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STUDY PROTOCOL MANUSCRIPT

Strategic Use of New generation antidepressants for Depression: SUN(^_^)D Study Protocol

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ABSTRACT

Background

After more than half a century of modern psychopharmacology, with billions of dollars spent on antidepressants annually world-wide, we lack good evidence to guide our everyday decisions in conducting antidepressant treatment of patients with major depression. First we did not know which antidepressant to use as first line treatment. Second we do not know which dosage we should be aiming at with that antidepressant. Because more than half of the patients with major depression starting treatment do not remit after adequate trial with the first agent, they will need a second line treatment. Dose escalation, augmentation and switching are the three often recommended second line strategies but we do not know which is better than the others. Moreover, we do not know when to start considering this second line treatment.

The recently published multiple-treatments meta-analysis of 12 new generation antidepressants has provided some partial answers to the first question. Starting with these findings, this proposed trial aims to establish the optimum 1st line and 2nd line antidepressant treatment strategy among adult patients with a non-psychotic unipolar major depressive episode.

Methods/Design

SUN(^_^)D, the Strategic Use of New generation antidepressants for Depression, is an assessor-blinded, parallel-group, multi-centre randomised controlled trial. Step I is a cluster-randomised trial comparing titration up to the minimum vs maximum of the recommended dose range among patients starting with sertraline. The primary outcome is the change in the Patient Health Questionnaire (PHQ)-9 scores administered by a blinded rater via telephone at week 1 through 3. Step II is an individually randomised trial comparing staying on sertraline, augmentation of sertraline with mirtazapine, and switching to mirtazapine among patients who have not remitted on the first line treatment by week 3. The primary outcome is the change in the PHQ-9 scores at week 4 through 9. Step III represents a continuation phase to Steps I and II and aims to establish longer-term effectiveness and acceptability of the above-examined treatment strategies up to week 25. The trial is supported by the Grant-in-Aid by the Ministry of Health, Labour and Welfare, Japan.

Discussion

When finished, SUN(^_^)D will provide much- and long-awaited guidance to clinicians and their patients as to (i) what dosage they should be aiming at when starting treatment with sertraline, (ii) when and what to do if the first line treatment is not fully successful in bringing about remission, both from the viewpoints of effectiveness and acceptability.

Trial registration

ClinicalTrials.gov identifier: NCT01109693

BACKGROUND

Depression is costly

Major depression is the 1st leading cause of disability adjusted life years (DALY) lost excluding death, and the 3rd leading cause of DALY including death in the world according to the most recent WHO estimates [1]. Moreover, this burden is expected to rise in the next 20 years. According to the same estimates, major depression is currently the 1st leading cause of DALY excluding death and the 2nd leading cause of DALY including death after cerebrovascular disease in Japan, comprising approximately 6% of all DALY lost among its people.

Major depression is indeed one of the most prevalent mental disorders in the United States and Europe, with 16.2% and 6.6% lifetime prevalence for American women and men [2] and with 16.5% and 8.9% for European women and men [3]. In Japan, while the point estimates are lower than in US or Europe, it is still the most prevalent mental disorder for its people, affecting one in 12 women (8.5%) and one in 29 men (3.5%) at least once in their lifetime [4].

Both pharmacotherapy and psychotherapy have been found to be equally effective in treating major depression [5] but the former remains the mainstay in everyday clinical practices due to its greater availability, tighter quality control and cheaper costs. Effective antidepressive agents include heterocyclic antidepressants (HCA), monoamine oxidase inhibitors (MAOI), selective serotonin reuptake inhibitors (SSRI), serotonin and noradrenaline reuptake inhibitors (SNRI), noradrenalinergic and specific serotonergic antidepressant (NaSSA) and others (such as bupropion). The dramatic rise in the consumption of antidepressants in developed countries in the past two decades has been mainly due to increase in use of SSRI, SNRI and other new generation antidepressants, which now are the most commonly prescribed antidepressants in the world [6]. In Japan the market for antidepressants had been hovering around 15 billion yen (166 million US dollars) per year up to 1999 but has been expanding by some 20% annually, reaching 120 billion yen (1.3 billion US dollars) in 2009, in which new generation antidepressants holds 89% share.

Evidence on 1st line choice of antidepressants

There is no question that we need a specific, detailed and appropriate guidelines in the treatment of major depression. However, all the guidelines up to 2008, including the one by the American Psychiatric Association [7], the one by the Canadian Psychiatric Association [8], the one by the National Institute of Clinical Excellence in the United Kingdom [9] and the Japanese one [10], recommend that the choice of antidepressants be made "on the basis of adverse effect profiles, cost, and patient preferences" [11] because there are differences in side effect profiles but not in effectiveness among various antidepressants [12].

However, in 2009, the research group from Japan, Italy and UK published the results of a systematic review of 117 RCTs (25928 subjects) of 12 new generation antidepressants in the acute phase treatment of major depression [13]. The Meta-analyses of New Generation Antidepressants (MANGA) study is based on the most comprehensive dataset of RCTs involving new generation antidepressants from the Cochrane Collaboration Depression, Anxiety and Neurosis Group and makes use of a new meta-analytic method called multiple-treatments meta-analysis (MTM; also sometimes referred to as network meta-analysis), which integrates data from direct (when treatments are compared within a randomised trial) and indirect comparisons (when treatments are compared between trials by combining results on how effective they are compared with a common comparator treatment). MTM thus allows a more precise estimate of comparative effectiveness with narrower confidence intervals than the traditional meta-analyses because it makes use of all direct and indirect comparisons. MTM also minimizes the influence of publication bias because a possible publication bias favoring a particular antidepressant can be counterbalanced by other similar biases favoring other antidepressants when all direct and indirect comparisons are combined through MTM.

The MANGA Study observed many statistically significant and clinical meaningful differences among the 12 new generation antidepressants. In terms of efficacy, mirtazapine, escitalopram, venlafaxine and sertraline were among the top four drugs; in terms of acceptability, escitaloporam, sertraline, bupropion and citalopram were superior to the others. The authors concluded that sertraline might be

the best choice when starting treatment for moderate to severe major depression in adults because it has the most favorable balance between benefits, acceptability, and acquisition cost.

Evidence on 2nd line choice of antidepressants

Treatment of major depression is not easy because only some 50% respond, i.e. achieve depression severity less than half that at baseline, or only some 30% achieve remission, i.e. return to an euthymic state, after treatment with an adequate dose of antidepressant given for an adequate duration [14]. When patients show no to only partial response to the 1st line treatment, 2nd line treatments must be initiated. Guidelines recommendations for the 2nd line treatment include dose escalation, switching to a different antidepressant possibly from a different class and augmentation [9, 15]. Unfortunately, however, when many RCTs are planned and executed with the purpose of drug approval by the regulatory agency and as part of initial marketing strategy, evidence on the 2nd line treatment is much scanter than that on the 1st line.

First, with regard to dose escalation strategy, three systematic reviews have been published and all concluded that there is no evidence to suggest that dose escalation increases efficacy in comparison with continuing on the same dosage after failure to respond to the 1st line antidepressant [16-18]. Next, with regard to switching, we find two systematic reviews in the literature [19, 20] both of which was able to identify only one RCT that directly compared continuing on the same drug and switching to another. In this trial, 104 patients not responding to 6 weeks of fluoxetine 20 mg/d were randomly assigned to further 6 weeks of fluoxetine and switching to mianserin 60 mg/d; the remission rate was 18% and 36%, respectively (p=0.10) [21]. When different switching options are compared, switching to venlafaxine after failure to respond on an SSRI may be marginally better than switching to another SSRI but there was no strong evidence to recommend other classes of antidepressants [20]. Lastly, many RCTs and systematic reviews have been published on various augmentation strategies. The ones with most randomized evidence include lithium augmentation [22], thyroid hormone augmentation [23] and augmentation with atypical antipsychotics [24]. Other options include augmentation with mirtazapine/mianserin [21, 25, 26] and augmentation with pindolol [27].

Even less evidence can be found comparing these different 2nd line strategies against each other than comparing each strategy with staying on the former treatment. For example, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D), which was funded by the NIMH and cost approximately 3 million dollars, examined five switching strategies and four augmentation strategies among the patients who had not achieved remission to the 1st line SSRI treatment but was unable to compare switching versus augmentation as few patients agreed to this randomization [28, 29].

How to establish the optimum treatment strategy with new generation antidepressants

Review of the literature has revealed that there are indeed many urgent and critical clinical questions that must be answered before clinicians can confidently and competently administer pharmacotherapy for major depression. Urgent because every practitioner encounters these clinical questions almost on a daily basis. Critical because answers to these clinical questions can materially affect the patients' lives. Bandolier (http://www.bandolier.com), an independent evidence review journal in UK, concluded its review on the MANGA Study by saying, "What the meta-analysis provides is the raw material for the next step, namely creating and testing a care pathway or pathways for depression that provides good results for the largest number of sufferers in the shortest time and at the lowest cost." (http://www.medicine.ox.ac.uk/bandolier/booth/mental/cipriani.html). This proposed study precisely aims to create and test this optimum care pathway for depression.

1st line treatment

According to the results of the MANGA Study, it is wise to use sertraline as 1st line treatment of major depression in Japan because it represents the best balance in effectiveness and acceptability. However, practitioners immediately face an important clinical decision question at this stage, namely the problem of initial dosing strategy. The standard dosage range for sertraline is 50-100 mg/d but should clinicians aim at achieving 50 mg/d or 100 mg/d in the initial dosing strategy? Papakostas et al [30] published a systematic review of fixed-dose trials comparing different starting doses of SSRIs. In comparison with

starting with the minimum of the standard dose range, starting with the maximum of the standard range may be more effective (RR=1.12, 95%CI: 0.99 to 1.27) but less acceptable (0.74, 0.54 to 1.00). The response rate may increase from 51% to 54%, at the expense of the dropout rate also rising from 10% to 17%. It must be noted that they compared different starting doses, i.e. they administered the minimum or maximum of the standard dose range from the very beginning, and the dropouts are accounted for by last-observation-carried forward which is bound to affect and bias the results in an unknown way.
Can the initial dosing strategy to gradually increase the dosage up to the maximum of the standard range, recommended by many guidelines [8, 10, 31], be more effective and at least not any more unacceptable than the strategy to aim at the minimum of the standard range? No one knows the answer. It is truly unacceptable that a clinical question as urgent as this, because every single patient with major depression starting treatment with antidepressant faces this decision point, is not yet answered. We therefore planned an RCT to answer this question.

2nd line treatment

Even if we optimize the 1st line antidepressant treatment strategy, more than half the patients cannot achieve remission [32]. What should we do as the 2nd line treatment, and when should we make this decision?
No systematic review has found evidence for dose escalation and the present study will therefore not examine this option. There are many RCTs examining various augmentation strategies but only mirtazapine or mianserin augmentation is allowable according to the current Japanese regulations. As reviewed, we do not yet know which of augmentation or switching is superior in terms effectiveness and acceptability. Furthermore, we do not yet know when we should make this clinical decision to consider the 2nd line treatment. Since each clinical research can answer only a limited number of well formulated clinical questions, this study will focus on switching to mirtazapine, which was the most effective antidepressant according to the MANGA study, and compare it to mirtazapine augmentation of SSRI, for which a number of RCTs provide some support.
Switching to mirtazapine is a plausible option as the 2nd line treatment for the following reasons. (i) MANGA study showed mirtazapine may be the most effective new generation antidepressant. Due to its less favorable acceptability profile, it was not recommended as the 1st line treatment but, when the latter fails, it is only logical to consider the more effective antidepressant. (ii) Switching is arguably to be preferred over augmentation because combining two drugs may lead to more known and unknown side effects than staying on the same drug.
Mirtazapine augmentation of SSRI is another option as the 2nd line treatment for the following reasons. (i) A number of RCTs have provided some evidence to suggest its effectiveness. One small RCT randomly assigned 26 patients who had not responded to SSRI, bupropion or venlafaxine to augmentation either with mirtazapine 15-30 mg/d or with placebo. The remission rates were 46% versus 13% (p=0.068) [26]. Another RCT administered fluoxetine plus mirtazapine or fluoxetine alone from the beginning of the acute phase treatment and the remission rates were 25% vs 52% (p=0.052) [33]. (ii) It makes sense pharmacologically to combine sertraline, which is an SSRI (specific serotonin reuptake inhibitor), with mirtazapine, which is a NaSSA (noradrenergic specific serotonergic antidepressant). Mirtazapine increases noradrenaline and serotonin release through antagonism of central α_2-adrenergic autoreceptors and heteroreceptors. Mirtazapine also exhibits antagonism to both 5-HT_{2A}, 5-HT_{2C} and 5-HT_3 receptors, which results in a net increase in 5-HT_1-mediated neurotransmission which is believed to be the primary mediator of efficacy of most antidepressant drugs. Antagonsim of the 5-HT_{2A} receptors has beneficial effects on sexual dysfunction and insomnia, that of the 5-HT_{2B} receptors on anxiety, and that of 5-HT_3 on gastrointestinal symptoms, all of which constitute major side effects of SSRIs. (iii) Mirtazapine does not inhibit any liver enzymes and poses very low risk of interaction with other drugs. Sertraline exerts mild inhibition against CYP2D6 and 3A4 but is generally believed to be a safer drug when administered concomitantly with other drugs than many other SSRIs.
Another very important clinical question to be answered with regard to the 2nd line treatment is when to consider it. As far as practitioners are concerned, this represents just as urgent a clinical question as

that of initial titration strategy but, to the best of the authors' knowledge, no RCT has explicitly examined this issue and the guidelines are ambiguous and self-contradictory. For example, the guideline by the American College of Physicians [11] recommends that clinicians modify treatment if the patient does not have an adequate response to pharmacotherapy within 6 to 8 weeks of the initiation of therapy but this time frame appears to be based on the average length of clinical trials conducted mainly for drug approval. The NICE guidelines are self-contradctory as it recommends 3-4 weeks at one place and 6-8 weeks at another before considering the 2nd line treatment alternatives [9]. We therefore decided to randomize the patients with regard to the 2nd line treatment as early as 3 weeks and aimed to examine if considering the 2nd line treatment at this early stage may or may not be beneficial in comparison with continuing the 1st line treatment for 6 more weeks.

Continuation treatment

The last but not least factor to be considered in constructing the optimum treatment strategy for the 1st and 2nd line treatments is the continuation treatment following the acute phase treatment. A systematic review has unambiguously demonstrated that discontinuing antidepressants at the end of acute phase treatment can double the relapse/recurrence rates [34], and all the guidelines recommend continuation treatment of at least several months following acute phase treatment. However, in reality, many patients do not stay on the continuation phase [35]. It therefore follows that another very important factor in deciding the 1st and 2nd line treatment strategies is how easy and acceptable it is for patients to continue into the continuation treatment after acute phase treatment, in addition to their effectiveness and acceptability during the acute phase treatment.

AIMS

The current randomized trial aims to elucidate "pathways for depression that provides good results for the largest number of sufferers in the shortest time and at the lowest cost" (Bandolier 2009). More specifically, the objectives of this trial are to examine the following treatment options among patients with an untreated, non-psychotic unipolar major depressive episode:

(1) When the 1st line treatment is started with sertraline, which is better as an initial prescription strategy up to 3 weeks in terms of effectiveness and safety (i.e. side effects and treatment continuation), to titrate to the lowest dosage of the effective range or to its highest dosage?

(2) When the patients do not remit on the 1st line treatment at 3 weeks, which is better as acute phase treatment up to 9 weeks in terms of effectiveness and safety, to continue sertraline, to augment sertraline with mrtazapine or to switch to mirtazapine?

(3) Which of the above strategies of 1st and 2nd line treatments is better as acute phase and continuation treatments up to 25 weeks in terms of effectiveness and safety?

TRIAL DESIGN

This is an assessor-blinded, parallel-group, multi-centre randomized controlled trial.

PARTICIPANTS

Participants will be recruited from among those visiting the clinical trial sites according to the following eligibility criteria.

Inclusion criteria

1) The participant fulfills criteria for non-psychotic unipolar major depressive episode (DSM-IV) within one month before starting sertraline
2) Age between 25 and 75 on the day when sertraline is started
3) The treating physician has judged sertraline to be the appropriate 1st line treatment
4) Tolerability to sertaline has been ascertained after 3-16 days of treatment with sertraline 25 mg/d
5) The participant is able to understand and sign written informed consent
6) The participant is available on the phone for assessment of symptoms and side effects

Exclusion criteria

1) Having taken antidepressants, mood stabilizers (lithium, valproate, carbamazepine), antipsychotics, psychostimulants (methylphenidate, pemoline, atmoxetine), electroconvulsive therapy, or depression-specific psychotherapies (cognitive-behavior therapy, interpersonal therapy) within one month before starting sertraline
2) History of schizophrenia, schizoaffective disorder or bipolar disorder (DSM-IV) as judged by treating physician
3) Current dementia, borderline personality disorder, eating disorder or substance dependence (DSM-IV) as judged by treating physician
4) Physical diseases which may contraindicate treatment with sertraline or mirtazaapine
5) Allergy to sertraline or mirtazapine
6) Terminal physical diseases
7) Women who are pregnant or breastfeeding (if there is a possibility of getting pregnant within 6 months of trial entry, participation is allowed only after providing signed consent to avoid pregnancy during the trial period)
8) Imminent high risk of suicide as judged by treating physician
9) Needing non-voluntary hospitalization
10) High probability of changing hospital due to relocation etc within 6 months of trial entry
11) Cohabiting family members of research staff members of the trial
12) Inability to understand written Japanese

NB

1) A comprehensive systematic review and meta-analysis has shown that antidepressants increase suicidality in comparison with placebo for people under age 25 but decreases suicidality for people aged 25 or older [36].
2) Both males and females are accepted.
3) There is no eligibility criteria for severity of depression as long as the participant meets the diagnostic criteria for major depression. Both outpatients and inpatients are accepted.
4) Patients having taken benzodiazepine anxiolytics, tandospirone, hydroxyzine, hypnotic medications, traditional Kanpo medications within one month before starting sertraline are not excluded.
5) Patients having received psychotherapies other than depression-specific ones (cognitive-behavior therapy and interpersonal therapy) are not excluded.
6) Patients with physical diseases that the treating physician judged would not interfere with treatment with sertraline or mirtazapine are not excluded.
7) The participant will continue the trial even if his/her diagnosis is changed after trial entry.

TRIAL SITE RECRUITMENT

Eligibility criteria for a trial site

A participating trial site must fulfill the following eligibility criteria.

1) It must have a department of psychiatry or of psychosomatic medicine.
2) The principal trial physician and all the participating trial physicians at the site must have understood the study protocol (e.g. cluster randomization to 50 mg/d or 100 mg/d of sertraline at Step I) and have agreed to collaborate.

NB

A site-visiting CRC will be dispatched to a trial site which

1) Is located within one hour at most approximately from the regional centre
2) Has more than 100 first-visit patients with major depression per annum
3) Has a separate room that the CRC can use for informed consent and that the central assessor can use for telephone assessment.

Such trial sites will open, if possible, "a trial clinic" on a certain day of the week to facilitate patients' participation.

Procedure for a trial site to participate

Each regional centre will recruit collaborating trial sites (psychiatric private practice, department of psychiatry of a general hospital, psychiatric hospital) in units of 4-5.
If the trial site has its own Institutional Review Board, the principal trial physician will seek approval from his/her own IRB and then fax the document of approval to the national centre office. The national centre office will examine the document(s) and return the review results to the trial site principal physician by email.
If the trial site does not have its own IRB, the principal trial physician will send a proxy form to the IRB at Nagoya City University Hospital or at Kochi Medical School and seek approval there.
Before the trial site starts recruiting the participants, all the principal trial physician and the participating trial physicians must attend the start-up meeting held either at the trial site or at the national centre. The co-PI and CRC at the regional centre will visit each trial site in order to make sure that the site has finished the preparation and to rehearse the EDC system and blinded central telephone assessment.

PROCEDURES

The overall procedure of the trial is shown in Figure 1.

Step I

Ascertaining eligibility criteria

The trial physician and/or site CRC will seek informed consent from a participant at week 1, i.e. 3-16 days after starting sertraline 25 mg/d. The "3-16 days" time frame was chosen to allow two possible visit days to accommodate the participant's schedule at a site where the site CRC makes his/her visits every week. After obtaining the written informed consent, the trial physician or the site CRC makes a face-to-face interview or the central CRC or the central rater will make a telephone interview to assess

1) PHQ9 at week 1
2) FIBSER at week 1

These week 1 assessment results will be entered into the EDC along with the complete data on the "Eligibility Form."

Allocation to treatments

Eligible participants will be allocated 1:1 to the sertraline 50 mg/d arm and to the sertraline 100 mg/d arm. We will employ cluster randomization by trial site. This cluster randomization will be made by an independent statistician separate from the statistician of the Steering Committee. It will be stratified by the number of probable entries as judged by the principal investigator and co-principal investigators (40 or more participants per year vs less than 40 participants per year).
We employ cluster randomization for Step I for the following reasons.

1) The comparison for Step I is between physician's choice of a strategy to titrate sertraline used as the 1st line antidepressant up to the minimum effective range or up to the maximum effective range. It is therefore logical to randomize by physician.
2) In reality, because this is an open trial in which the trial physician gradually titrates the dosage taking into account the side effects, having one patient in the sertraline 100 mg/d arm and another in the sertraline 50 mg/d arm may at the same time create contamination in the doctor's decisions. That is, if we randomized by patient, the doctor might tend to stick to his/her personally preferred titration schedule regardless of the individual patient's assignment and reported side effects.
3) Likewise, having different doctors with different titration policies within the same trial site might cause unnecessary confusion among the physicians and co-medical staff at the site.
4) Asking the participant to undergo individual randomization twice might increase the barrier to participation.

5) A number of previous studies have repeatedly reported negligible to very small intra-cluster correlation coefficients [37, 38].

Treatments

The trial physician will prescribe according to either of the following schedule, depending on his/her own allocated treatment strategy.

1) In the 100 mg/d arm, prescribe 50 mg/d (once after dinner or before bedtime) for one week at week 1, then prescribe 100 mg/d (once or divided twice per day) for one week at week 2
2) In the 50 mg/d arm, prescribe 50 mg/d (once after dinner or before bedtime) for one week at week 1, then prescribe the same regimen for one week at week 2

Outcome assessments

The trial physician or the site CRC will ask the participant to fill in BDI2 upon week 2 and week 3 visits. The CRC or the physician will enter the data into EDC.

At week 3, the central rater will administer

1) PHQ9 at week 3
2) FIBSER at week 3

by telephone. The central CRC will obtain the patient's name and phone number and will keep the rater blind to the name of the clinic and the treatment the participant is receiving. This telephone assessment will normally be conducted in a separate room after the patient arrives at the clinic and before the consultation with the trial physician, so that imminent suicidality may be handled promptly and appropriately according to the "Suicidality Management Manual." If the patient has dropped from the treatment, the telephone call will be made to the mobile phone which he/she has previously registered upon entry into the trial. If strong suicidal wishes are expressed, the central rater will follow the "Suicidality Management Manual."

Step II

Ascertaining eligibility criteria

If the patient scores 5 or more on PHQ9 at week 3, as assessed by the central rater, he/she will be randomized for Step II according to the following procedures.

If the patient scores 4 or less on PHQ9 at week 3, he/she will continue on the same regimen, and receive the assessments at week 9 and week 25 as planned.

Allocation to treatments

The patients scoring 5 or more on PHQ9 at week 3 will be allocated 1:1:1 to the continue-sertraline arm, the mirtazapine augmentation arm, and the mirtazapine switch arm. This randomization will be stratified by (i) site, (ii) whether 50% or greater reduction on PHQ9 is achieved or not, and (iii) whether "moderate" or greater impairment due to side effects is reported on item 4 of FIBSER. The randomization will use variable block or minimization method.

The central CRC and the central rater will enter the necessary data from PHQ9 and FIBSER into EDC. EDC will then output "The patient is making steady recovery. Please continue with the same regimen" if the PHQ9 score is 4 or less, and any one of "Augment with mirtazapine. Please add mirtazapine 15 mg/d," "Switch to mirtazapine. Decrease sertraline to half the current dose and add mirtazapine 15 mg/d," or "Continue with sertraline" if thePHQ9 score is 5 or more according to the above randomization. The central CRC will fax the output to the trial physician and the site CRC, so that the physician need not start up the computer every time.

If the EDC server is down and/or the trial site cannot use the EDC system for various reasons, the randomization can be done by calling up the central CRC or the data centre.

Treatments

The details of the three intervention arms are as follows.

1) Continue sertraline as specified by Step I cluster randomization. Between week 4 and week 9, sertraline must be kept as specified by Step I cluster randomization.

2) Continue sertraline as specified by Step I cluster randomization and add mirtazapine 15 mg/d at bedtime to augment sertraline. Between week 4 and week 9, sertraline must be kept as specified by Step I cluster randomization. Mirtazapine can be given in 7.5-45 mg/d at bedtime.
3) Decrease sertraline to half the current dose and add mirtazapine 15 mg/d at bedtime in order to switch to mirtazapine. Stop sertraline by week 4 or week 5 (sertraline should no longer be prescribed at week 7 at the latest), so that the patient will receive mirtazapine 7.5-45 mg/d only between week 7 and week 9.

Outcome assessments

The trial physician or the site CRC will continue to ask the participant to fill in BDI2 at every visit between week 4 and week 9. The CRC or the physician will enter the data into EDC.
At week 9, the central rater will administer
1) PHQ9 at week 9
2) FIBSER at week 9
by telephone. The central CRC will obtain the patient's name and phone number and will keep the rater blind to the name of the clinic and the treatment the participant is receiving. This telephone assessment will normally be conducted in a separate room after the patient arrives at the clinic and before the consultation with the trial physician, so that imminent suicidality may be handled promptly and appropriately according to the "Suicidality Management Manual." If the patient has dropped from the treatment, the telephone call will be made to the mobile phone which he/she has previously registered upon entry into the trial. If strong suicidal wishes are expressed, the central rater will follow the "Suicidality Management Manual."

Step III

Ascertaining eligibility criteria

All the participants who have entered the trial are eligible.

Treatments

All the available treatment guidelines for depression recommends that the acute phase treatment, if successful, be continued at least several months. All the treatments between week 9 and week 25 are at the treating physician's discretion. He/she may continue with the same regimen or completely change the regimen. Electroconvulsive therapy and depression-specific psychotherapies can also be administered.

Outcome assessments

The trial physician or the site CRC will continue to ask the participant to fill in BDI2 at every visit between week 10 and week 25. The physician or the CRC will enter the data into EDC.
At week 25, i.e. approximately 6 months after trial entry and 4 months after week 9 assessments, the central rater will administer
1) PHQ9 at week 25
2) FIBSER at week 25
3) History of prescription up to week 25, especially how long the treatment assigned at week 3 was adhered to
by telephone. The central CRC will obtain the patient's name and phone number and will keep the rater blind to the name of the clinic and the treatment the participant is receiving. This telephone assessment will normally be conducted in a separate room after the patient arrives at the clinic and before the consultation with the trial physician, so that imminent suicidality may be handled promptly and appropriately according to the "Suicidality Management Manual." If the patient has dropped from the treatment, the telephone call will be made to the mobile phone which he/she has previously registered upon entry into the trial. If strong suicidal wishes are expressed, the central rater will follow the "Suicidality Management Manual."

CONCURRENT TREATMENTS

Permitted concurrent treatments

The following medications are allowed throughout the trial at the discretion of the trial physician.

1) Benzodiazepine anxiolytics and hypnotics
2) Tandospirone, hydroxyzine
3) Gastrointestinal and digestive drugs (except for sulpiride)
4) Medications for concurrent physical diseases
5) Non-specific psychotherapies (psychotherapies other than depression-specific CBT and IPT), exercise therapy, music therapy, family psychoeducation

Prohibited concurrent treatments

Through Step I and Step II, the following treatments are prohibited in principle. However, the patient's safety should be the utmost concern and takes priority over everything else, all appropriate care should be given depending on the patient's condition.

1) Antidepressants other than sertraline or mirtazapine
2) Antipsychotics
3) Mood stabilizers (lithium, valproate, carbamazepine)
4) Depression-specific psychotherapies (CBT, IPT)
5) Electroconvulsive therapy

There is no prohibited treatments for Step III.

STOPPING RULES FOR PARTICIPANTS & TRIAL SITES

Stopping intervention

If the participant meets any one of the following conditions, the trial physician will stop the protocol treatment at his/her discretion. The participant, however, will not be considered to have dropped out of the study at this stage and will receive the protocol assessments.

1) The participant wishes to stop the protocol treatment.
2) The trial physician judges that it is difficult to continue the protocol treatment because of emergence of serious adverse events (SAE) as defined below.
3) The trial physician judges that the risk outweighs benefit in continuing the protocol treatment even when no SAE is reported.
4) The participant becomes pregnant and the trial physician judges that the risk outweighs benefit in continuing the protocol treatment.
5) The trial physician judges that it is inappropriate to continue the protocol treatment for any other reason.

Stopping assessment

If the participant meets any one of the following conditions, he/she will never be contacted for assessments.

1) The participant withdraws consent to receiving protocol assessments, regardless of whether he/she is continuing the protocol treatment.

Dropping trial sites

If the trial site meets any of the following conditions, it will be judged "dropout" and will no longer be able to recruit patients. However, the patients who have already entered the study will be followed-up.

1) The principal trial physician withdraws his consent.
2) No study entry was made within 6 months.
3) The Steering Committee judges that it is inappropriate to continue recruitment at this site.

ASSESSMENTS

Measures

Patient Health Questionnaire-9 (PHQ9)

The Patient Health Questionnaire was developed in 1999 as a self-report version of the Primary Care Evaluation of Mental Disorders (PRIME-MD) which aims at criteria-based diagnosis of several mental disorders commonly seen in primary care [39]. The depression module of the PHQ is called PHQ9 and consists of the nine diagnostic criteria items of the DSM-IV. Each item is rated between 0="Not at all" through 3="Nearly every day," making the total score range between 0-27. Excellent test-retest reliability (ICC=0.92) [40] and internal consistency reliability (Cronbach's alpha=0.89) [39] have been reported. Good construct validity has been demonstrated through associations with various severity indices [41]. The sensitivity to change is as good as or better than extant scales [42].

Kroenke and his colleagues have provided the following rules of thumb for interpreting the continuous PHQ9 scores [41].

0-4	no depression
5-9	mild depression
10-14	moderate depression
15-19	moderately severe depression
20-	severe depression

The minimal clinically important difference, i.e. the smallest difference in score that is considered to be a clinically important intra-individual change, was established to be 5 [42].

The PHQ9 should require less than one minute to fill in for the patient and less than one minute to administer for the clinician [41]. The Japanese version has been established by Muramatsu through backtranslation [43].

In this trial, PHQ9 will be administered 5 times at week1, week 3, week 9 and week 25. The central rater will receive training in administering PHQ9 through simulated interviews and will have demonstrated satisfactory reliability. The blindness of the central rater as to the participant's treatment will be assessed by asking the central rater to guess the allocated treatment at week 3, 9 and 25 assessments.

Beck Depression Inventory-II (BDI2)

BDI2 is a 21-item self-report instrument to measure the severity of depression in adolescents and adults. Its first version was developed in 1961 and slightly amended in 1979 but in 1996 a major revision was undertaken to make the scale more congruent with the modern diagnostic criteria for major depression. In its 40 years of usage, the BDI has become one of the most widely used instruments for detecting possible depression in normal populations and for assessing severity of depression in diagnosed patients [44].

The time frame for evaluation is set to the past 2 weeks including the day of assessment. Each item in the BDI2 has a series of four statements, which describe symptom severity along an ordinal continuum from absent or mild (a score of 0) to severe (a score of 3). The total score therefore ranges from 0 through 63.

Good reliability and validity have been reported for the original [45] as well as the Japanese version [46].

The original authors proposed the following rules of thumb for interpreting the BDI2 scores [45]

0-13	Minimal
14-19	Mild
20-28	Moderate
29-63	Severe

Two subsequent studies from the US and from Japan basically confirmed these interpretations [46, 47].

A rough guide for interpreting the changes in BDI2 scores may be [46]

0–9	no or slight change, with 5 indicating a minimally important clinical difference
10–19	moderate change
>=20	large change.

Most patients are comfortable with this 21-item questionnaire and can complete them within 5-10 minutes.

In this trial, BDI2 will be filled in by the patient at each visit.

Frequency, Intensity, and Burden of Side Effects Rating (FIBSER)

FIBSER was originally used in STAR*D as a global rating scale for side effects. This is an observer-rated scale and the Japanese translation has not gone through backtranslation.

Continuation of protocol treatment

Continuation of protocol treatment without stopping intervention or stopping assessment as defined above is called "treatment continuation." In Step III, concurrent treatments prohibited in Steps I and II can be used and this will not constitute "treatment continuation."

Timing of assessments

Assessments at week 3, 9 and 25 may be made within the following time frames after week 1.

1) ±4 days for assessments at week 3 through 9
2) ±14 days for assessments after week 9

Table 1 shows the planned assessments.

Data monitoring and surveillance

Regular monitoring

The data centre will provide the following regular monitoring report to the Steering Committee and the DSMB every six months. The chair of the DSMB will assess the regular monitoring report, and if he/she finds an ethical problem in the continuation of the trial from the viewpoints of safety or effectiveness, he/she will convene the DSMB and advise the principal investigator to change or stop the study.
The regular monitoring report will include:

1) Progress of the trial regarding trial entry and follow-up
2) Implementation of assessments (allocation will be masked)
3) Occurrence of serious adverse events (allocation will be masked)
4) Any other problems.

Site surveillance

Each site will be surveyed within 6 months after the study commencement. The surveillance team nominated by the Steering Committee will survey the sites according to the Site Surveillance Manual. The surveillance team will report the results to the Steering Committee, which will review them.

FORMULATION OF CLINICAL QUESTIONS

Clinical questions to be answered at each step can be formulated as follows.

Step I

Patients: Patients with non-psychotic unipolar major depressive episode who had not received treatment for the index episode before starting sertraline and who tolerate sertraline 25 mg/d
Exposure1: Strategy to titrate sertraline up to the maximum of the effective range, i.e. 25 mg/d -> 50 mg/d -> 100 mg/d
Exposure2: Strategy to titrate sertraline upt to the minimum of the effective range, i.e. 25 mg/d -> 50 mg/d -> 50 mg/d
Outcomes: The primary outcome is the change inPHQ9 scores at week 1 through week 3
The secondary outcomes include:

1) Change in BDI2 scores at week 1 through week 3
2) Proportion of remission (4 or less on PHQ9) at week 3
3) Proportion of response (50% or greater reduction on PHQ9) at week 3
4) Proportion of successful continuation of the allocated treatment up to week 3
5) Change in FIBSER at week 1 through week 3
6) Change inPHQ9 at week1 through week 9
7) Change in BDI2 at week 1 through week 9

8) Proportion of remission (4 or less on PHQ9) at week 9
9) Proportion of response (50% or greater reduction on PHQ9) at week 9
10) Proportion of successful continuation of the allocated treatment up to week 9
11) Change in FIBSER at week 1 through week 9

Step II

Patients: Patients whose major depressive episode did not remit (5 or more on PHQ9) at week 3 to the 1st line treatment with sertraline
Exposure1: Continue sertraline 50 mg/d or 100 mg/d for 6 more weeks
Exposure2: Augment sertraline with mirtazapine 15-45 mg/d
Exposure3: Switch to mirtazapine 15-45 mg/d
Outcome: The primary outcome is the change in PHQ9 at week4 through week 9
The secondary outcomes include:
1) Change in BDI2 at week 4 through week 9
2) Proportion of remission (4 or less on PHQ9) at week 9
3) Proportion of response (50% or greater reduction on PHQ9) at week 9
4) Proportion of successful continuation of the allocated treatment up to week 9
5) Change in FIBSER at week 4 through week 9

Step IIIa [exploratory analysis of continuation treatment for Step I]

Patients: Patients with non-psychotic unipolar major depressive episode who had not received treatment for the index episode before starting sertraline and who tolerate sertraline 25 mg/d
Exposure1: Strategy to titrate sertraline up to the maximum of the effective range, i.e. 25 mg/d -> 50 mg/d -> 100 mg/d by week 3, then allocated to continue sertraline between week 3 and week 9, then treated at the discretion of the trial physician
Exposure2: Strategy to titrate sertraline upt to the minimum of the effective range, i.e. 25 mg/d -> 50 mg/d -> 50 mg/d by week 3, then allocated to continue sertraline between week 3 and week 9, then treated at the discretion of the trial physician
Outcome: The primary outcome is the proportion of patients who continue the allocated treatment up to week 25 and are in remission (4 or less on PHQ9) at week 25
The secondary outcomes include:
1) Proportion of patients who continue the allocated treatment up to week 25 and are showing response (50% or greater reduction on PHQ9) at week 25
2) Continuation of allocated treatments up to week 25 (survival analysis)
3) Change in PHQ9 at week 1 through week 25
4) Change in BDI2 at week 1 through week 25

Step IIIb [exploratory analysis of continuation treatment for Step II]

Patients: Patients whose major depressive episode did not remit (5 or more on PHQ9) at week 3 to the 1st line treatment with sertraline
Exposure1: Continue sertraline 50 mg/d or 100 mg/d for 6 more weeks, then treated at the discretion of the trial physician
Exposure2: Augment sertraline with mirtazapine 15-45 mg/d up to week 9, then treated at the discretion of the trial physician
Exposure3: Switch to mirtazapine 15-45 mg/d up to week 9, then treated at the discretion of the trial physician
Outcome: The primary outcome is the proportion of patients who continue the allocated treatment up to week 25 and are in remission (4 or less on PHQ9) at week 25
The secondary outcomes include:
5) Proportion of patients who continue the allocated treatment up to week 25 and are showing response (50% or greater reduction on PHQ9) at week 25
6) Continuation of allocated treatments up to week 25 (survival analysis)
7) Change in PHQ9 at week 4 through week 25

8) Change in BDI2 at week 4 through week 25

Pilot study

In order to test the feasibility of the study, a pilot study will be run according to this same protocol between 2010 and September 2011. The pilot study will be a multi-centre study involving:

- Nagoya City University Hospital and its affiliated private practices and departments of psychiatry in a general hospital
- Kochi Medical School Hospital and its affiliated private practices, departments of psychiatry in a general hospital and psychiatric hospitals
- Private practices in Yokohama

The Nagoya site will test recruitment using site CRCs, the Kochi site will test recruitment using site CRCs and direct recruitment by trial physicians, and the Yokohama site will test recruitment using site CRCs dispatched from a commercial site management organization. Feasibility and efficiency of these different recruitment methods will be examined.

The pilot study will use data of the 1st 200 patients up to week 25. The pilot study will be analyzed by DSMB who will advise the Steering Committee on the feasibility and safety of the study and on appropriateness of continuing the study. The final decision about whether to continue the study will be made by the Steering Committee. Before continuing the study, the protocol may be amended if necessary and additional trial sites will be recruited.

REPORTING OF ADVERSE EVENTS AND PROTECTION OF PARTICIPANTS

Definition of adverse events

An adverse event is defined as any unwanted or unintended sign (including laboratory exams), symptom or disease seen in participants of the trial, regardless of the causal relationship with the study intervention.

Reportings according to Pharamceutical Affairs Act (1950 Law 145)

All the protocol interventions in the current trial are within the approved dosage and administration in Japan and will therefore have to follow the Japanese Pharmaceutical Affairs Act.

Adverse events will be assessed according to the "Adverse Events Manual" which follows the Japanese Ministry of Health, Labour and Welfare's "Manual for rating the severity of side effects by pharmaceutical products," with an amendment to allow more detailed assessment of suicidality according to Columbia Classification Algorithm for Suicide Assessment (C-CASA) [48].

Adverse events will be classified into:

Grade 1: minor side effects
Grade 2: neither major nor minor side effects
Grade 3: major side effects, i.e. side effects that may lead to death or to enduring severe impairment depending on the patient's conditions and circumstances

All grade 3, and unforeseeable grade 2 adverse events shall be reported to the relevant section of the Ministry of Health, Labour and Welfare as well as to the national centre office. Foreseeable adverse events are judged according to the package inserts of respective drugs. Any grade 3 adverse events that occurred within 30 days of the completion of the protocol treatment shall be reported to the Ministry and the national centre office. The reporting shall be done using the attached "Reporting form on safety of pharmaceutical products."

The principal investigator, upon receiving the report, will consult with the trial physician to discuss the course of actions to be taken with regard to the patient in question and also with regard to the study.

Reportings according to the Ethics Guideline for Clinical Research (Ministry of Health, Labour and Welfare, revised in 2008)

When a serious adverse event occurs, the trial physician must take all the necessary and appropriate measures to ensure safety of the participant. He/she must also notify the principal investigator immediately. The principal investigator must notify co-principal investigators at all the regional centres

within 24 hours, and report to the head of the clinical research institution (Director of Nagoya City University Hospital or Director of Kochi Medical School Hospital) through the co-principal investigators. The principal investigator must also notify all the collaborators. The head of the clinical research institution must report to its own IRB and, if it concerns an unforeseeable serious adverse event, must report to the Ministry of Health, Labour and Welfare.
"A serious adverse event" is defined here 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
   1.1. All deaths regardless of causal relationship with the protocol treatment, if it is a death during the protocol treatment
   1.2. Deaths whose causal relationship with the protocol treatment cannot be denied, if it is a death within 30 days after completion of the protocol treatment.
2. Life-threatening event
3. Event leading to enduring and severe impairment and dysfunction

When treatment is required, the trial physician will provide and/or arrange appropriate treatments including hospital admission.

Foreseeable adverse events

Sertraline

Frequent side effects
Nausea (18.9%), somnolence (15.2%), dry mouth (9.3%), headache (7.8%), diarrhea (6.4%), dizziness (5.0%) etc.
Serious side effects
Serotonin syndrome (unknown frequency), malignant syndrome (unknown frequency), convulsion (unknown frequency), coma (unknown frequency), liver dysfunction (unknown frequency), SIADH (unknown frequency), Lyell syndrome & toxic epidermal necrolysis (unknown frequency), anaphylactoid symptoms (unknown frequency)

Mirtazapine

Frequent side effects
Somnolence (50.0%), dry mouth (20.6%), fatigue (15.2%), constipation (12.7%), increased AST/ALT (12.4%)
Serious side effects
Serotonin syndrome (unknown frequency), agranulocytosis/neutropenia (unknown frequency), convulsion (unknown frequency), liver dysfunction/jaundice (unknown frequency), SIADH (unknown frequency)

STOPPING RULE FOR STUDY

The study will be discontinued by the Steering Committee (or the principal investigator in the case of an emergency) upon advice from the DSMB if any of the following conditions is met.

1) The causal relationship between any of the protocol treatments and serious adverse events including death is established by this study or by any other study.
2) Provision of study drugs becomes impossible for any reason.

DATA MANAGEMENT AND PUBLICATION POLICY

Data management

The data management will be done by the data centre. The electronic data is anonymized in a linkable fashion, and the participants' names and ID numbers will be recorded only on non-electronic media (e.g. paper notebook) and kept at each trial site.
The central CRC will check the progress of all the entered participants every day by use of the EDC and will contact the site CRC or the trial physician should any doubt arise.

The data centre will perform similar checks and will contact the central CRC should any doubt arise.

Publication policy

The protocol will be published, with TAF as first author.
The main papers stemming from Steps I, II and III , especially the one from Step II, will be submitted to a high impact journal. The first author of these three papers can be different from TAF but TAF will remain the corresponding author for them all. All the trial principal physicians and the trial participating physicians who have entered more than 10 patients will appear as co-author of at least one paper.
Trial principal physicians, trial participating physicians and other members of the Steering Committee, if they do not appear as co-author, will be listed at the end of the article. Such authors may be counted as co-authors in some journals but not in others.
The results shall be reflected in treatment guidelines and systematic reviews.

STUDY PERIOD

The study period of this trial will be between November 2010 and March 2013, with the patient entry period between November 2010 and September 2012.
The patient entry period for the pilot study will be between November 2010 and March 2011.

STATISTICAL ANALYSES

Sample size calculation

Sample size for Step I

Assuming an intra-cluster correlation coefficient to be 0.05 [37, 38], with alpha error at 0.05 and statistical power at 0.80, to detect a difference of 1 point on PHQ9 (SD=5), i.e. to detect an effect size of 0.2, we need 66 patients at each of 30 sites. The total sample size is therefore 1980.

Sample size for Step II

The clinical question for Step II is the main hypothesis of this trial. Previous studies using PHQ9 in the acute phase treatment of major depression have shown that, on average, the PHQ9 scores will drop from 15 (SD=5) at baseline to 10 (SD=6) at end of treatment, with a mean change of 5 (SD=5) [49-51]. We expect a difference of 20% (1 point) in the PHQ9 change scores among the intervention arms and consider this to be a clinically meaningful difference in effect. With alpha error set at 0.05 and statistical power at 0.80, in order to detect a between-group difference of 1 point (SD=5) in the reduction of PHQ9 scores from baseline, we need 522 per group and 1566 in toto at Step II. Assuming a dropout rate of 20% and a remission rate of 10% at week 3, we need 2175 participants for Step I.
One point difference in the mean change score on PHQ9 corresponds with an effect size of 0.2. This is a small effect according to Cohen's rough rule of thumb for effect size interpretation [52]. However, because the present trial represents comparison among active treatments and because the true effect size of antidepressants over placebo appears to be around 0.3 [53] and the average effect size of all the health interventions examined in the Cochrane Library appears to be between 0.3 and 0.4 [54], we consider this to be a clinically meaningful difference in effectiveness worth detecting in a large clinical trial. As a matter of fact, an effect size of 0.2 will be translated into an NNT of 10 if the control event rate is around 50% (e.g. response as defined usually by 50% or greater reduction in depression severity from baseline) and 20 if the control event rate is around 20% (e.g. remission of depression) [55]. They therefore represent clinically meaningful difference in effect.
The sample size will be revisited after completion of the pilot study.

Sample size for Step III

Step III represents continuation treatment for Steps I and II, and will therefore be examined as exploratory studies. We therefore will not calculate sample size necessary to detect a significant difference. However, we will calculate the obtained statistical power post-hoc.