as published articles in peer reviewed journals. The study will be implemented and reported in line with the CONSORT statement.

Clinical Trial Registration Number

UMIN Clinical Trials Registry: UMIN000001218.

Strengths and limitations of this study

- This protocol will provide new evidence for administering CBT for major depression as an augmentation strategy for patients who have failed to respond to pharmacotherapy in psychiatric care settings.
- Central randomisation and blinded assessment have been used.
- The study cannot examine the efficacy of CBT itself because we did not choose attention-placebo as control. Concern about the generalizability is compromised due to small number of study sites.

Introduction

As in other high-income countries, major depression is a common mental disorder in Japan [1]. Left untreated, major depression can cause substantial distress and impairment on individual that negatively affect their quality of life, medical morbidity, and mortality, and place an enormous burden on society [2-4]. Latest estimates from Global Burden of Disease study GBD 2010 indicate that major depression accounts for 2.5% of the global disease burden [5], and by 2030 major depression is predicted to be the leading cause of disability in high-income countries [6]. For this debilitating mental disorder, treatment guidelines recommend antidepressants for first-line treatment of moderate to severe acute major depression [7, 8], and it is the most widely used treatment modality in routine practices and remains the mainstay. However, available evidence indicates that only a third of patients fully respond to the first trial of antidepressant [9-11]. Thus, many patients with major depression are left with considerable symptomatology after initial treatment and are referred as treatment resistant (refractory) depression (TRD).

Although many treatment studies have been published to investigate the best treatment strategies for TRD [12, 13], no standard treatment modality has yet been established [14]. When patients fail to respond to an adequate course of antidepressant treatment, the most currently available treatment guideline recommends the subsequent option of increasing the dose of current antidepressant, switching to a different antidepressant, or augmenting with another pharmacotherapy [7]. However, one major problem of TRD is its lack of consensual operational definitions [15, 16]. Given the heterogeneity of TRD associated with complex etiologic pathways, a non-pharmacological approach such as depression-specific psychotherapy may have a role in their treatment [17].

It is well established that cognitive behavioral therapy (CBT), the most published structured form of psychotherapy developed on the basis of the Beck's cognitive theory [18], is efficacious for the treatment of depression [7, 8]. Numerous randomized controlled studies have shown that CBT is superior to wait-list, non-specific controls, or treatment as usual [19]. Further evidence shows that combining psychotherapy to pharmacotherapy is more effective than pharmacotherapy alone [20].

Few empirical studies have evaluated the effectiveness of CBT as a next-step option for patients who have failed to respond to antidepressants[21-23]. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) examined CBT and pharmacotherapy as a sequential approaches to manage patients who failed the initial 12-14 weeks of citalopram treatment by using either augmentation or switch strategies [24]. No differences in outcome at post-treatment were observed between augmenting CBT and augmenting other pharmacotherapy, and this finding was similar among the switching option. However, STAR*D trial implemented a unique equipoise-stratified randomisation design which refused the non-preferred treatment arm; only a quarter of the STAR*D participants were randomized to CBT for their second-step treatment and this selection bias makes difficult to interpret the outcomes. Next, Kennedy and colleagues [25] compared cognitive therapy and lithium augmentation as a sequential treatment option for 44 outpatients with major depression who had a partial response during 8 to 14 weeks of

antidepressant treatment in an 8-week randomized controlled trial. They found that there was no significant benefit of cognitive therapy over lithium augmentation. However, the sample size was small which may limit power to detect the differences in changes over time and the duration of trial was relatively short. Furthermore, the trial focused on partial responders (defined as HAMD score of 8-15) and excluded non-responders to the initial antidepressant treatment. Finally, the recent CoBalT trial [26] examined the effectiveness of CBT as a next-step option for patients whose depression did not respond to usual depression care delivered by general practitioner in the UK. In this pragmatic clinical trial with a sample size of 469, augmenting CBT to usual care increased the treatment response 3-fold at 6 months compared to those with usual care alone. However, the primary outcome of this trial was a self-reported measure (i.e. BDI-II) that might be affected by the process of treatment. Further, it is unclear if this result could be applied to different clinical setting such as in psychiatric care or in other socio-cultural contexts.

There is little evidence to guide next-step option for patients who have failed to respond to antidepressants in psychiatric care settings. We therefore planned to carry out a randomised controlled trial to examine the effectiveness of CBT as an augmentation strategy for antidepressant non-responders compared with pharmacotherapy as part of usual care for patient. The aim of this paper is to describe the study protocol of the current study.

Objectives

1. The primary objective of this study is to compare the effectiveness of CBT as an augmentation strategy to treatment as usual (that includes antidepressant treatment) versus treatment as usual alone in a 16-week randomized controlled trial with a 12-month follow-up for patients with non-psychotic major depression who were identified as suboptimal responders to usual depression care.
2. The secondary objective of the study is to evaluate the safety (incidence of treatment discontinuation and adverse events) of CBT as an augment strategy to treatment as usual for patients with non-psychotic major depression who have not adequately responded to usual depression care.

Methods and Analysis

Study design and setting

The current study is a 16-week assessor-blinded, randomised, controlled superiority trial of two parallel-groups with a 12-month follow-up at an outpatient clinic as part of usual depression care (**Figure 1**). Random allocation to treatment will be done at the individual level.

Patients will be recruited from two sites in Tokyo. One will be a university teaching hospital and other will be a psychiatric hospital. The university teaching hospital department of psychiatry located in central Tokyo has 31-beds

(1,044 beds as for the entire university teaching hospital) and, offers advanced psychiatric care services for patients with complex problems serving largely the Japanese middle class. On the other hand, the psychiatric hospital located in suburban Tokyo has 467-beds and offers wide range of psychiatric care services, mainly serving secondary to tertiary psychiatric care to diverse Japanese population including socioeconomically disadvantaged groups. It is noteworthy that a feature of Japan's healthcare is its universal health insurance system in which all patients receive free access to specialized medical services at any institutions including university teaching hospital.

Participants

1. Inclusion criteria

Patients are eligible to be included in the study if they meet the following criteria: (1) have Major Depressive Disorder, as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [27] criteria for single or recurrent without psychotic features assessed with the Structured Clinical Interview for DSM-IV (SCID) [28] administrated by trained psychiatrist; (2) age between 20 and 65 years; (3) identified as suboptimal responders to usual depression care defined as those who experience at least moderate level of depression symptoms based on at least 16 on the GRID-Hamilton Depression Rating Scale-17 item ($GRID\text{-}HAMD_{17}$) [29, 30] and evidence of at least minimal level of treatment resistance by obtaining at least 3 on the Maudsley Staging Method for treatment-resistant depression [31] despite taking antidepressant treatment at an adequate therapeutic dose (based on package insert (Available at: http://www.info.pmda.go.jp/info/iyaku_index.html)) for at least 8-weeks as part of usual depression care, and (4) must be competent and able to give informed consent.

2. Exclusion criteria

Patients will be excluded from the study if they meet the following criteria: (1) having past or current manic or psychotic episode; (2) having comorbid alcohol or substance use disorder in 6 months prior to the study entry; (3) having any DSM-IV Axis I disorders other than Major Depressive Disorder to be the primary diagnosis assessed by the Mini-International Neuropsychiatric Interview (M.I.N.I.) [32, 33]; (4) having antisocial personality disorder; (5) having serious and imminent suicidal ideation; (6) having a serious or unstable medical illness; (7) having organic brain lesions or major cognitive deficits in a year prior to the study entry; (8) have previously completed full-session of CBT program and (9) those who were highly anticipated to fail to attend less than 8 visits during the 16-week trial phase (e.g. due to relocation).

Procedures

1. Recruitment

Treating psychiatrist will provide brief information about the study using a brochure and invite patient to take part in the study during their usual consultation. If the patient shows interest in the study and provides contact details to the research team, a face-to-face appointment with a study psychiatrist will be set. The details of the study and potential benefits and risks will be explained thoroughly to patients by study psychiatrist and discussed. If the patient agrees to study participation, written informed consent will be obtained. After obtaining informed consent, patients will be assessed by study psychiatrist for eligibility. A diagnosis of Major Depressive Disorder will be evaluated with the SCID [28] and other Axis I disorders will be evaluated with M.I.N.I [32, 33]. Of note, Axis II disorders will be evaluated with the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II) [34] at week 8 (i.e. a considerable time frame for depressive symptoms to have abated). Diagnostic interviewers will be study psychiatrists (AN and MS) who have received extensive training in the administration of semi-structured interviews.

2. Baseline assessment

Acute psychopathology will be assessed at study entry by study psychiatrists or psychologists. Objective depressive symptoms will be assessed by the 17-item and 21-item GRID-HAMD. Patients' subjective perception of depression severity will be assessed by the self-reported Beck Depression Inventory-Second Edition (BDI-II)[35, 36] and 16-item Quick Inventory of Depressive Symptomatology Self-Reported ($QIDS\text{-}SR_{16}$)[37, 38]. Health related quality of life will be measured by the European Quality of Life Questionnaire–5 Dimensions (EQ-5D)[39, 40] and 36-Item Short-Form Health Survey (SF-36)[41]. Work performance and productivity will be measured by the World Health Organization Health and Work Performance Questionnaire (HPQ)[42, 43]. Life stressors will be measured using the St. Paul-Ramsey Questionnaire (available from the authors), which rates the severity of individual stressors from 1 (none) to 7 (catastrophic) in six categories ranging from marital to occupational and gives a final global measure of the stressors.

Demographic and other clinical data will be also collected as part of baseline assessment such as marital status, number of children, residential status, level of education, duration of current and lifetime episode of depression, number of lifetime depression episodes, history of depression treatment including past pharmacotherapy and hospitalized treatment, past suicide attempt, history of medical complication, and family psychiatric history. Level of treatment resistance will be evaluated operationally with the Maudsley Staging Method for Treatment Resistant Depression [44]. A history of childhood abuse and traumatic brain injury will be rated as present or absent. Current cigarette and alcohol use will be assessed by the subject's report. Assessments will also be conducted at 8 and 16 weeks after the randomisation.

3. Randomisation

All eligible patients who give consent for participation will be randomized to treatment as usual or to CBT plus treatment as usual at the end of baseline assessment (1:1 allocation ratio). Randomisation will be conducted using central computerized registration system that automatically randomizes patients and generates a message notifying their assigned treatment. Allocation is concealed through the use of central computerized registration system designed for this study by the Project Management Office at the Keio Center for Clinical Research. Allocation will be stratified by site (n=2) with minimisation method to balance age of participants at study entry (older versus younger) and baseline GRID-HAMD$_{17}$ score (severer versus non-severer). The cut-off age and GRID-HAMD$_{17}$ score for minimization will not be disclosed until the study termination to ensure concealment.

4. Intervention phase (16 week)

4-1. CBT

Therapists will follow the individual CBT treatment manual for depression developed by the authors (YO, DF, AN, KT and MS) (Available at the Japanese Ministry of Health, Labor and Welfare website: http://www.mhlw.go.jp/bunya/shougaihoken/kokoro/dl/01.pdf). This manual is developed based on Beck's treatment manual [45], with some adaptation to address the cultural characteristics of the Japanese patients such as more emphasis on interpersonal relationships and consideration of family as an essential part of the treatment [46]. The overview of the program is shown in **Table 1**. Problem-solving techniques and specific approaches to address interpersonal issues and cognitive behavioral avoidance are emphasized. Therapists are encouraged to refer to the relevant approaches whenever necessary. Furthermore, the therapists are encouraged to give feedbacks to the patients about the case conceptualization and collaboratively set the treatment goal during the earlier phase of the program. Patients allocated to CBT will typically receive a course of 16 weekly sessions, with up to 4 additional sessions if deemed clinically appropriate by the study therapist (maximum of 20, and minimum of 8 sessions). Sessions will last approximately 50 minutes. Therapy will take place in an outpatient consultation room at each site. During CBT treatment, other depression-specific empirical psychotherapy (i.e. interpersonal therapy (IPT)) and electroconvulsive therapy are prohibited.

4-2. Training and supervision of therapists

Six therapists will deliver CBT at the two sites. The study therapists have been trained as psychiatrists (n=4), a master's-degree clinical psychologist (n=1), and a psychiatric nurse (n=1). Of the six therapists, two are female (n=2, 33.3%). On average, the study therapists had 4.0 (SD 2.1) years of experience as CBT therapists and have completed 12.5 (SD 7.3) cases at the time of participation. All therapists have received CBT training at the Keio

University Cognitive Behavioral Therapy Training and Research Program and will continuously receive supervision throughout the study.

To ensure treatment fidelity, all therapists completed a two-day workshop and will participate in two-hour bi-weekly group supervision with other therapists during the study. At the group supervision, therapists will present the case formulation and treatment plan. The group supervision will be led by one of the authors (YO), the founder and the president of the Japanese Association for Cognitive Therapy and a fellow of Academy of Cognitive Therapy, who will facilitate discussion of therapeutic difficulties and impasses and provide skills acquisition, and peer support. To assess CBT competences, a random sample of audiotaped sessions will be rated using the Cognitive Therapy Rating Scale (CTRS)[45, 47]. A score of 40 or greater is defined as an adequate level of technical competency in the CBT sessions.

4-3. Treatment as usual (Usual depression care by psychiatrists)

Although appropriate flexibility will be allowed for scheduling sessions, patients will typically receive a bi-weekly, 5-30 minutes consultation by treating psychiatrist during the treatment phase with minimum of 8 sessions. Typical session will comprise of symptom assessment and standard clinical management such as brief psychoeducation and pharmacotherapy when appropriate. Although there will be no restriction on pharmacotherapy, it should basically be concordant with major practice guidelines for major depression such as the American Psychiatric Association practice guideline[8]. Prescribed medicine and dose will be recorded and medication adherence will also be assessed at each visit using the self-reported Treatment and Medication Compliance Data Scale (TMCDS) (available from the authors upon request). Patients can enter the study receiving any medication(s) for concurrent general medical conditions. No depression-specific empirical psychotherapies (CBT or IPT) or electroconvulsive therapy are permitted during the intervention phase and will result in withdrawal from the study. Treatment will be delivered by seven treating psychiatrists who have practiced for a mean of 7.3 (SD 4.4) years and are working at the two sites. .

5. Follow-up phase

There will be no restrictions on treatment options for patients who receive depression care by treating psychiatrists during this phase. Thus, treating psychiatrists are allowed to refer patients for psychotherapies to appropriate mental health professionals and electroconvulsive therapy if deemed clinically appropriate. However, those who receive depression-specific empirical psychotherapies (CBT and IPT) and electroconvulsive therapy will be documented and considered deviation from the study protocol. The patient, however, will not be considered to have dropped out of the study at this phase and will receive protocol assessments. Although CBT literacy has deepened among Japanese mental health professionals after the approval of CBT as treatment for mood disorder by

Japan's national health insurance scheme in 2010, the number of mental health facilities capable of providing CBT is still very limited. Therefore, it is unlikely for patients to receive CBT that may substantially influence the primary outcome. The current situation for IPT in Japan is similar.

6. Discontinuations

6-1. Discontinuation of intervention phase

If patients meet any one of the following criteria, the treating psychiatrist will discontinue the study intervention. The patient will not be considered to have dropped out of the study and will be invited to enter the follow-up phase and receive periodical assessments through the remainder of the study period.

1. Patient withdraws the consent to receive study intervention.
2. The treating psychiatrist judges that it is inappropriate to continue the study intervention such as emergence of severe psychotic or manic episode, serious and imminent suicidal ideation, and severe medical conditions.
3. The treating psychiatrist judges that it is difficult to continue the study intervention because of emergence of adverse events or other appropriate reason that outweighs the benefit of receiving study intervention.
4. The treating psychiatrist judges that it is more appropriate to receive inpatient psychiatric care.

6-2. Discontinuation of periodical assessments

If patient withdraws the consent to receive periodical study assessments, it will be considered as dropout and the patient will not be contacted for periodical assessments in the future.

Outcome measures

The outcome measures are shown in **Table 2.**

1. Primary outcome

The primary outcome is the change in clinician-rated 17-item GRID-HAMD score at 16-weeks, which accord with the end of intervention. The GRID-HAMD will be also administered at week 8 (midpoint of intervention). Follow-up assessments will be administered at 3-month (7-months post-randomisation), 6-month (10-months post-randomisation), and 12-month follow-up visits (16-months post-randomisation). All the assessors have received extensive GRID-HAMD training and achieved excellent inter-rater reliability (ICC=0.98). The GRID-HAMD will be conducted by an assessor blind to treatment randomisation. Due to the nature of the intervention, neither patients, treating psychiatrists, nor study therapists can be blinded to randomisation, but are strongly inculcated not to disclose the randomisation status of the patient at periodical assessments.

2. Secondary outcomes

2-1. Clinical outcomes

- Severity and change in scores of subjective depression symptoms as measured by the BDI-II and QIDS-SR_{16}
- Proportion of responders, defined as 50% or greater reduction on 17-item and 21-item GRID-HAMD, BDI-II and QIDS-SR_{16} relative to baseline.
- Proportion of patients who achieve remission, defined as a 17-item GRID-HAMD score <=7[48], BDI-II score <=13[49] and QIDS-SR_{16}<=5[37].

2-2. Safety outcomes

- Proportion of patients who discontinue from the study will be recorded. The reasons for discontinuation will be asked of the patient at site or by telephone and will be ascertained by the treating psychiatrist.
- Spontaneously reported Adverse Event (AEs) and Serious Adverse Events (SAEs).

2-3. Health outcomes

- Level and change in the degree of health-related quality of life as measured by the EQ-5D and SF-36.

2-4. Work performance outcomes

- Self-reported sick leave hours (absenteeism), degree of job performance reduction (presenteeism), and the actual hours worked in the past 4 weeks as measured by the HPQ.

2-5. Economic evaluation

- Degree of quality of life (EQ-5D) and depression severity (GRID-HAMD, BDI-II and QIDS-SR16) will be used for estimating Quality Adjusted Life Years (QALYs) for cost-utility analyses.

3. Instruments

GRID- Hamilton Depression Rating Scale

The Hamilton Depression Rating Scale (HAMD) has been the gold standard assessment for the observer rated depression symptomatology for more than 50 years. The GRID-HAMD was developed to set standards for scoring and administering the original HAMD. The seven day period prior to assessment is the usual time frame for assessing symptom severity. The GRID-HAMD has three components: the GRID scoring system based upon assessment of symptom intensity and symptom frequency, the manual of scoring conventions, and a semi-structured interview guide based on the SIGH-D[50]. Inter-rater reliability of the Japanese version of the GRID-HAMD total score is excellent[29].

Beck Depression Inventory-Second Edition (BDI-II)

The BDI-II has been one of the most widely used self-report instruments to assess the severity of depressive

symptoms which was developed by Beck and colleagues and its first version was published in 1961[51]. The BDI-II is a 21-item questionnaire and each item is answered by circling a number between 0 and 3, with larger numbers indicating greater severity. The time frame for assessing symptom severity for BDI-II should be in the past two weeks to better coincide with DSM criteria. Good reliability and validity has been reported for the original [35] as well as the Japanese version [49].

16-item Quick Inventory of Depressive Symptomatology Self-Reported (QIDS-SR$_{16}$)

The QIDS-SR$_{16}$ is an abbreviated self-report version of the clinician-rated 30-item Inventory of Depressive Symptomatology (IDS) designed to assess the severity of depressive symptoms which was developed by John Rush and colleagues. The QIDS-SR$_{16}$ assesses all the criterion symptom domains to diagnose a DSM Major Depressive Episode. The seven day period prior to assessment is the usual time frame for assessing symptom severity. Internal consistency is high with a Chronbach's alpha ranged from 0.81 to 0.94 and validity is high with a high correlation with HAMD [37] as well as the Japanese version[38] .

36-Item Short-Form Health Survey (SF-36)

The SF-36 is a multi-purpose health survey with 36 items. It yields the 8 health domains of functional health (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and metal health),level of well-being, physical and mental health summary measures, and a health utility index. Good validity has been reported for the original [52] as well as the Japanese version[41].

World Health Organization Health and Work Performance Questionnaire (HPQ)

The HPQ is the most widely used self-report instrument designed to estimate the workplace costs of health problems in terms of reduced job performance, sickness absence, and work-related accidents and injuries. It assesses work hours, sick-leaves, occupational accidents, and self-rated productivity in past seven days and past four weeks. The validity of the HPQ absenteeism and presenteeism measures has been confirmed [53].

European Quality of Life Questionnaire–5 Dimensions (EQ-5D)

The EQ-5D is a generic, multidimensional, health-related, quality-of-life instrument that contains two parts: a health status profile and a VAS to rate global health-related quality of life [39]. Health status profile yields the 5 health domains (mobility, self-care, usual activities, pain/discomfort, and mood) and the outcome rating of the 5 domains will be mapped to a single index value through an algorithm. The index value ranges between 0 and 1 with the higher score indicating a better health state perceived by the patient. The index value is used for calculating QALYs.

The EQ-5D is the measure of health-related quality of life in adults preferred by the National Institute for Health and Clinical Excellence.[7]

Sample size estimation

The sample size is calculated based on the primary outcome of depression symptoms as measured by the 17-item GRID-HAMD score at 16 weeks after the randomisation. Our previous single group study on CBT with treatment as usual for acute major depression have shown that the 17-item GRID-HAMD will drop from 24.3 (SD 7.4) to 10.0 (SD 5.0) at week 16 [46]. We expect a mean difference of 40% (4 point) in the 17-item GRID-HAMD total scores between the groups at endpoint and consider this to be a clinically meaningful difference. With a two-sided significance level of 5% and statistical power at 90% and allowing for 15% drop-out, the sample size was calculated to be 40 per arm, i.e., 80 in total.

Statistical analyses

The primary analysis population in this study will be the intention-to-treat (ITT), defined as all randomised patients. For the primary outcome, the least squares means and their 95% confidence intervals will be estimated using analysis of covariance (with treatment group as a factor and baseline scores as a covariate) to compare the two group, with a last-observation-carried-forward approach for missing values. To examine the robustness of the last-observation-carried-forward approach, a mixed-effects model for repeated-measures (MMRM) that contains treatment group, week, and group-by-week interaction as factors with compound symmetry covariance matrix among time points, and Kenward-Roger degrees of freedom adjustment will be performed with all the primary outcomes and also for continuous secondary outcomes. Categorical outcomes will be analyzed using chi-square test or Fisher's exact test. Summary statistics (means and standard deviation) of patients' characteristics will be calculated. When appropriate, t-test and Mann-Whitney U test will be used to compare baseline continuous outcomes (means). Time to all cause discontinuation will be summarized using Kaplan-Meier estimates and compared with log-rank test. The significance level will be set at 0.05 (2-tailed). Statistical analyses will be performed with SAS version 9.3.

Data collection and management

To ensure accurate, complete, and reliable data, the following countermeasures will be conducted: 1) provide standardized operational procedure material to the study sites regarding data collection, data encoding, and storing, 2) hold a training session to give instruction on the protocol, the completion of the EDCs, and study procedures for study psychiatrists, study therapist, and study coordinators, 3) hold a periodic meeting among the study site personnel to share issues related to conducting the study and to elaborate, 4) principal and co-principal investigator

will be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax, 5) data manager will review and evaluate EDC data, use standard computer edits to detect errors during data collection, and conduct a quality review of the database.

To ensure the safety of participants in the study and to ensure accurate, complete, and reliable data, the study psychiatrist will keep records of paper instruments and clinical records in the patient files as source documents for the study at the site. The principal investigator (YO), the co-principal investigator (AN), the study statistician (TA) and other steering committee members (MS, DF, TK) will be given access to the cleaned data sets.

1. Electronic data capture system

An electronic data capture system will be used in this study. The site maintains the original source for the data entered by the site into the electronic data capture system. The eCRF data collected by the study psychiatrists, therapist, or the clinical research coordinators will be encoded and stored electronically in the database system. Data will be managed by data manager at the Keio Center for Clinical Research and will be stored electronically in the database system.

2. Study monitoring

Data manager at the Keio Center for Clinical Research will conduct periodic inspection of the accumulating outcome data throughout the course of the study. The Data Safety Monitoring Committee (DSMC) may request additional evaluation or follow-up of patients who have clinically significant events.

3. Interim analyses

Interim analyses are planned for safety and futility when 50% of patients (n=40) have been randomized and have completed the 16 week post-randomisation assessment. The interim analysis will be performed by the member of DSMC who is blind to the allocated treatment. Incidence of serious adverse events in the sample and the 17-item GRID-HAMD score at post-treatment (16 week) will be compared between groups to consider whether the intervention is futile (i.e. a 15% or less mean difference between the groups). The results of the interim analyses will be discussed with the principal investigator, who will decide to continue, stop, or modify the trial.

4. Premature termination rule of the entire study

Study will be aborted if principal investigator, upon advice from the DSMC, judges it necessary for medical safety reason such as when causal relationship between study intervention and serious adverse events is established or serious ethical violation occurs that is out of line with the Ethics Guideline for Clinical Research (Ministry of Health, Labour and Welfare, revised 2008).

Reporting of adverse events

All adverse events reported spontaneously by the patients or observed by the treating psychiatrists will be recorded. When an adverse event occurs, the treating psychiatrist will take all the necessary and appropriate measures to ensure safety of the patient.

When a serious adverse event (SAE) occurs, the treating psychiatrist must take all the necessary and appropriate measures to ensure safety of the study patient and provide appropriate treatments including hospital admission. Based on the Ethics Guideline for Clinical Research (Ministry of Health, Labour and Welfare, revised in 2008) a SAE is defined as "an adverse event that may lead to death or to enduring severe impairment depending on the patient's conditions and circumstances" and will include 1) death (all deaths regardless of causal relationship with the intervention or whose causal relationship with the intervention cannot be denied during the intervention phase or up to 30 days after the completion of intervention), 2) life-threatening event, 3) event leading to enduring and severe impairment and dysfunction and 4) hospitalization (all hospitalization regardless of causal relationship with the intervention or whose causal relationship with the intervention cannot be denied during the intervention phase or up to 30 days after the completion of intervention).The treating psychiatrist must notify the SAE to principal investigator (YO) immediately, and the principal investigator must also notify all the collaborating investigators. The head investigator of the study site must report to its own ethical review committee and, if it concerns an unforeseeable SAE, must report to the Japanese Ministry of Health, Labour and Welfare.

Ethical Considerations and Dissemination

Ethical approval of the study protocol was obtained by the Ethical Review Committee of Keio University School of Medicine (reference no. 20070070, 19-70-4) and the Ethical Review Committee of Sakuragaoka Memorial Hospital. The trial is registered under UMIN Clinical Trials Registry: UMIN000001218.

Informed Consent

The study psychiatrist is responsible for ensuring that the patient understands the potential risks and benefits of participating in the study, including answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the study.

The Informed Consent Form will be used to explain the potential risks and benefits of study participation to the patient in simple terms before the patient is entered into the study and to document that the patient is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

The study psychiatrist is responsible for ensuring that informed consent is given to each patient. This includes obtaining the appropriate signatures and dates on the Informed Consent Form prior to the administration of protocol intervention.

Ethical Review

The principal investigator (YO) and the co-principal investigator (AN) must agree with the protocol and Informed Consent Form before they are submitted to the ethical review committee and are used at sites. All protocol and Informed Consent Form must be compliant with the Ethics Guideline for Clinical Research (Ministry of Health, Labour and Welfare, revised in 2008). The ethical review committee will review the protocol as required. When an amendment of protocol is needed for legitimate reason, such as safety concerns, the protocol will be revised and after the agreement of the principal investigator and the co-principal investigator, it will be submitted to the ethical review committee for review.

Compensation and insurance for harmed patients

We cannot completely negate there is a possibility of developing unforeseen serious complications or other health damage during or after completion of participation in this study. In that case, appropriate responses will be taken, the same as with treatment for health damage in usual medical care. Basically, the medical expenses shall be borne by the patient, since the treatment will be provided as health-care services provided under national health insurance, the same as usual treatment. There will be no special financial compensation, however, if there is any negligence on the part of the physician, it may be covered with the doctors' liability insurance.

Conflict of interest

The objectivity of research and commitment to academic integrity is of paramount importance and the basis for obtaining and maintaining public trust, all investigators will comply with the site's policy on Conflict of Interest in research and relevant COI guidelines.

Dissemination

The results of the study will be disseminated at several research conferences and as published articles in peer-reviewed journals. The study will be implemented and reported in line with the CONSORT statement.

Discussion

The ECAM study aims to provide new evidence for administering CBT for major depression as a next-step option

for patients who have failed to respond to pharmacotherapy in psychiatric care settings. The design of the study is expected to detect a meaningful difference in clinical effectiveness outcomes. The ECAM study is distinguished from previous studies in that the study design standardizes psychiatric interview to assess depression symptomatology by blind-raters, recruits patients from secondary to tertiary psychiatric care that tend to be more severe and more difficult-to-treat, and evaluates the long-term effects of CBT for up to 12 months.

Challenges and limitation of this study is that we cannot examine the efficacy of CBT itself because we did not choose attention-placebo, such as relaxation, as control. Our aim is to conduct a study to examine the effectiveness of augmenting CBT to usual clinical care rather than examine the efficacy of CBT itself. We are also aware that the participating sites of this study are, clinically speaking, experienced in the treatment of depressed patients. Thus, concern about the generalizability of the results is compromised. Nevertheless, this is the first randomized controlled study to assess the effectiveness of CBT for treatment resistant depression in Japan. The results of the current study will hopefully improve the evidence-based knowledge of patients who suffer with residual symptoms of depression despite adequate pharmacotherapy.

Current study status

The ECAM study began recruiting patients in September, 2008 and closed recruitment at August 2013. Data collection will be completed in December, 2014.

Author's contribution

AN and MS conceived and designed the study. AN drafted the protocol manuscript, organized and supervised study implementation. DF and TK refined the study protocol and study implementation. TA and YS provided methodological and statistical expertise. TA and AN conducted the statistical analyses. YO provided CBT expertise and supervision to the therapists. YO drafted the grant and was responsible for the entire study implementation. AN was responsible for study management, staff training, and supervision. DM managed day-to-day study responsibilities, including monitoring recruitment, collecting data, and liaising with recruitment sites. SI and MM are the directors of the site and provided clinical expertise and on-site management of the study. All authors critically reviewed and approved the final version of the manuscript.

Acknowledgements

The authors would like to thank our recruitment sites for their support. Clinical ratings will be completed by the clinical evaluation staff at the Sakuragaoka Memorial Hospital and the Department of Neuropsychiatry, Keio University School of Medicine. Thanks are also given to the member of Data Safety Monitoring Committee, Dr. Kimio Yoshimura. We appreciate the informatics support provided by Yoko Ito, Kayoko Kikuchi, and Naoki Tomotsugu of the Project Management Office at the Keio Center for Clinical Research in the construction and data management of the electronic data capture system.

Competing interests

AN, MS, DF, TK, and YO developed and have written the Japanese CBT manual for depression, are involved in National CBT Training and Supervision Project funded by the Japanese Ministry of Health Labour and Welfare. YO is the president of the Japanese Association for Cognitive Therapy. None other authors have any conflicts to declare.

Funding source

This study is supported by the Health Labour Sciences Research Grant (H22-Seishin-Ippan-005, H25-Seishin-Ippan-002) from the Japanese Ministry of Health Labour and Welfare. The funding source has no role in study design; in the data collection, analysis and interpretation; in the writing of the report; and will not have any role in the decision to submit the paper for publication.

Figure 1. Diagram of the ECAM study

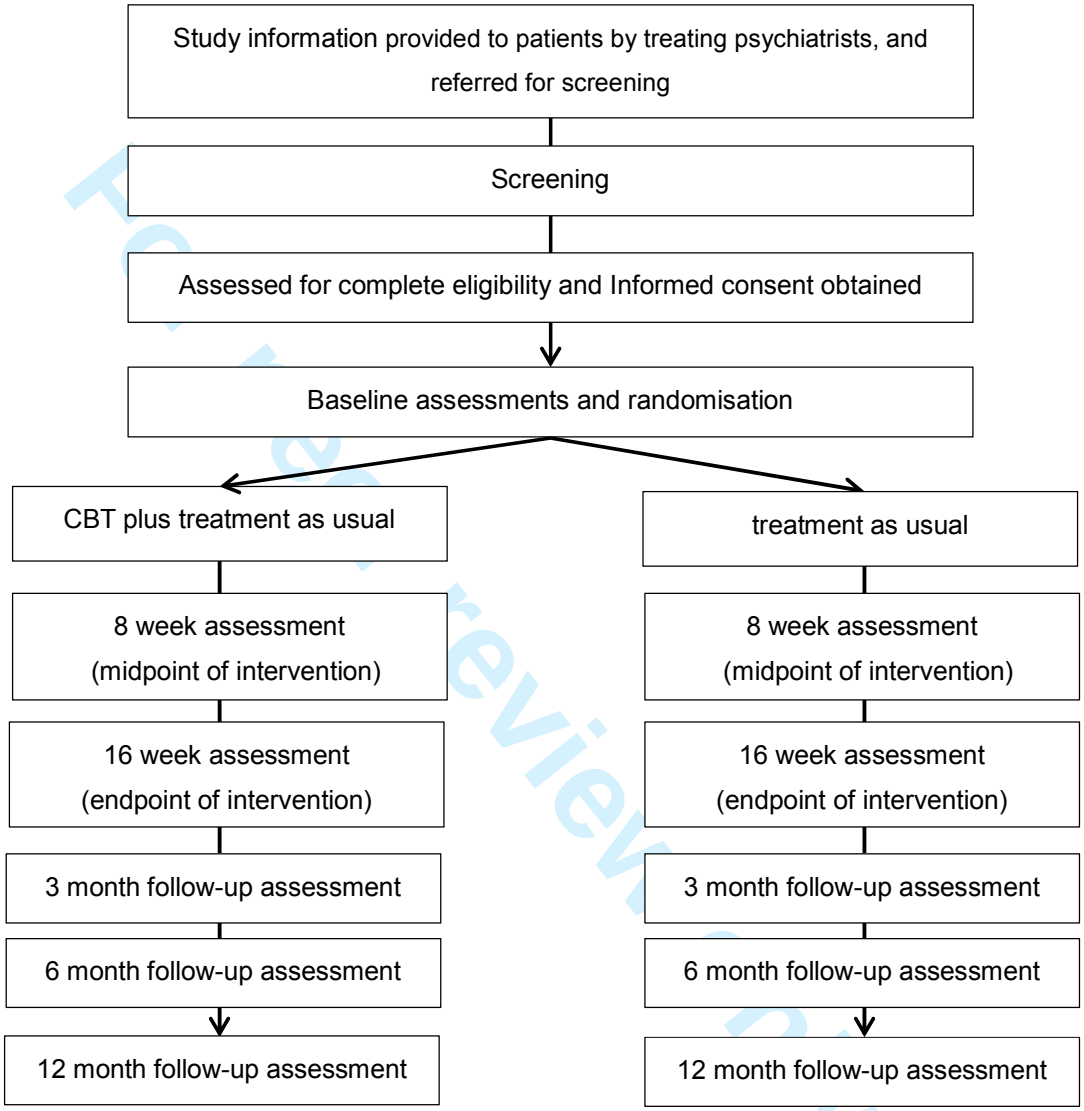

Table 1. Framework of the 16 weekly CBT program for depression

Session number	Session goals	Suggested structure	Suggested Tools/homework
1, 2	· Establish rapport · Gather information about patient's problem and develop a problem list · Psychoeducation about depression and the process of CBT	· Review on symptoms, course of illness and developmental history · Identify patient's main problem · Educate the patient about depression and CBT · Provide summary and elicit feedback	· Provide education sheets · "What is depression?" · "What is CBT?"
3, 4	· Case conceptualization · Set goals for treatment · Activate the patient	· Collaboratively set the agenda and review homework · Collaboratively set treatment goals · Activity scheduling · Provide brief summary on case conceptualization · Assign homework; Elicit feedback and check for understanding	· Problem list · Activity record
5, 6	· Identify mood and automatic thoughts	· Collaboratively set the agenda and review homework · Dysfunctional thought record (triple column) · Assign homework · Elicit feedback and check for understanding	· Provide education sheets · "How to identify your moods and thoughts
7-12	· Test automatic thoughts · (Optional – dissolve interpersonal conflicts/problem solving) · Solidify patient's ability to use cognitive techniques to change automatic thoughts	· Collaboratively set the agenda and review homework · Dysfunctional thought record (seven columns) · (Optional structure- assertive training/problem solving) · Assign homework; Elicit feedback and check for understanding	· Provide education sheets "How to balance your thoughts" · Interpersonal module · Problem-solving module
13, 14	· Identify schemas · Reinforce use of cognitive and behavioral change techniques	· Collaboratively set the agenda and review homework · Dysfunctional thought record · Discussion on schemas · Assign homework; Elicit feedback and check for understanding	· Provide education sheets "Rules of your mind"
15, 16	· Termination · Relapse prevention	· Collaboratively set the agenda and review homework · Review of the overall therapy · Identify the triggers for relapse and target specific schemas, utilize relapse prevention strategies · Preparation for booster sessions · Provide final summary and elicit feedback	· Provide education sheets "Upon ending your therapy"

Table 2. Schedule of the assessments

	Enrolment	Baseline/ Randomisation	*Intervention*		*Follow-up*		
TIMEPOINT	***-1***	**0**	***8wk***	***16wk***	***Post3 M***	***Post6 M***	***Post12M***
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Allocation		X					
INTERVENTIONS:							
CBT plus treatment as usual			◆———	———◆			
Treatment as usual			◆———	———◆			
ASSESSMENTS:							
Demographics questionnaire	X						
SCID-I	X						
M.I.N.I.	X						
SCID-II			X				
GRID-HAMD		X	X	X	X	X	X
BDI-II		X	X	X	X	X	X
QIDS-SR16*		X	X	X	X	X	X
EQ-5D		X	X	X	X	X	X
SF-36		X	X	X	X	X	X
HPQ		X	X	X	X	X	X

Abbreviations: SCID-I, Structured Clinical Interview for DSM-IV Axis I Disorders; M.I.N.I, Mini-International Neuropsychiatric Interview, SCID-II, Structured Clinical Interview for DSM-IV Axis II Disorders, GRID-HAMD, GRID-Hamilton Depression Rating Scale; BDI-II, Beck Depression Inventory-Second Edition; QIDS-SR16, 16-item Quick Inventory of Depressive Symptomatology Self-Reported; EQ-5D, European Quality of Life Questionnaire–5 Dimensions; SF-36, 36-Item Short-Form Health Survey; HPQ, World Health Organization Health and Work Performance Questionnaire

*QIDS is also assessed at each visit during the intervention phase.

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	18
	5b	Name and contact information for the trial sponsor	18
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4,5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5,6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8,9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8,9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10, 11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	21

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10, 11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13, 14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	16

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13, 14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	16
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
	31b	Authorship eligibility guidelines and any intended use of professional writers	
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Effectiveness of Cognitive behavioral therapy Augmentation in Major depression treatment (ECAM study): study protocol for a randomised clinical trial

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Keywords:	major depressive disorder, cognitive behavior therapy, randomized controlled trial, clinical protocols

Word count: abstract- 293 words, main text- 5,710 words

Effectiveness of Cognitive behavioral therapy Augmentation in Major depression treatment (ECAM study): study protocol for a randomised clinical trial

September 16, 2014

Atsuo Nakagawa[1,2,5], Mitsuhiro Sado[2], Dai Mitsuda[2,5], Daisuke Fujisawa[2], Toshiaki Kikuchi[3], Takayuki Abe[1,4], Yuji Sato[1], Satoru Iwashita[5], Masaru Mimura[2], and Yutaka Ono[6]

[1] Center for Clinical Research, Keio University School of Medicine, Tokyo, Japan

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

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

[4] Department of Preventive Medicine and Public Health, Keio University School of Medicine, Tokyo, Japan

[5] Department of Psychiatry, Sakuragaoka Memorial Hospital, Tokyo, Japan

[6] National Center for Cognitive Behavioral Therapy and Research, National Center of Neurology and Psychiatry, Tokyo, Japan

Corresponding author

Atsuo Nakagawa, MD, PhD

Center for Clinical Research, Keio University School of Medicine

Shinanomachi 35, Shinjuku-ku

Tokyo 160-8582

Tel +81-3-5363-3235, FAX +81-3-5363-3480

e-mail: anakagawa@z2.keio.jp

Keywords: major depressive disorder, cognitive behavior therapy, randomized controlled trial, clinical protocols

Abstract (293 words)

Introduction

Major depression is a serious mental disorder that causes substantial distress and impairment on individual and society. Although antidepressant treatment is the most widely used treatment modality in routine practices, there is little evidence to guide second-line option for patients who have failed to respond to antidepressants. The aim of this paper is to describe the study protocol for a randomized controlled trial that measures the clinical effectiveness of cognitive behavioral therapy (CBT) as an augmentation strategy to treat patients with non-psychotic major depression who were identified as suboptimal responders to usual depression care.

Methods and analysis

The current study is a 16-week assessor-blinded randomised, parallel-groups superiority trial with a 12-month follow-up at an outpatient clinic as part of usual depression care. Patients aged 20-65 years with DSM-IV Major Depressive Disorder who have experienced at least one failed trial of antidepressants as part of usual depression care, will be randomly assigned to receive CBT plus treatment as usual, or treatment as usual alone. The primary outcome is the change in clinician-rated 17-item GRID-HAMD score at 16-weeks, and secondary outcomes include severity and change in scores of subjective depression symptoms, proportion of responders and remitters, safety and quality of life. The primary population will be the intention-to-treat.

Ethics and dissemination

All protocol and Informed Consent Form are compliant with the Ethics Guideline for Clinical Research (Japanese Ministry of Health, Labour and Welfare). Ethical Review Committees at the Keio University School of Medicine and the Sakuragaoka Memorial Hospital approved the study protocol. The results of the study will be disseminated at several research conferences and as published articles in peer reviewed journals. The study will be implemented and reported in line with the CONSORT statement.

Clinical Trial Registration Number

UMIN Clinical Trials Registry: UMIN000001218.

Strengths and limitations of this study

- This protocol will provide new evidence for administering CBT for major depression as an augmentation strategy for patients who have failed to respond to pharmacotherapy in psychiatric care settings.
- Central randomisation and blinded assessment have been used.
- The study cannot examine the efficacy of CBT itself because we did not choose attention-placebo as control. Concern about the generalizability is compromised due to small number of study sites.

Introduction

As in other high-income countries, major depression is a common mental disorder in Japan [1]. Left untreated, major depression can cause substantial distress and impairment on individuals to negatively affect their quality of life, medical morbidity and mortality, and place an enormous burden on society [2-4]. Latest estimates from Global Burden of Disease study GBD 2010 indicate that major depression accounts for 2.5% of the global disease burden [5], and by 2030 major depression is predicted to be the leading cause of disability in high-income countries [6]. For this debilitating mental disorder, treatment guidelines recommend antidepressants for first-line treatment of moderate to severe acute major depression [7, 8], and it is the most widely used treatment modality in routine practices and remains the mainstay. However, available evidence indicates that only a third of patients fully respond to the first trial of antidepressant [9-11]. Thus, many patients with major depression are left with considerable symptomatology after the initial treatment and are referred as treatment resistant (refractory) depression (TRD).

Although many treatment studies have been published to investigate the best treatment strategies for TRD [12, 13], no standard treatment modality has yet been established [14]. When patients fail to respond to an adequate course of antidepressant treatment, the most currently available treatment guideline recommends the subsequent option of increasing the dose of the current antidepressant, switching to a different antidepressant, or augmenting with another pharmacotherapy [7]. However, one major problem of TRD is its lack of consensual operational definitions [15, 16]. Given the heterogeneity of TRD associated with complex etiologic pathways, a non-pharmacological approach such as depression-specific psychotherapy may have a role in their treatment [17].

It is well established that cognitive behavioral therapy (CBT), the most published structured form of psychotherapy developed on the basis of the Beck's cognitive theory [18], is efficacious for the treatment of depression [7, 8]. Numerous randomized controlled studies have shown that CBT is superior to wait-list, non-specific controls, or treatment as usual [19]. Further evidence shows that combining psychotherapy to pharmacotherapy is more effective than pharmacotherapy alone [20]. Based on the mounting evidence as above, CBT has been drawing considerable attention in Japan as an efficacious treatment for depression not only among clinicians and academics but also the general public. The Japanese Ministry of Health, Labour and Welfare has been encouraging training for, and practical implementation of CBT, as exemplified by the coverage of CBT for mood disorders by the Japanese national health insurance scheme since 2010 [21].

Despite these developments, few empirical studies have evaluated the effectiveness of CBT as a next-step option for patients who have failed to respond to antidepressants[22-24]. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) examined CBT and pharmacotherapy as a sequential approaches to manage patients who failed the initial 12-14 weeks of citalopram treatment by using either augmentation or switch strategies [25]. No differences in outcome at post-treatment were observed between augmenting CBT and augmenting other pharmacotherapy, and this finding was similar among the switching option. However, STAR*D trial implemented a

unique equipoise-stratified randomisation design which refused the non-preferred treatment arm; only a quarter of the STAR*D participants were randomized to CBT for their second-step treatment and this selection bias makes difficult to interpret the outcomes. Next, Kennedy and colleagues [26] compared cognitive therapy and lithium augmentation as a sequential treatment option for 44 outpatients with major depression who had a partial response during 8 to 14 weeks of antidepressant treatment in an 8-week randomized controlled trial. They found that there was no significant benefit of cognitive therapy over lithium augmentation. However, the sample size was small which may limit power to detect the differences in the changes over time, and the duration of trial was relatively short. Furthermore, the trial focused on partial responders (defined as HAMD score of 8-15) and excluded non-responders to the initial antidepressant treatment. Finally, the recent CoBalT trial [27] examined the effectiveness of CBT as a next-step option for patients whose depression did not respond to usual depression care delivered by general practitioner in the UK. In this pragmatic clinical trial with a sample size of 469, augmenting CBT to usual care increased the treatment response 3-fold at 6 months compared to those with usual care alone. However, the primary outcome of this trial was a self-reported measure (i.e. BDI-II) that might be affected by the treatment process. Further, it is unclear if this result could be applied to different clinical settings such as in psychiatric care or to other socio-cultural contexts.

There is little evidence to guide next-step option for patients who have failed to respond to antidepressants in psychiatric care settings. We therefore planned to carry out a randomised controlled trial to examine the effectiveness of CBT as an augmentation strategy for antidepressant non-responders compared with pharmacotherapy as part of usual care for patient. The aim of this paper is to describe the study protocol of the current study.

Objectives

1. The primary objective of this study is to compare the effectiveness of CBT as an augmentation strategy to treatment as usual (that includes antidepressant treatment) versus treatment as usual alone in a 16-week randomized controlled trial with a 12-month follow-up for patients with non-psychotic major depression who were identified as suboptimal responders to usual depression care.
2. The secondary objective of the study is to evaluate the safety (incidence of treatment discontinuation and adverse events) of CBT as an augment strategy to treatment as usual for patients with non-psychotic major depression who have not adequately responded to usual depression care.

Methods and Analysis

Study design and setting

The current study is a 16-week assessor-blinded, randomised, controlled superiority trial of two parallel-groups with a 12-month follow-up at an outpatient clinic as part of usual depression care (**Figure 1**). Random allocation to treatment will be done at the individual level.

Patients will be recruited from two sites in Tokyo. One will be a university teaching hospital, the other a psychiatric hospital. The university teaching hospital department of psychiatry located in central Tokyo has 31 beds (1,044 beds for the entire university teaching hospital) and, offers advanced psychiatric care services for patients with complex problems, who are largely middle-class Japanese. On the other hand, the psychiatric hospital located in suburban Tokyo has 467 beds and offers wide range of psychiatric care services, mainly serving secondary to tertiary psychiatric care to a diverse Japanese population that also include socioeconomically disadvantaged groups. It is noteworthy that a feature of Japan's healthcare is its universal health insurance system in which all patients receive free access to specialized medical services at any institutions including university teaching hospital.

Participants

1. Inclusion criteria

Patients are eligible to be included in the study if they meet the following criteria: (1) outpatients with a diagnosis of Major Depressive Disorder, as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [28] criteria for single or recurrent without psychotic features assessed with the Structured Clinical Interview for DSM-IV (SCID) [29] administrated by trained psychiatrist; (2) age between 20 and 65 years; (3) identified as suboptimal responders to usual depression care defined as those who experience at least moderate level of depression symptoms based on at least 16 on the GRID-Hamilton Depression Rating Scale-17 item ($GRID\text{-}HAMD_{17}$) [30, 31] and evidence of at least minimal level of treatment resistance by obtaining at least 3 on the Maudsley Staging Method for treatment-resistant depression [32] despite taking antidepressant treatment at an adequate therapeutic dose (based on package insert (Available at: http://www.info.pmda.go.jp/info/iyaku_index.html)) for at least 8-weeks as part of usual depression care, and (4) must be competent and able to give informed consent.

2. Exclusion criteria

Patients will be excluded from the study if they meet the following criteria: (1) having past or current manic or psychotic episode; (2) having comorbid alcohol or substance use disorder in 6 months prior to the study entry; (3) having any DSM-IV Axis I disorders other than Major Depressive Disorder to be the primary diagnosis assessed by the Mini-International Neuropsychiatric Interview (M.I.N.I.) [33, 34]; (4) having antisocial personality disorder; (5)

having serious and imminent suicidal ideation; (6) having a serious or unstable medical illness; (7) having organic brain lesions or major cognitive deficits in a year prior to the study entry; (8) have previously completed full-session of CBT program and (9) those who were highly anticipated to fail to attend less than 8 visits during the 16-week trial phase (e.g. due to relocation).

Procedures

1. Recruitment

Treating psychiatrist will, during their usual consultation, provide brief information about the study using a brochure and invite patient to take part in the study. If the patient shows interest in the study and provides contact details to the research team, a face-to-face appointment with a study psychiatrist will be set. The details of the study and potential benefits as well as risks will be explained thoroughly to the patient by the study psychiatrist and discussed. If the patient agrees to study participation, a written informed consent will be obtained. After obtaining the informed consent, the patient will be assessed by the study psychiatrist for eligibility. A diagnosis of Major Depressive Disorder will be evaluated with the SCID [29] , while other Axis I disorders will be evaluated with M.I.N.I [33, 34]. Of note, Axis II disorders will be evaluated with the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II) [35] at week 8 (i.e. a considerable time frame for depressive symptoms to have abated). Diagnostic interviewers will be the study psychiatrists (AN and MS) who have received extensive training in the administration of semi-structured interviews.

2. Baseline assessment

Acute psychopathology will be assessed at study entry by the study psychiatrists or psychologists. Objective depressive symptoms will be assessed by the 17-item and 21-item GRID-HAMD. Patients' subjective perception of depression severity will be assessed by the self-reported Beck Depression Inventory-Second Edition (BDI-II)[36, 37] and 16-item Quick Inventory of Depressive Symptomatology Self-Reported ($QIDS\text{-}SR_{16}$)[38, 39]. Health related quality of life will be measured by the European Quality of Life Questionnaire–5 Dimensions (EQ-5D)[40, 41] and 36-Item Short-Form Health Survey (SF-36)[42]. Work performance and productivity will be measured by the World Health Organization Health and Work Performance Questionnaire (HPQ)[43, 44]. Life stressors will be measured using the St. Paul-Ramsey Questionnaire (available from the authors), which rates the severity of individual stressors from 1 (none) to 7 (catastrophic) in six categories ranging from marital to occupational and gives a final global measure of the stressors.

Demographic and other clinical data will be also collected as a part of the baseline assessment, such as marital status, number of children, residential status, level of education, duration of current and lifetime episode of depression, number of lifetime depression episodes, history of depression treatment including past

pharmacotherapy and hospitalized treatment, past suicide attempt, history of medical complication, and family psychiatric history. Level of treatment resistance will be evaluated operationally with the Maudsley Staging Method for Treatment Resistant Depression[45]. A history of childhood abuse and traumatic brain injury will be rated as present or absent. Current cigarette and alcohol use will be assessed by the subject's report. Assessments will also be conducted at 8 and 16 weeks after the randomisation.

3. Randomisation

All eligible patients who give consent for participation will be randomized to treatment as usual or to CBT plus treatment as usual at the end of baseline assessment (1:1 allocation ratio). Randomisation will be conducted using central computerized registration system that automatically randomizes patients and generates a message notifying their assigned treatment. Allocation is concealed through the use of central computerized registration system designed for this study by the Project Management Office at the Keio Center for Clinical Research. Allocation will be stratified by site (n=2) with minimisation method to balance the age of the participants at study entry (older versus younger) and baseline GRID-$HAMD_{17}$ score (severer versus non-severer). The cut-off age and GRID-$HAMD_{17}$ score for minimisation will not be disclosed until the study termination to ensure concealment.

4. Intervention phase (16 week)

4-1. CBT

Therapists will follow the individual CBT treatment manual for depression developed by the authors (YO, DF, AN, KT and MS) (Available at the Japanese Ministry of Health, Labor and Welfare website: http://www.mhlw.go.jp/bunya/shougaihoken/kokoro/dl/01.pdf). This manual is developed based on Beck's treatment manual [46], with some adaptation to address the cultural characteristics of the Japanese patients such as more emphasis on interpersonal relationships and consideration of family as an essential part of the treatment [47]. The overview of the program is shown in **Table 1**. Problem-solving techniques and specific approaches to address interpersonal issues and cognitive behavioral avoidance are emphasized. Therapists are encouraged to refer to the relevant approaches whenever necessary. Furthermore, the therapists are encouraged to give feedbacks to the patients about the case conceptualization and collaboratively set the treatment goal during the earlier phase of the program. The patients allocated to CBT will typically receive a course of 16 weekly sessions, with up to 4 additional sessions if deemed clinically appropriate by the study therapist (maximum of 20, and minimum of 8 sessions). Sessions will last approximately 50 minutes. Therapy will take place in an outpatient consultation room at each site. During CBT treatment, other depression-specific empirical psychotherapy (i.e. interpersonal therapy (IPT)) and electroconvulsive therapy are prohibited.

4-2. Training and supervision of therapists

Six therapists will deliver CBT at the two sites. The study therapists have been trained as psychiatrists (n=4), a master's-degree clinical psychologist (n=1), and a psychiatric nurse (n=1). Of the six therapists, two are female (n=2, 33.3%). On average, the study therapists had 4.0 (SD 2.1) years of experience as CBT therapists and have completed 12.5 (SD 7.3) cases at the time of participation. All therapists have received CBT training at the Keio University Cognitive Behavioral Therapy Training and Research Program and will continuously receive supervision throughout the study.

To ensure treatment fidelity, all therapists completed a two-day workshop and will participate in two-hour bi-weekly group supervision with other therapists during the study. At the group supervision, therapists will present the case formulation and treatment plan. The group supervision will be led by one of the authors (YO), the founder and the president of the Japanese Association for Cognitive Therapy and a fellow of Academy of Cognitive Therapy, who will facilitate discussion of therapeutic difficulties and impasses and provide skills acquisition, and peer support. To assess CBT competences, a random sample of audiotaped sessions will be rated using the Cognitive Therapy Rating Scale (CTRS)[46, 48]. A score of 40 or greater is defined as an adequate level of technical competency in the CBT sessions.

4-3. Treatment as usual (Usual depression care by psychiatrists)

Although appropriate flexibility will be allowed for scheduling sessions, the patients will typically receive a bi-weekly, 5-30 minutes consultation by the treating psychiatrist during the treatment phase with a minimum of 8 sessions. A typical session will comprise of symptom assessment and standard clinical management such as brief psychoeducation and pharmacotherapy when appropriate. Although there will be no restriction on pharmacotherapy, it should basically be concordant with major practice guidelines for major depression such as the American Psychiatric Association practice guideline[8]. Prescribed medicine and dose will be recorded and medication adherence will also be assessed at each visit using the self-reported Treatment and Medication Compliance Data Scale (TMCDS) (available from the authors upon request). Patients can enter the study receiving any medication(s) for concurrent general medical conditions. No depression-specific empirical psychotherapies (CBT or IPT) or electroconvulsive therapy are permitted during the intervention phase and will result in withdrawal from the study. Treatment will be delivered by seven treating psychiatrists who have practiced for a mean of 7.3 (SD 4.4) years and are working at the two sites. .

5. Follow-up phase

There will be no restrictions on treatment options for the patients who receive depression care by the treating psychiatrists during this phase. Thus, the treating psychiatrists are allowed to refer the patients to appropriate

mental health professionals for psychotherapies and electroconvulsive therapy if deemed clinically appropriate. However, those who receive depression-specific empirical psychotherapies (CBT and IPT) and electroconvulsive therapy will be documented and considered as a deviation from the study protocol. The patient, however, will not be considered to have dropped out of the study at this phase and will receive protocol assessments. Although CBT literacy has deepened among Japanese mental health professionals after the approval of CBT as treatment for mood disorder by Japan's national health insurance scheme in 2010, the number of mental health facilities capable of providing CBT is still very limited. Therefore, it is unlikely for patients to receive CBT that may substantially influence the primary outcome. The current situation for IPT in Japan is similar.

6. Discontinuations

6-1. Discontinuation of intervention phase

If the patients meet any one of the following criteria, the treating psychiatrist will discontinue the study intervention. The patient will not be considered to have dropped out of the study and will be invited to enter the follow-up phase and receive periodical assessments through the remainder of the study period.

1. The patient withdraws the consent to receive study intervention.
2. The treating psychiatrist judges that it is inappropriate to continue the study intervention due to e.g., emergence of severe psychotic or manic episode, serious and imminent suicidal ideation, and severe medical conditions.
3. The treating psychiatrist judges that it is difficult to continue the study intervention because of emergence of adverse events or other appropriate reason that outweighs the benefit of receiving study intervention.
4. The treating psychiatrist judges that it is more appropriate to receive inpatient psychiatric care.

6-2. Discontinuation of periodical assessments

If the patient withdraws the consent to receive periodical study assessments, it will be considered as dropout and the patient will not be contacted for periodical assessments in the future.

Outcome measures

The outcome measures are shown in **Table 2.**

1. Primary outcome

The primary outcome is the change in clinician-rated 17-item GRID-HAMD score at 16-weeks, which accord with the end of the intervention. The GRID-HAMD will be also administered at week 8 (midpoint of intervention). Follow-up assessments will be administered at 3-month (7-months post-randomisation), 6-month (10-months post-randomisation), and 12-month follow-up visits (16-months post-randomisation). All the assessors

(psychiatrists and licensed clinical psychologists) have received extensive GRID-HAMD training and achieved excellent inter-rater reliability (ICC=0.98). The GRID-HAMD will be conducted by an assessor blind to treatment randomisation. Due to the nature of the intervention, neither the patients, nor the treating psychiatrists, nor the study therapists can be completely blinded to randomisation, but are strongly instructed not to disclose the randomisation status of the patient at periodical assessments. Further, the assessors will not be present during the treatment administration.

2. Secondary outcomes

2-1. Clinical outcomes

- Severity and change in scores of subjective depression symptoms as measured by the BDI-II and QIDS-SR_{16}
- Proportion of responders, defined as 50% or greater reduction on 17-item and 21-item GRID-HAMD, BDI-II and QIDS-SR_{16} relative to baseline.
- Proportion of patients who achieve remission, defined as a 17-item GRID-HAMD score <=7[49], BDI-II score <=13[50] and QIDS-SR_{16}<=5[38].

2-2. Safety outcomes

- Proportion of patients who discontinue from the study will be recorded. The reasons for discontinuation will be asked of the patient at site or by telephone and will be ascertained by the treating psychiatrist.
- Spontaneously reported Adverse Event (AEs) and Serious Adverse Events (SAEs).

2-3. Health outcomes

- Level and change in the degree of health-related quality of life as measured by the EQ-5D and SF-36.

2-4. Work performance outcomes

- Self-reported sick leave hours (absenteeism), degree of job performance reduction (presenteeism), and the actual hours worked in the past 4 weeks as measured by the HPQ.

2-5. Economic evaluation

- Degree of quality of life (EQ-5D) and depression severity (GRID-HAMD, BDI-II and QIDS-SR16) will be used for estimating Quality Adjusted Life Years (QALYs) for cost-utility analyses.

3. Instruments

GRID- Hamilton Depression Rating Scale

The Hamilton Depression Rating Scale (HAMD) has been the gold standard assessment for the observer rated depression symptomatology for more than 50 years. The GRID-HAMD was developed to set standards for scoring and administering the original HAMD. The seven-day period prior to assessment is the usual time frame for assessing symptom severity. The GRID-HAMD has three components: the GRID scoring system based upon assessment of symptom intensity and symptom frequency, the manual of scoring conventions, and a

semi-structured interview guide based on the SIGH-D[51]. Inter-rater reliability of the Japanese version of the GRID-HAMD total score is excellent[30].

Beck Depression Inventory-Second Edition (BDI-II)

The BDI-II has been one of the most widely used self-report instruments to assess the severity of depressive symptoms which was developed by Beck and colleagues and its first version was published in 1961[52]. The BDI-II is a 21-item questionnaire and each item is answered by circling a number between 0 and 3, with larger numbers indicating greater severity. The time frame for assessing symptom severity for BDI-II should be in the past two weeks to better coincide with DSM criteria. Good reliability and validity has been reported for the original [36] as well as the Japanese version [50].

16-item Quick Inventory of Depressive Symptomatology Self-Reported (QIDS-SR_{16})

The QIDS-SR_{16} is an abbreviated self-report version of the clinician-rated 30-item Inventory of Depressive Symptomatology (IDS), designed to assess the severity of depressive symptoms, which was developed by John Rush and colleagues. The QIDS-SR_{16} assesses all the criterion symptom domains to diagnose a DSM Major Depressive Episode. The seven day period prior to assessment is the usual time frame for assessing symptom severity. Internal consistency is high with a Chronbach's alpha ranged from 0.81 to 0.94 and validity is high with a high correlation with HAMD [38] as well as the Japanese version[39] .

36-Item Short-Form Health Survey (SF-36)

The SF-36 is a multi-purpose health survey with 36 items. It yields the 8 health domains of functional health (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and metal health),level of well-being, physical and mental health summary measures, and a health utility index. Good validity has been reported for the original [53] as well as the Japanese version[42].

World Health Organization Health and Work Performance Questionnaire (HPQ)

The HPQ is the most widely used self-report instrument designed to estimate the workplace costs of health problems in terms of reduced job performance, sickness absence, and work-related accidents and injuries. It assesses work hours, sick-leaves, occupational accidents, and self-rated productivity in past seven days and past four weeks. The validity of the HPQ absenteeism and presenteeism measures has been confirmed [54].

European Quality of Life Questionnaire–5 Dimensions (EQ-5D)

The EQ-5D is a generic, multidimensional, health-related, quality-of-life instrument that contains two parts: a health status profile and a VAS to rate global health-related quality of life [40]. Health status profile yields the 5 health domains (mobility, self-care, usual activities, pain/discomfort, and mood) and the outcome rating of the 5 domains will be mapped to a single index value through an algorithm. The index value ranges between 0 and 1 with the higher score indicating a better health state perceived by the patient. The index value is used for calculating QALYs. The EQ-5D is the measure of health-related quality of life in adults preferred by the National Institute for Health and Clinical Excellence.[7]

Sample size estimation

The sample size is calculated based on the primary outcome of depression symptoms as measured by the 17-item GRID-HAMD score at 16 weeks after the randomisation. Our previous single group study on CBT with treatment as usual for acute major depression have shown that the 17-item GRID-HAMD will drop from 24.3 (SD 7.4) to 10.0 (SD 5.0) at week 16 [47]. We expect a mean difference of 40% (4 point) in the 17-item GRID-HAMD total scores between the groups at endpoint and consider this to be a clinically meaningful difference. With a two-sided significance level of 5% and statistical power at 90% and allowing for 15% drop-out, the sample size was calculated to be 40 per arm, i.e., 80 in total.

Statistical analyses

The primary analysis population in this study will be the intention-to-treat (ITT), defined as all randomised patients. For the primary outcome, the least squares means and their 95% confidence intervals will be estimated using analysis of covariance (with treatment group as a factor and baseline scores as a covariate) to compare the two group, with a last-observation-carried-forward approach for missing values. To examine the robustness of the last-observation-carried-forward approach, a mixed-effects model for repeated-measures (MMRM) that contains treatment group, week, and group-by-week interaction as factors with compound symmetry covariance matrix among time points, and Kenward-Roger degrees of freedom adjustment will be performed with all the primary outcomes and also for continuous secondary outcomes. Categorical outcomes will be analyzed using chi-square test or Fisher's exact test. Summary statistics (means and standard deviation) of patients' characteristics will be calculated. When appropriate, t-test and Mann-Whitney U test will be used to compare baseline continuous outcomes (means). Time to all cause discontinuation will be summarized using Kaplan-Meier estimates and compared with log-rank test. The significance level will be set at 0.05 (2-tailed). Statistical analyses will be performed with SAS version 9.3.

Data collection and management

To ensure accurate, complete, and reliable data, the following countermeasures will be conducted: 1) provide standardized operational procedure material to the study sites regarding data collection, data encoding, and storing, 2) hold a training session to give instruction on the protocol, the completion of the EDCs, and study procedures for study psychiatrists, study therapist, and study coordinators, 3) hold a periodic meeting among the study site personnel to share issues related to conducting the study and to elaborate, 4) the principal and co-principal investigator will be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax, 5) a data manager will review and evaluate EDC data, use standard computer edits to detect errors during data collection, and conduct a quality review of the database.

To ensure the safety of the participants in the study and to ensure accurate, complete, and reliable data, the study psychiatrist will keep records of paper instruments and clinical records in the patient files as source documents for the study at the site. The principal investigator (YO), the co-principal investigator (AN), the study statistician (TA) and other steering committee members (MS, DF, TK) will be given access to the cleaned data sets.

1. Electronic data capture system

An electronic data capture system will be used in this study. The site maintains the original source for the data entered by the site into the electronic data capture system. The eCRF data collected by the study psychiatrists, therapist, or the clinical research coordinators will be encoded and stored electronically in the database system. Data will be managed by data manager at the Keio Center for Clinical Research and will be stored electronically in the database system.

2. Study monitoring

Data manager at the Keio Center for Clinical Research will conduct periodic inspection of the accumulating outcome data throughout the course of the study. The Data Safety Monitoring Committee (DSMC) may request additional evaluation or follow-up of patients who have clinically significant events.

3. Interim analyses

Interim analyses are planned for safety and futility when 50% of patients (n=40) have been randomized and have completed the 16 week post-randomisation assessment. The interim analysis will be performed by a member of DSMC who is blind to the allocated treatment. Incidence of serious adverse events in the sample and the 17-item GRID-HAMD score at post-treatment (16 week) will be compared between groups to consider whether the intervention is futile (i.e. a 15% or less mean difference between the groups). The results of the interim analyses will be discussed with the principal investigator, who will decide to continue, stop, or modify the trial.

4. Premature termination rule of the entire study

Study will be aborted if the principal investigator, upon advice from the DSMC, judges it necessary for medical safety reason such as when causal relationship between study intervention and serious adverse events is established or serious ethical violation occurs that is out of line with the Ethics Guideline for Clinical Research (Ministry of Health, Labour and Welfare, revised 2008).

Reporting of adverse events

All adverse events reported spontaneously by the patients or observed by the treating psychiatrists will be recorded. When an adverse event occurs, the treating psychiatrist will take all the necessary and appropriate measures to ensure safety of the patient.

When a serious adverse event (SAE) occurs, the treating psychiatrist must take all the necessary and appropriate measures to ensure safety of the study patient and provide appropriate treatments including hospital admission. Based on the Ethics Guideline for Clinical Research (Ministry of Health, Labour and Welfare, revised in 2008) a SAE is defined as "an adverse event that may lead to death or to enduring severe impairment depending on the patient's conditions and circumstances" and will include 1) death (all deaths regardless of causal relationship with the intervention or whose causal relationship with the intervention cannot be denied during the intervention phase or up to 30 days after the completion of intervention), 2) life-threatening event, 3) event leading to enduring and severe impairment and dysfunction and 4) hospitalization (all hospitalization regardless of causal relationship with the intervention or whose causal relationship with the intervention cannot be denied during the intervention phase or up to 30 days after the completion of intervention).The treating psychiatrist must notify the SAE to the principal investigator (YO) immediately, and the principal investigator must also notify all the collaborating investigators. The head investigator of the study site must report to its own ethical review committee and, if it concerns an unforeseeable SAE, must report to the Japanese Ministry of Health, Labour and Welfare.

Ethical Considerations and Dissemination

Ethical approval of the study protocol was obtained from the Ethical Review Committee of Keio University School of Medicine (reference no. 20070070, 19-70-4) and the Ethical Review Committee of Sakuragaoka Memorial Hospital. The trial is registered under UMIN Clinical Trials Registry: UMIN000001218.

Informed Consent

The study psychiatrist is responsible for ensuring that the patient understands the potential risks and benefits of participating in the study, including answering any questions the patient may have throughout the study and sharing

in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the study.

An Informed Consent Form will be used to explain the potential risks and benefits of study participation to the patient in simple terms before the patient is entered into the study and to document that the patient is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study. The study psychiatrist is responsible for ensuring that informed consent is given to each patient. This includes obtaining the appropriate signatures and dates on the Informed Consent Form prior to the administration of protocol intervention.

Ethical Review

The principal investigator (YO) and the co-principal investigator (AN) must agree with the protocol and Informed Consent Form before they are submitted to the ethical review committee and are used at sites. All protocol and Informed Consent Form must be compliant with the Ethics Guideline for Clinical Research (Ministry of Health, Labour and Welfare, revised in 2008). The ethical review committee will review the protocol as required. When an amendment of protocol is needed for legitimate reason, such as safety concerns, the protocol will be revised and after the agreement of the principal investigator and the co-principal investigator, it will be submitted to the ethical review committee for review.

Compensation and insurance for harmed patients

We cannot completely negate there is a possibility of developing unforeseen serious complications or other health damage during or after completion of participation in this study. In that case, appropriate responses will be taken, the same as with treatment for health damage in usual medical care. Basically, the medical expenses shall be borne by the patient, since the treatment will be provided as health-care services provided under national health insurance, the same as usual treatment. There will be no special financial compensation, however, if there is any negligence on the part of the physician, it may be covered with the doctors' liability insurance.

Conflict of interest

The objectivity of research and commitment to academic integrity is of paramount importance and the basis for obtaining and maintaining public trust, all investigators will comply with the site's policy on Conflict of Interest in research and relevant COI guidelines.

Dissemination

The results of the study will be disseminated at several research conferences and as published articles in

peer-reviewed journals. The study will be implemented and reported in line with the CONSORT statement.

Discussion

The ECAM study aims to provide new evidence for administering CBT for major depression as a next-step option for the patients who have failed to respond to pharmacotherapy in psychiatric care settings. The design of the study is expected to detect a meaningful difference in clinical effectiveness outcomes. The ECAM study is distinguished from the previous studies in that the study design standardizes psychiatric interview to assess depression symptomatology by blind-raters, recruits patients from secondary to tertiary psychiatric care that tend to be more severe and more difficult-to-treat, and evaluates the long-term effects of CBT for up to 12 months.

Challenges and limitation of this study is that we cannot examine the efficacy of CBT itself because we did not choose attention-placebo, such as relaxation, as control. Our aim is to conduct a study to examine the effectiveness of augmenting CBT to usual clinical care rather than examine the efficacy of CBT itself. We are also aware that the participating sites of this study are, clinically speaking, experienced in the treatment of depressed patients. Thus, concern about the generalizability of the results can be compromised. Nevertheless, this is the first randomized controlled study to assess the effectiveness of CBT for treatment resistant depression in Japan. The results of the current study will hopefully improve the evidence-based knowledge of the patients who suffer residual symptoms of depression despite adequate pharmacotherapy.

Current study status

The ECAM study began recruiting patients in September, 2008 and closed recruitment at August 2013. Data collection will be completed in December, 2014.

Author's contribution

AN and MS conceived and designed the study. AN drafted the protocol manuscript, organized and supervised study implementation. DF and TK refined the study protocol and study implementation. TA and YS provided methodological and statistical expertise. TA and AN conducted the statistical analyses. YO provided CBT expertise and supervision to the therapists. YO drafted the grant and was responsible for the entire study implementation. AN was responsible for study management, staff training, and supervision. DM managed day-to-day study responsibilities, including monitoring recruitment, collecting data, and liaising with recruitment sites. SI and MM are the directors of the site and provided clinical expertise and on-site management of the study. All authors critically reviewed and approved the final version of the manuscript.

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Competing interests

AN, MS, DF, TK, and YO developed and have written the Japanese CBT manual for depression, are involved in National CBT Training and Supervision Project funded by the Japanese Ministry of Health Labour and Welfare. YO is the president of the Japanese Association for Cognitive Therapy. None other authors have any conflicts to declare.

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Table 1. Framework of the 16 weekly CBT program for depression

Session number	Session goals	Suggested structure	Suggested Tools/homework
1, 2	· Establish rapport · Gather information about patient's problem and develop a problem list · Psychoeducation about depression and the process of CBT	· Review on symptoms, course of illness and developmental history · Identify patient's main problem · Educate the patient about depression and CBT · Provide summary and elicit feedback	· Provide education sheets · "What is depression?" · "What is CBT?"
3, 4	· Case conceptualization · Set goals for treatment · Activate the patient	· Collaboratively set the agenda and review homework · Collaboratively set treatment goals · Activity scheduling · Provide brief summary on case conceptualization · Assign homework; Elicit feedback and check for understanding	· Problem list · Activity record
5, 6	· Identify mood and automatic thoughts	· Collaboratively set the agenda and review homework · Dysfunctional thought record (triple column) · Assign homework · Elicit feedback and check for understanding	· Provide education sheets · "How to identify your moods and thoughts
7-12	· Test automatic thoughts · (Optional – dissolve interpersonal conflicts/problem solving) · Solidify patient's ability to use cognitive techniques to change automatic thoughts	· Collaboratively set the agenda and review homework · Dysfunctional thought record (seven columns) · (Optional structure- assertive training/problem solving) · Assign homework; Elicit feedback and check for understanding	· Provide education sheets "How to balance your thoughts" · Interpersonal module · Problem-solving module
13, 14	· Identify schemas · Reinforce use of cognitive and behavioral change techniques	· Collaboratively set the agenda and review homework · Dysfunctional thought record · Discussion on schemas · Assign homework; Elicit feedback and check for understanding	· Provide education sheets "Rules of your mind"
15, 16	· Termination · Relapse prevention	· Collaboratively set the agenda and review homework · Review of the overall therapy · Identify the triggers for relapse and target specific schemas, utilize relapse prevention strategies · Preparation for booster sessions · Provide final summary and elicit feedback	· Provide education sheets "Upon ending your therapy"

Table 2. Schedule of the assessments

	Enrolment	Baseline/ Randomisation	*Intervention*		*Follow-up*		
TIMEPOINT	*-1*	0	*8wk*	*16wk*	*Post3 M*	*Post6 M*	*Post12M*
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Allocation		X					
INTERVENTIONS:							
CBT plus treatment as usual			⟷	⟷			
Treatment as usual			⟷	⟷			
ASSESSMENTS:							
Demographics questionnaire	X						
SCID-I	X						
M.I.N.I.	X						
SCID-II			X				
GRID-HAMD		X	X	X	X	X	X
BDI-II		X	X	X	X	X	X
QIDS-SR16*		X	X	X	X	X	X
EQ-5D		X	X	X	X	X	X
SF-36		X	X	X	X	X	X
HPQ		X	X	X	X	X	X

Abbreviations: SCID-I, Structured Clinical Interview for DSM-IV Axis I Disorders; M.I.N.I, Mini-International Neuropsychiatric Interview, SCID-II, Structured Clinical Interview for DSM-IV Axis II Disorders, GRID-HAMD, GRID-Hamilton Depression Rating Scale; BDI-II, Beck Depression Inventory-Second Edition; QIDS-SR16, 16-item Quick Inventory of Depressive Symptomatology Self-Reported; EQ-5D, European Quality of Life Questionnaire–5 Dimensions; SF-36, 36-Item Short-Form Health Survey; HPQ, World Health Organization Health and Work Performance Questionnaire

*QIDS is also assessed at each visit during the intervention phase.

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Effectiveness of Cognitive behavioral therapy Augmentation in Major depression treatment (ECAM study): study protocol for a randomised clinical trial

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Atsuo Nakagawa[1,2,45], Mitsuhiro Sado[2], Dai Mitsuda[2,45], Daisuke Fujisawa[2], Toshiaki Kikuchi[3], Takayuki Abe[1,4], Yuji Sato[1], Satoru ~~Iwashita~~[4]Iwashita[5], Masaru Mimura[2], and Yutaka ~~Ono~~[5]Ono[6]

[1] Center for Clinical Research, Keio University School of Medicine, Tokyo, Japan

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

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

[4] Department of Preventive Medicine and Public Health, Keio University School of Medicine, Tokyo, Japan

[4,5] Department of Psychiatry, Sakuragaoka Memorial Hospital, Tokyo, Japan

[5,6] National Center for Cognitive Behavioral Therapy and Research, National Center of Neurology and Psychiatry, Tokyo, Japan

Corresponding author

Atsuo Nakagawa, MD, PhD

Center for Clinical Research, Keio University School of Medicine

Shinanomachi 35, Shinjuku-ku

Tokyo 160-8582

Tel +81-3-5363-3235, FAX +81-3-5363-3480

e-mail: anakagawa@z2.keio.jp

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Abstract (293 words)

Introduction

Major depression is a serious mental disorder that causes substantial distress and impairment on individual and society. Although antidepressant treatment is the most widely used treatment modality in routine practices, there is little evidence to guide second-line option for patients who have failed to respond to antidepressants. The aim of this paper is to describe the study protocol for a randomized controlled trial that measures the clinical effectiveness of cognitive behavioral therapy (CBT) as an augmentation strategy to treat patients with non-psychotic major depression who were identified as suboptimal responders to usual depression care.

Methods and analysis

The current study is a 16-week assessor-blinded randomised, parallel-groups superiority trial with a 12-month follow-up at an outpatient clinic as part of usual depression care. Patients aged 20-65 years with DSM-IV Major Depressive Disorder who have experienced at least one failed trial of antidepressants as part of usual depression care, will be randomly assigned to receive CBT plus treatment as usual, or treatment as usual alone. The primary outcome is the change in clinician-rated 17-item GRID-HAMD score at 16-weeks, and secondary outcomes include severity and change in scores of subjective depression symptoms, proportion of responders and remitters, safety and quality of life. The primary population will be the intention-to-treat.

Ethics and dissemination

All protocol and Informed Consent Form are compliant with the Ethics Guideline for Clinical Research (Japanese Ministry of Health, Labour and Welfare). Ethical Review Committees at the Keio University School of Medicine and the Sakuragaoka Memorial Hospital approved the study protocol. The results of the study will be disseminated at several research conferences and as published articles in peer reviewed journals. The study will be implemented and reported in line with the CONSORT statement.

Clinical Trial Registration Number

UMIN Clinical Trials Registry: UMIN000001218.

Strengths and limitations of this study

- This protocol will provide new evidence for administering CBT for major depression as an augmentation strategy for patients who have failed to respond to pharmacotherapy in psychiatric care settings.
- Central randomisation and blinded assessment have been used.
- The study cannot examine the efficacy of CBT itself because we did not choose attention-placebo as control. Concern about the generalizability is compromised due to small number of study sites.

Introduction

As in other high-income countries, major depression is a common mental disorder in Japan [1]. Left untreated, major depression can cause substantial distress and impairment on individuals that to negatively affect their quality of life, medical morbidity, and mortality, and place an enormous burden on society [2-4]. Latest estimates from Global Burden of Disease study GBD 2010 indicate that major depression accounts for 2.5% of the global disease burden [5], and by 2030 major depression is predicted to be the leading cause of disability in high-income countries [6]. For this debilitating mental disorder, treatment guidelines recommend antidepressants for first-line treatment of moderate to severe acute major depression [7, 8], and it is the most widely used treatment modality in routine practices and remains the mainstay. However, available evidence indicates that only a third of patients fully respond to the first trial of antidepressant [9-11]. Thus, many patients with major depression are left with considerable symptomatology after the initial treatment and are referred as treatment resistant (refractory) depression (TRD).

Although many treatment studies have been published to investigate the best treatment strategies for TRD [12, 13], no standard treatment modality has yet been established [14]. When patients fail to respond to an adequate course of antidepressant treatment, the most currently available treatment guideline recommends the subsequent option of increasing the dose of the current antidepressant, switching to a different antidepressant, or augmenting with another pharmacotherapy [7]. However, one major problem of TRD is its lack of consensual operational definitions [15, 16]. Given the heterogeneity of TRD associated with complex etiologic pathways, a non-pharmacological approach such as depression-specific psychotherapy may have a role in their treatment [17].

It is well established that cognitive behavioral therapy (CBT), the most published structured form of psychotherapy developed on the basis of the Beck's cognitive theory [18], is efficacious for the treatment of depression [7, 8]. Numerous randomized controlled studies have shown that CBT is superior to wait-list, non-specific controls, or treatment as usual [19]. Further evidence shows that combining psychotherapy to pharmacotherapy is more effective than pharmacotherapy alone [20]. Based on the mounting evidence as above, CBT has been drawing considerable attention in Japan as an efficacious treatment for depression not only among clinicians and academics but also the general public. The Japanese Ministry of Health, Labour and Welfare has been encouraging training for, and practical implementation of CBT, as exemplified by the coverage of CBT for mood disorders by the Japanese national health insurance scheme since 2010 [21].

Despite these developments, few empirical studies have evaluated the effectiveness of CBT as a next-step option for patients who have failed to respond to antidepressants[22-24]. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) examined CBT and pharmacotherapy as a sequential approaches to manage patients who failed the initial 12-14 weeks of citalopram treatment by using either augmentation or switch strategies [25]. No differences in outcome at post-treatment were observed between augmenting CBT and augmenting other pharmacotherapy, and this finding was similar among the switching option. However, STAR*D trial implemented a

unique equipoise-stratified randomisation design which refused the non-preferred treatment arm; only a quarter of the STAR*D participants were randomized to CBT for their second-step treatment and this selection bias makes difficult to interpret the outcomes. Next, Kennedy and colleagues [26] compared cognitive therapy and lithium augmentation as a sequential treatment option for 44 outpatients with major depression who had a partial response during 8 to 14 weeks of antidepressant treatment in an 8-week randomized controlled trial. They found that there was no significant benefit of cognitive therapy over lithium augmentation. However, the sample size was small which may limit power to detect the differences in the changes over time, and the duration of trial was relatively short. Furthermore, the trial focused on partial responders (defined as HAMD score of 8-15) and excluded non-responders to the initial antidepressant treatment. Finally, the recent CoBalT trial [27] examined the effectiveness of CBT as a next-step option for patients whose depression did not respond to usual depression care delivered by general practitioner in the UK. In this pragmatic clinical trial with a sample size of 469, augmenting CBT to usual care increased the treatment response 3-fold at 6 months compared to those with usual care alone. However, the primary outcome of this trial was a self-reported measure (i.e. BDI-II) that might be affected by the ~~process of treatment~~treatment process. Further, it is unclear if this result could be applied to different clinical settings such as in psychiatric care or ~~in~~ to other socio-cultural contexts.

There is little evidence to guide next-step option for patients who have failed to respond to antidepressants in psychiatric care settings. We therefore planned to carry out a randomised controlled trial to examine the effectiveness of CBT as an augmentation strategy for antidepressant non-responders compared with pharmacotherapy as part of usual care for patient. The aim of this paper is to describe the study protocol of the current study.

Objectives

1. The primary objective of this study is to compare the effectiveness of CBT as an augmentation strategy to treatment as usual (that includes antidepressant treatment) versus treatment as usual alone in a 16-week randomized controlled trial with a 12-month follow-up for patients with non-psychotic major depression who were identified as suboptimal responders to usual depression care.
2. The secondary objective of the study is to evaluate the safety (incidence of treatment discontinuation and adverse events) of CBT as an augment strategy to treatment as usual for patients with non-psychotic major depression who have not adequately responded to usual depression care.

Methods and Analysis

Study design and setting

The current study is a 16-week assessor-blinded, randomised, controlled superiority trial of two parallel-groups with a 12-month follow-up at an outpatient clinic as part of usual depression care (**Figure 1**). Random allocation to treatment will be done at the individual level.

Patients will be recruited from two sites in Tokyo. One will be a university teaching hospital ~~and~~, the other ~~will be~~ a psychiatric hospital. The university teaching hospital department of psychiatry located in central Tokyo has 31 -beds (1,044 beds ~~as~~ for the entire university teaching hospital) and, offers advanced psychiatric care services for patients with complex problems, who are ~~serving~~ largely middle-class~~the~~ Japanese ~~middle class~~. On the other hand, the psychiatric hospital located in suburban Tokyo has 467 -beds and offers wide range of psychiatric care services, mainly serving secondary to tertiary psychiatric care to a diverse Japanese population ~~including~~ that also include socioeconomically disadvantaged groups. It is noteworthy that a feature of Japan's healthcare is its universal health insurance system in which all patients receive free access to specialized medical services at any institutions including university teaching hospital.

Participants

1. Inclusion criteria

Patients are eligible to be included in the study if they meet the following criteria: (1) outpatients with a diagnosis of Major Depressive Disorder, as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [28] criteria for single or recurrent without psychotic features assessed with the Structured Clinical Interview for DSM-IV (SCID) [29] administrated by trained psychiatrist; (2) age between 20 and 65 years; (3) identified as suboptimal responders to usual depression care defined as those who experience at least moderate level of depression symptoms based on at least 16 on the GRID-Hamilton Depression Rating Scale-17 item ($GRID\text{-}HAMD_{17}$) [30, 31] and evidence of at least minimal level of treatment resistance by obtaining at least 3 on the Maudsley Staging Method for treatment-resistant depression [32] despite taking antidepressant treatment at an adequate therapeutic dose (based on package insert (Available at: http://www.info.pmda.go.jp/info/iyaku_index.html)) for at least 8-weeks as part of usual depression care, and (4) must be competent and able to give informed consent.

2. Exclusion criteria

Patients will be excluded from the study if they meet the following criteria: (1) having past or current manic or psychotic episode; (2) having comorbid alcohol or substance use disorder in 6 months prior to the study entry; (3) having any DSM-IV Axis I disorders other than Major Depressive Disorder to be the primary diagnosis assessed by

the Mini-International Neuropsychiatric Interview (M.I.N.I.) [33, 34]; (4) having antisocial personality disorder; (5) having serious and imminent suicidal ideation; (6) having a serious or unstable medical illness; (7) having organic brain lesions or major cognitive deficits in a year prior to the study entry; (8) have previously completed full-session of CBT program and (9) those who were highly anticipated to fail to attend less than 8 visits during the 16-week trial phase (e.g. due to relocation).

Procedures

1. Recruitment

Treating psychiatrist will, during their usual consultation, –provide brief information about the study using a brochure and invite patient to take part in the study ~~during their usual consultation~~. If the patient shows interest in the study and provides contact details to the research team, a face-to-face appointment with a study psychiatrist will be set. The details of the study and potential benefits ~~and~~as well as risks will be explained thoroughly to the patient~~s~~ by the study psychiatrist and discussed. If the patient agrees to study participation, a written informed consent will be obtained. After obtaining the informed consent, the patient~~s~~ will be assessed by the study psychiatrist for eligibility. A diagnosis of Major Depressive Disorder will be evaluated with the SCID [29] ~~and~~ , while other Axis I disorders will be evaluated with M.I.N.I [33, 34]. Of note, Axis II disorders will be evaluated with the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II) [35] at week 8 (i.e. a considerable time frame for depressive symptoms to have abated). Diagnostic interviewers will be the study psychiatrists (AN and MS) who have received extensive training in the administration of semi-structured interviews.

2. Baseline assessment

Acute psychopathology will be assessed at study entry by the study psychiatrists or psychologists. Objective depressive symptoms will be assessed by the 17-item and 21-item GRID-HAMD. Patients' subjective perception of depression severity will be assessed by the self-reported Beck Depression Inventory-Second Edition (BDI-II)[36, 37] and 16-item Quick Inventory of Depressive Symptomatology Self-Reported ($QIDS\text{-}SR_{16}$)[38, 39]. Health related quality of life will be measured by the European Quality of Life Questionnaire–5 Dimensions (EQ-5D)[40, 41] and 36-Item Short-Form Health Survey (SF-36)[42]. Work performance and productivity will be measured by the World Health Organization Health and Work Performance Questionnaire (HPQ)[43, 44]. Life stressors will be measured using the St. Paul-Ramsey Questionnaire (available from the authors), which rates the severity of individual stressors from 1 (none) to 7 (catastrophic) in six categories ranging from marital to occupational and gives a final global measure of the stressors.

Demographic and other clinical data will be also collected as a part of the baseline assessment, such as marital status, number of children, residential status, level of education, duration of current and lifetime episode of

depression, number of lifetime depression episodes, history of depression treatment including past pharmacotherapy and hospitalized treatment, past suicide attempt, history of medical complication, and family psychiatric history. Level of treatment resistance will be evaluated operationally with the Maudsley Staging Method for Treatment Resistant Depression[45]. A history of childhood abuse and traumatic brain injury will be rated as present or absent. Current cigarette and alcohol use will be assessed by the subject's report. Assessments will also be conducted at 8 and 16 weeks after the randomisation.

3. Randomisation

All eligible patients who give consent for participation will be randomized to treatment as usual or to CBT plus treatment as usual at the end of baseline assessment (1:1 allocation ratio). Randomisation will be conducted using central computerized registration system that automatically randomizes patients and generates a message notifying their assigned treatment. Allocation is concealed through the use of central computerized registration system designed for this study by the Project Management Office at the Keio Center for Clinical Research. Allocation will be stratified by site (n=2) with minimisation method to balance the age of the participants at study entry (older versus younger) and baseline GRID-HAMD$_{17}$ score (severer versus non-severer). The cut-off age and GRID-HAMD$_{17}$ score for minimisation will not be disclosed until the study termination to ensure concealment.

4. Intervention phase (16 week)

4-1. CBT

Therapists will follow the individual CBT treatment manual for depression developed by the authors (YO, DF, AN, KT and MS) (Available at the Japanese Ministry of Health, Labor and Welfare website: http://www.mhlw.go.jp/bunya/shougaihoken/kokoro/dl/01.pdf). This manual is developed based on Beck's treatment manual [46], with some adaptation to address the cultural characteristics of the Japanese patients such as more emphasis on interpersonal relationships and consideration of family as an essential part of the treatment [47]. The overview of the program is shown in **Table 1**. Problem-solving techniques and specific approaches to address interpersonal issues and cognitive behavioral avoidance are emphasized. Therapists are encouraged to refer to the relevant approaches whenever necessary. Furthermore, the therapists are encouraged to give feedbacks to the patients about the case conceptualization and collaboratively set the treatment goal during the earlier phase of the program. The pPatients allocated to CBT will typically receive a course of 16 weekly sessions, with up to 4 additional sessions if deemed clinically appropriate by the study therapist (maximum of 20, and minimum of 8 sessions). Sessions will last approximately 50 minutes. Therapy will take place in an outpatient consultation room at each site. During CBT treatment, other depression-specific empirical psychotherapy (i.e. interpersonal therapy (IPT)) and electroconvulsive therapy are prohibited.

4-2. Training and supervision of therapists

Six therapists will deliver CBT at the two sites. The study therapists have been trained as psychiatrists (n=4), a master's-degree clinical psychologist (n=1), and a psychiatric nurse (n=1). Of the six therapists, two are female (n=2, 33.3%). On average, the study therapists had 4.0 (SD 2.1) years of experience as CBT therapists and have completed 12.5 (SD 7.3) cases at the time of participation. All therapists have received CBT training at the Keio University Cognitive Behavioral Therapy Training and Research Program and will continuously receive supervision throughout the study.

To ensure treatment fidelity, all therapists completed a two-day workshop and will participate in two-hour bi-weekly group supervision with other therapists during the study. At the group supervision, therapists will present the case formulation and treatment plan. The group supervision will be led by one of the authors (YO), the founder and the president of the Japanese Association for Cognitive Therapy and a fellow of Academy of Cognitive Therapy, who will facilitate discussion of therapeutic difficulties and impasses and provide skills acquisition, and peer support. To assess CBT competences, a random sample of audiotaped sessions will be rated using the Cognitive Therapy Rating Scale (CTRS)[46, 48]. A score of 40 or greater is defined as an adequate level of technical competency in the CBT sessions.

4-3. Treatment as usual (Usual depression care by psychiatrists)

Although appropriate flexibility will be allowed for scheduling sessions, the patients will typically receive a bi-weekly, 5-30 minutes consultation by the treating psychiatrist during the treatment phase with a minimum of 8 sessions. ~~Typical~~ A typical session will comprise of symptom assessment and standard clinical management such as brief psychoeducation and pharmacotherapy when appropriate. Although there will be no restriction on pharmacotherapy, it should basically be concordant with major practice guidelines for major depression such as the American Psychiatric Association practice guideline[8]. Prescribed medicine and dose will be recorded and medication adherence will also be assessed at each visit using the self-reported Treatment and Medication Compliance Data Scale (TMCDS) (available from the authors upon request). Patients can enter the study receiving any medication(s) for concurrent general medical conditions. No depression-specific empirical psychotherapies (CBT or IPT) or electroconvulsive therapy are permitted during the intervention phase and will result in withdrawal from the study. Treatment will be delivered by seven treating psychiatrists who have practiced for a mean of 7.3 (SD 4.4) years and are working at the two sites. .

5. Follow-up phase

There will be no restrictions on treatment options for the patients who receive depression care by the treating

psychiatrists during this phase. Thus~~,~~ , the treating psychiatrists are allowed to refer the patients ~~for psychotherapies~~ to appropriate mental health professionals for psychotherapies and electroconvulsive therapy if deemed clinically appropriate. However, those who receive depression-specific empirical psychotherapies (CBT and IPT) and electroconvulsive therapy will be documented and considered as a deviation from the study protocol. The patient, however, will not be considered to have dropped out of the study at this phase and will receive protocol assessments. Although CBT literacy has deepened among Japanese mental health professionals after the approval of CBT as treatment for mood disorder by Japan's national health insurance scheme in 2010, the number of mental health facilities capable of providing CBT is still very limited. Therefore, it is unlikely for patients to receive CBT that may substantially influence the primary outcome. The current situation for IPT in Japan is similar.

6. Discontinuations

6-1. Discontinuation of intervention phase

If the patients meet any one of the following criteria, the treating psychiatrist will discontinue the study intervention. The patient will not be considered to have dropped out of the study and will be invited to enter the follow-up phase and receive periodical assessments through the remainder of the study period.

1. The p~~P~~atient withdraws the consent to receive study intervention.
2. The treating psychiatrist judges that it is inappropriate to continue the study intervention ~~such as~~ due to e.g., emergence of severe psychotic or manic episode, serious and imminent suicidal ideation, and severe medical conditions.
3. The treating psychiatrist judges that it is difficult to continue the study intervention because of emergence of adverse events or other appropriate reason that outweighs the benefit of receiving study intervention.
4. The treating psychiatrist judges that it is more appropriate to receive inpatient psychiatric care.

6-2. Discontinuation of periodical assessments

If the patient withdraws the consent to receive periodical study assessments, it will be considered as dropout and the patient will not be contacted for periodical assessments in the future.

Outcome measures

The outcome measures are shown in **Table 2.**

1. Primary outcome

The primary outcome is the change in clinician-rated 17-item GRID-HAMD score at 16-weeks, which accord with the end of the intervention. The GRID-HAMD will be also administered at week 8 (midpoint of intervention). Follow-up assessments will be administered at 3-month (7-months post-randomisation), 6-month (10-months

post-randomisation), and 12-month follow-up visits (16-months post-randomisation). All the assessors (psychiatrists and licensed clinical psychologists) have received extensive GRID-HAMD training and achieved excellent inter-rater reliability (ICC=0.98). The GRID-HAMD will be conducted by an assessor blind to treatment randomisation. Due to the nature of the intervention, neither the patients, nor the treating psychiatrists, nor the study therapists can be completely blinded to randomisation, but are strongly instructed not to disclose the randomisation status of the patient at periodical assessments. Further, the assessors will not be present during the treatment administration.

2. Secondary outcomes

2-1. Clinical outcomes

- Severity and change in scores of subjective depression symptoms as measured by the BDI-II and QIDS-SR_{16}
- Proportion of responders, defined as 50% or greater reduction on 17-item and 21-item GRID-HAMD, BDI-II and QIDS-SR_{16} relative to baseline.
- Proportion of patients who achieve remission, defined as a 17-item GRID-HAMD score <=7[49], BDI-II score <=13[50] and QIDS-SR_{16}<=5[38].

2-2. Safety outcomes

- Proportion of patients who discontinue from the study will be recorded. The reasons for discontinuation will be asked of the patient at site or by telephone and will be ascertained by the treating psychiatrist.
- Spontaneously reported Adverse Event (AEs) and Serious Adverse Events (SAEs).

2-3. Health outcomes

- Level and change in the degree of health-related quality of life as measured by the EQ-5D and SF-36.

2-4. Work performance outcomes

- Self-reported sick leave hours (absenteeism), degree of job performance reduction (presenteeism), and the actual hours worked in the past 4 weeks as measured by the HPQ.

2-5. Economic evaluation

- Degree of quality of life (EQ-5D) and depression severity (GRID-HAMD, BDI-II and QIDS-SR16) will be used for estimating Quality Adjusted Life Years (QALYs) for cost-utility analyses.

3. Instruments

GRID- Hamilton Depression Rating Scale

The Hamilton Depression Rating Scale (HAMD) has been the gold standard assessment for the observer rated depression symptomatology for more than 50 years. The GRID-HAMD was developed to set standards for scoring and administering the original HAMD. The seven--day period prior to assessment is the usual time frame for assessing symptom severity. The GRID-HAMD has three components: the GRID scoring system based upon

assessment of symptom intensity and symptom frequency, the manual of scoring conventions, and a semi-structured interview guide based on the SIGH-D[51]. Inter-rater reliability of the Japanese version of the GRID-HAMD total score is excellent[30].

Beck Depression Inventory-Second Edition (BDI-II)

The BDI-II has been one of the most widely used self-report instruments to assess the severity of depressive symptoms which was developed by Beck and colleagues and its first version was published in 1961[52]. The BDI-II is a 21-item questionnaire and each item is answered by circling a number between 0 and 3, with larger numbers indicating greater severity. The time frame for assessing symptom severity for BDI-II should be in the past two weeks to better coincide with DSM criteria. Good reliability and validity has been reported for the original [36] as well as the Japanese version [50].

16-item Quick Inventory of Depressive Symptomatology Self-Reported (QIDS-SR_{16})

The QIDS-SR_{16} is an abbreviated self-report version of the clinician-rated 30-item Inventory of Depressive Symptomatology (IDS), designed to assess the severity of depressive symptoms, which was developed by John Rush and colleagues. The QIDS-SR_{16} assesses all the criterion symptom domains to diagnose a DSM Major Depressive Episode. The seven day period prior to assessment is the usual time frame for assessing symptom severity. Internal consistency is high with a Chronbach's alpha ranged from 0.81 to 0.94 and validity is high with a high correlation with HAMD [38] as well as the Japanese version[39] .

36-Item Short-Form Health Survey (SF-36)

The SF-36 is a multi-purpose health survey with 36 items. It yields the 8 health domains of functional health (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and metal health),level of well-being, physical and mental health summary measures, and a health utility index. Good validity has been reported for the original [53] as well as the Japanese version[42].

World Health Organization Health and Work Performance Questionnaire (HPQ)

The HPQ is the most widely used self-report instrument designed to estimate the workplace costs of health problems in terms of reduced job performance, sickness absence, and work-related accidents and injuries. It assesses work hours, sick-leaves, occupational accidents, and self-rated productivity in past seven days and past four weeks. The validity of the HPQ absenteeism and presenteeism measures has been confirmed [54].

European Quality of Life Questionnaire–5 Dimensions (EQ-5D)

The EQ-5D is a generic, multidimensional, health-related, quality-of-life instrument that contains two parts: a health status profile and a VAS to rate global health-related quality of life [40]. Health status profile yields the 5 health domains (mobility, self-care, usual activities, pain/discomfort, and mood) and the outcome rating of the 5 domains will be mapped to a single index value through an algorithm. The index value ranges between 0 and 1 with the higher score indicating a better health state perceived by the patient. The index value is used for calculating QALYs. The EQ-5D is the measure of health-related quality of life in adults preferred by the National Institute for Health and Clinical Excellence.[7]

Sample size estimation

The sample size is calculated based on the primary outcome of depression symptoms as measured by the 17-item GRID-HAMD score at 16 weeks after the randomisation. Our previous single group study on CBT with treatment as usual for acute major depression have shown that the 17-item GRID-HAMD will drop from 24.3 (SD 7.4) to 10.0 (SD 5.0) at week 16 [47]. We expect a mean difference of 40% (4 point) in the 17-item GRID-HAMD total scores between the groups at endpoint and consider this to be a clinically meaningful difference. With a two-sided significance level of 5% and statistical power at 90% and allowing for 15% drop-out, the sample size was calculated to be 40 per arm, i.e., 80 in total.

Statistical analyses

The primary analysis population in this study will be the intention-to-treat (ITT), defined as all randomised patients. For the primary outcome, the least squares means and their 95% confidence intervals will be estimated using analysis of covariance (with treatment group as a factor and baseline scores as a covariate) to compare the two group, with a last-observation-carried-forward approach for missing values. To examine the robustness of the last-observation-carried-forward approach, a mixed-effects model for repeated-measures (MMRM) that contains treatment group, week, and group-by-week interaction as factors with compound symmetry covariance matrix among time points, and Kenward-Roger degrees of freedom adjustment will be performed with all the primary outcomes and also for continuous secondary outcomes. Categorical outcomes will be analyzed using chi-square test or Fisher's exact test. Summary statistics (means and standard deviation) of patients' characteristics will be calculated. When appropriate, t-test and Mann-Whitney U test will be used to compare baseline continuous outcomes (means). Time to all cause discontinuation will be summarized using Kaplan-Meier estimates and compared with log-rank test. The significance level will be set at 0.05 (2-tailed). Statistical analyses will be performed with SAS version 9.3.

Data collection and management

To ensure accurate, complete, and reliable data, the following countermeasures will be conducted: 1) provide standardized operational procedure material to the study sites regarding data collection, data encoding, and storing, 2) hold a training session to give instruction on the protocol, the completion of the EDCs, and study procedures for study psychiatrists, study therapist, and study coordinators, 3) hold a periodic meeting among the study site personnel to share issues related to conducting the study and to elaborate, 4) the principal and co-principal investigator will be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax, 5) a data manager will review and evaluate EDC data, use standard computer edits to detect errors during data collection, and conduct a quality review of the database.

To ensure the safety of the participants in the study and to ensure accurate, complete, and reliable data, the study psychiatrist will keep records of paper instruments and clinical records in the patient files as source documents for the study at the site. The principal investigator (YO), the co-principal investigator (AN), the study statistician (TA) and other steering committee members (MS, DF, TK) will be given access to the cleaned data sets.

1. Electronic data capture system

An electronic data capture system will be used in this study. The site maintains the original source for the data entered by the site into the electronic data capture system. The eCRF data collected by the study psychiatrists, therapist, or the clinical research coordinators will be encoded and stored electronically in the database system. Data will be managed by data manager at the Keio Center for Clinical Research and will be stored electronically in the database system.

2. Study monitoring

Data manager at the Keio Center for Clinical Research will conduct periodic inspection of the accumulating outcome data throughout the course of the study. The Data Safety Monitoring Committee (DSMC) may request additional evaluation or follow-up of patients who have clinically significant events.

3. Interim analyses

Interim analyses are planned for safety and futility when 50% of patients (n=40) have been randomized and have completed the 16 week post-randomisation assessment. The interim analysis will be performed by a ~~the~~ member of DSMC who is blind to the allocated treatment. Incidence of serious adverse events in the sample and the 17-item GRID-HAMD score at post-treatment (16 week) will be compared between groups to consider whether the intervention is futile (i.e. a 15% or less mean difference between the groups). The results of the interim analyses will be discussed with the principal investigator, who will decide to continue, stop, or modify the trial.

4. Premature termination rule of the entire study

Study will be aborted if the principal investigator, upon advice from the DSMC, judges it necessary for medical safety reason such as when causal relationship between study intervention and serious adverse events is established or serious ethical violation occurs that is out of line with the Ethics Guideline for Clinical Research (Ministry of Health, Labour and Welfare, revised 2008).

Reporting of adverse events

All adverse events reported spontaneously by the patients or observed by the treating psychiatrists will be recorded. When an adverse event occurs, the treating psychiatrist will take all the necessary and appropriate measures to ensure safety of the patient.

When a serious adverse event (SAE) occurs, the treating psychiatrist must take all the necessary and appropriate measures to ensure safety of the study patient and provide appropriate treatments including hospital admission. Based on the Ethics Guideline for Clinical Research (Ministry of Health, Labour and Welfare, revised in 2008) a SAE is defined as "an adverse event that may lead to death or to enduring severe impairment depending on the patient's conditions and circumstances" and will include 1) death (all deaths regardless of causal relationship with the intervention or whose causal relationship with the intervention cannot be denied during the intervention phase or up to 30 days after the completion of intervention), 2) life-threatening event, 3) event leading to enduring and severe impairment and dysfunction and 4) hospitalization (all hospitalization regardless of causal relationship with the intervention or whose causal relationship with the intervention cannot be denied during the intervention phase or up to 30 days after the completion of intervention).The treating psychiatrist must notify the SAE to the principal investigator (YO) immediately, and the principal investigator must also notify all the collaborating investigators. The head investigator of the study site must report to its own ethical review committee and, if it concerns an unforeseeable SAE, must report to the Japanese Ministry of Health, Labour and Welfare.

Ethical Considerations and Dissemination

Ethical approval of the study protocol was obtained ~~by~~ from the Ethical Review Committee of Keio University School of Medicine (reference no. 20070070, 19-70-4) and the Ethical Review Committee of Sakuragaoka Memorial Hospital. The trial is registered under UMIN Clinical Trials Registry: UMIN000001218.

Informed Consent

The study psychiatrist is responsible for ensuring that the patient understands the potential risks and benefits of

participating in the study, including answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the study.

~~The~~ An Informed Consent Form will be used to explain the potential risks and benefits of study participation to the patient in simple terms before the patient is entered into the study and to document that the patient is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study. The study psychiatrist is responsible for ensuring that informed consent is given to each patient. This includes obtaining the appropriate signatures and dates on the Informed Consent Form prior to the administration of protocol intervention.

Ethical Review

The principal investigator (YO) and the co-principal investigator (AN) must agree with the protocol and Informed Consent Form before they are submitted to the ethical review committee and are used at sites. All protocol and Informed Consent Form must be compliant with the Ethics Guideline for Clinical Research (Ministry of Health, Labour and Welfare, revised in 2008). The ethical review committee will review the protocol as required. When an amendment of protocol is needed for legitimate reason, such as safety concerns, the protocol will be revised and after the agreement of the principal investigator and the co-principal investigator, it will be submitted to the ethical review committee for review.

Compensation and insurance for harmed patients

We cannot completely negate there is a possibility of developing unforeseen serious complications or other health damage during or after completion of participation in this study. In that case, appropriate responses will be taken, the same as with treatment for health damage in usual medical care. Basically, the medical expenses shall be borne by the patient, since the treatment will be provided as health-care services provided under national health insurance, the same as usual treatment. There will be no special financial compensation, however, if there is any negligence on the part of the physician, it may be covered with the doctors' liability insurance.

Conflict of interest

The objectivity of research and commitment to academic integrity is of paramount importance and the basis for obtaining and maintaining public trust, all investigators will comply with the site's policy on Conflict of Interest in research and relevant COI guidelines.

Dissemination

The results of the study will be disseminated at several research conferences and as published articles in peer-reviewed journals. The study will be implemented and reported in line with the CONSORT statement.

Discussion

The ECAM study aims to provide new evidence for administering CBT for major depression as a next-step option for the patients who have failed to respond to pharmacotherapy in psychiatric care settings. The design of the study is expected to detect a meaningful difference in clinical effectiveness outcomes. The ECAM study is distinguished from the previous studies in that the study design standardizes psychiatric interview to assess depression symptomatology by blind-raters, recruits patients from secondary to tertiary psychiatric care that tend to be more severe and more difficult-to-treat, and evaluates the long-term effects of CBT for up to 12 months.

Challenges and limitation of this study is that we cannot examine the efficacy of CBT itself because we did not choose attention-placebo, such as relaxation, as control. Our aim is to conduct a study to examine the effectiveness of augmenting CBT to usual clinical care rather than examine the efficacy of CBT itself. We are also aware that the participating sites of this study are, clinically speaking, experienced in the treatment of depressed patients. Thus, concern about the generalizability of the results ~~is~~ can be compromised. Nevertheless, this is the first randomized controlled study to assess the effectiveness of CBT for treatment resistant depression in Japan. The results of the current study will hopefully improve the evidence-based knowledge of the patients who suffer ~~with~~ residual symptoms of depression despite adequate pharmacotherapy.

Current study status

The ECAM study began recruiting patients in September, 2008 and closed recruitment at August 2013. Data collection will be completed in December, 2014.

Author's contribution

AN and MS conceived and designed the study. AN drafted the protocol manuscript, organized and supervised study implementation. DF and TK refined the study protocol and study implementation. TA and YS provided methodological and statistical expertise. TA and AN conducted the statistical analyses. YO provided CBT expertise and supervision to the therapists. YO drafted the grant and was responsible for the entire study implementation. AN was responsible for study management, staff training, and supervision. DM managed day-to-day study responsibilities, including monitoring recruitment, collecting data, and liaising with recruitment sites. SI and MM are the directors of the site and provided clinical expertise and on-site management of the study. All authors critically reviewed and approved the final version of the manuscript.

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Competing interests

AN, MS, DF, TK, and YO developed and have written the Japanese CBT manual for depression, are involved in National CBT Training and Supervision Project funded by the Japanese Ministry of Health Labour and Welfare. YO is the president of the Japanese Association for Cognitive Therapy. None other authors have any conflicts to declare.

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Table 1. Framework of the 16 weekly CBT program for depression

Session number	Session goals	Suggested structure	Suggested Tools/homework
1, 2	· Establish rapport · Gather information about patient's problem and develop a problem list · Psychoeducation about depression and the process of CBT	· Review on symptoms, course of illness and developmental history · Identify patient's main problem · Educate the patient about depression and CBT · Provide summary and elicit feedback	· Provide education sheets · "What is depression?" · "What is CBT?"
3, 4	· Case conceptualization · Set goals for treatment · Activate the patient	· Collaboratively set the agenda and review homework · Collaboratively set treatment goals · Activity scheduling · Provide brief summary on case conceptualization · Assign homework; Elicit feedback and check for understanding	· Problem list · Activity record
5, 6	· Identify mood and automatic thoughts	· Collaboratively set the agenda and review homework · Dysfunctional thought record (triple column) · Assign homework · Elicit feedback and check for understanding	· Provide education sheets · "How to identify your moods and thoughts
7-12	· Test automatic thoughts · (Optional – dissolve interpersonal conflicts/problem solving) · Solidify patient's ability to use cognitive techniques to change automatic thoughts	· Collaboratively set the agenda and review homework · Dysfunctional thought record (seven columns) · (Optional structure- assertive training/problem solving) · Assign homework; Elicit feedback and check for understanding	· Provide education sheets "How to balance your thoughts" · Interpersonal module · Problem-solving module
13, 14	· Identify schemas · Reinforce use of cognitive and behavioral change techniques	· Collaboratively set the agenda and review homework · Dysfunctional thought record · Discussion on schemas · Assign homework; Elicit feedback and check for understanding	· Provide education sheets "Rules of your mind"
15, 16	· Termination · Relapse prevention	· Collaboratively set the agenda and review homework · Review of the overall therapy · Identify the triggers for relapse and target specific schemas, utilize relapse prevention strategies · Preparation for booster sessions · Provide final summary and elicit feedback	· Provide education sheets "Upon ending your therapy"

Table 2. Schedule of the assessments

	Enrolment	Baseline/ Randomisation	*Intervention*		*Follow-up*		
TIMEPOINT	*-1*	0	*8wk*	*16wk*	*Post3 M*	*Post6 M*	*Post12M*
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Allocation		X					
INTERVENTIONS:							
CBT plus treatment as usual			⟷	⟷			
Treatment as usual			⟷	⟷			
ASSESSMENTS:							
Demographics questionnaire	X						
SCID-I	X						
M.I.N.I.	X						
SCID-II			X				
GRID-HAMD		X	X	X	X	X	X
BDI-II		X	X	X	X	X	X
QIDS-SR16*		X	X	X	X	X	X
EQ-5D		X	X	X	X	X	X
SF-36		X	X	X	X	X	X
HPQ		X	X	X	X	X	X

Abbreviations: SCID-I, Structured Clinical Interview for DSM-IV Axis I Disorders; M.I.N.I, Mini-International Neuropsychiatric Interview, SCID-II, Structured Clinical Interview for DSM-IV Axis II Disorders, GRID-HAMD, GRID-Hamilton Depression Rating Scale; BDI-II, Beck Depression Inventory-Second Edition; QIDS-SR16, 16-item Quick Inventory of Depressive Symptomatology Self-Reported; EQ-5D, European Quality of Life Questionnaire–5 Dimensions; SF-36, 36-Item Short-Form Health Survey; HPQ, World Health Organization Health and Work Performance Questionnaire

*QIDS is also assessed at each visit during the intervention phase.

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Figure 1. Diagram of the ECAM study

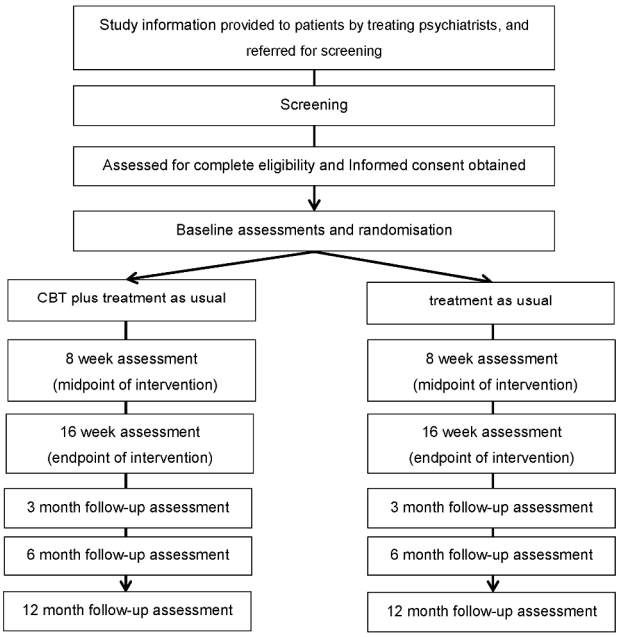

Diagram of the ECAM study
210x297mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	18
	5b	Name and contact information for the trial sponsor	18
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4,5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5,6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8,9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8,9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10, 11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	21

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10, 11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13, 14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	16

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___15_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	___13, 14_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___18_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	___14_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	___16_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	___16_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.