experiences, we have now set out to examine the needs of patients in order to develop a novel intervention program that will be more acceptable and satisfying to individual patients.

An assessment of needs offers a number of advantages. First, patients' perceived needs for help and patient-important outcomes can be directly assessed, enabling a more direct indication of the needed resources. Actually, the patients' problems and symptoms do not necessarily reflect the actual need for help [13]. Second, it allows the magnitude of the need for help to be identified, thereby allowing some prioritization of service needs so that the available resources can be allocated where the need is most urgent. Third, a needs assessment enables individuals and/or patient subgroups with higher need levels to be identified, potentially enabling problems to be prevented or reduced through appropriate early interventions [14]. Thus, understating the perceived needs of patients will enable the medical staff to develop services or interventions designed to meet these specific needs. Additionally, there are no large studies investigating the needs of breast cancer patients in an Asian country.

The purposes of the study were to investigate the association between patients' perceived needs and psychological distress and/or QOL and to clarify the characteristics of Japanese patients with a high degree of unmet needs. Our first hypothesis was that there would be statistically significant and more than moderate associations between patients' perceived needs and psychological distress and/or QOL. Our second hypothesis was that the clinical factors associated with patients with a high degree of unmet needs would be multi-factorial and that younger patients and patients with advanced cancer would have more unmet needs because some previous studies have suggested that younger breast cancer patients and patients with advanced breast cancer are more likely to experience clinical psychological distress [1,15,16].

Methods

Subjects

The study subjects were ambulatory female patients with breast cancer attending the outpatient clinic for Oncology, Immunology, and Surgery at Nagoya City University Hospital between February 2006 and February 2007. Potential participants were sampled at random using a visiting list and a random number table.

The eligibility criteria for inclusion in the study were as follows: (1) a diagnosis of breast cancer (all stages and at any time point after diagnosis), (2) an age of 20 years or older, (3) an awareness of the cancer diagnosis, and (4) a general condition sufficient to enable the completion of the survey questionnaire (0–3 on the Eastern Cooperative Oncology Group [ECOG] performance status). The exclusion criteria were patients with (1) severe mental or cognitive disorders or (2) an inability to understand the Japanese language.

This study was approved by the Institutional Review Board and Ethics Committee of Nagoya City University Graduate School of Medical Sciences, Japan, and was conducted in accordance with the principles laid down in the Helsinki Declaration. Written consent was obtained from each patient after a thorough explanation of the purpose and method of the study had been provided.

Procedure

After informed consent had been obtained, the patients were asked to complete the self-administered questionnaires (described below) at home and return them the following day. When questions were answered inadequately, clarifications were sought over the telephone.

Patients' perceived needs: The Short-form Supportive Care Needs Survey questionnaire (SCNS-SF34)

The SCNS-SF34 is a self-administered instrument for assessing the perceived needs of patients with cancer. The SCNS-SF34 consists of 34 items covering five domains of need: psychological (10 items), health system and information (11 items), physical and daily living (5 items), patient care and support (5 items), and sexuality (3 items). The respondents were asked to indicate the level of their need for help over the last month in relation to their having cancer using the following five response options (1 [No Need (Not applicable)], 2 [No Need (Satisfied)], 3 [Low Need], 4 [Moderate Need], 5 [High Need]). Subscale scores were obtained by summing the individual items. In addition, the total score was obtained by summing all the subscales (range = 34–170). A higher score indicated a higher perceived need. As an alternative use, the scale can be used to obtain information on the presence/absence and number of perceived unmet needs (a rating of 3 or higher was regarded as an unmet need), depending on the researcher's clinical question. The validity and reliability of the Japanese version of the SCNS-SF34 have been established [17].

Psychological distress: Hospital Anxiety and Depression Scale (HADS)

The HADS has been developed for use in medically ill patients and does not contain any questions regarding physical symptoms. The HADS is a self-reported

questionnaire consisting of 14 items. The subjects are asked to rate how they felt during the previous week using a 4-point Likert scale. The HADS consists of an anxiety and a depression subscale (0–21 points each), and the total score can range from 0 to 42. A higher score indicates more severe depression and anxiety [18]. The Japanese version of the HADS has been validated for cancer populations [19]. The optimal cut-off point for screening for adjustment disorders and/or major depressive disorders (indicating psychological distress) was 10/11, while the cut-off for major depression (indicating serious psychological distress) was 19/20.

QOL: EORTC QLQ-C 30

Patient QOL was assessed using the European Organization for the Research and Treatment of Cancer (EORTC) QLQ-C30 [20]. The QLQ-C30 is a 30-item, self-reported questionnaire covering functional and symptom-related aspects of QOL in cancer patients. The validity and reliability of the Japanese version of the EORTC QLQ-C30 has been confirmed [21]. In this study, the Global Health Status score was used. A high Global Health Status score represents a high QOL.

Sociodemographic and biomedical factors

An ad-hoc self-administered questionnaire was used to obtain information on the patients' sociodemographic statuses, including their marital status, level of education, and employment status. The performance status, as defined by the ECOG, was evaluated by the attending physicians. All other medical information (duration since diagnosis, clinical stage, and anti-cancer treatment) was obtained from the patients' medical records.

Statistical analysis

To investigate the association between the patients' perceived needs and psychological distress and/or QOL, Pearson's and/or Spearman's correlation analyses were conducted, as appropriate. To identify potential demographic, biomedical, and psychosocial factors associated with a high degree of unmet needs, we conducted a preliminary univariate analysis. In this preliminary analysis, the total and each of the five domains of the SCNS score were entered as dependent variables. The independent variables included age, marital status, employment status, living alone, education, duration since diagnosis (less than 6 months vs 6 months or longer), clinical stage (IV or recurrence vs other stages), performance status (defined by ECOG) and currently receiving anti-cancer therapy (surgery, chemotherapy, trastuzumab, and hormonal therapy: these therapies were rated as currently receiving when the subjects had received these therapeutic interventions within the previous month). For the univariate analyses, an unpaired *t*-test, Mann–Whitney test, chi-square test, Fisher's exact test, and Pearson's and/or Spearman's correlation analyses were conducted, as appropriate. After the univariate analysis, we used a multiple regression analysis to examine the final factors associated with patients' perceived needs. Independent variables with p values less than 0.10 in the preliminary univariate analysis were entered into the multiple regression analysis.

A p-value of less than 0.05 was regarded as being statistically significant, and all reported p-values were two tailed. All statistical procedures were conducted using SPSS version 15.0J version software for Windows (SPSS Inc., 2006).

Results

Patient characteristics

A pool of 420 potential participants was identified for the study. Twelve patients were excluded: 7 refused to participate, 2 were excluded because of cognitive disturbances, 1 was excluded because of very advanced disease, and 2 were excluded for not providing responses despite consenting to participate. The sociodemographic and clinical characteristics of the remaining 408 patients are shown in Table 1. The mean ($\pm$SD) and median age of the study population was 56.1 ($\pm$12.1) and 55 years, respectively. More than three-fourths of the subjects were early breast cancer patients, and most of the patients did not have impairments of physical functioning. The mean ($\pm$SD) and median duration of days since diagnosis were 1040 ($\pm$1353) and 701 (range = 11–17915) days, respectively. The 25th and 75th percentiles of the duration of days since diagnosis were 200 and 1419 days, respectively. A total of 23% of the subjects had been diagnosed as having breast cancer within 180 days (6 months). Among the participants, 381 patients (93.4%) had undergone surgery. The HADS score suggest that 35% of the subjects suffer from clinical psychological distress (HADS$\geqslant$11) and 6% of the subjects experience serious distress (HADS$\geqslant$20).

Frequency of unmet needs

The most common unmet need (rated 3 or more on the 5-point Likert scale) was shown in Table 2. 'Fears cancer spreading' was the commonest, followed by 'Having one member of the hospital staff with whom you can talk to about all aspects of your condition, treatment and follow-up', 'Anxiety', and 'Being informed about things you can do to help yourself to get well'. The prevalence of the ten most frequent unmet needs was over 40%, and all of these unmet needs belonged to the

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psychological domain or the health system and information domain. Each patient had a mean (±SD) of 12 (±10) and a median of 10 unmet needs. The mean/median numbers of unmet needs in each domain were as follows: psychological needs (10 items), 4.4/4; health system and information (11 items), 4.4/3; physical and daily living needs (5 items), 1.4/0; patient care and support needs (5 items), 1.3/0; sexuality needs (3 items), 0.4/0.

Table 1. Characteristics of the study participants ($n = 408$)

Characteristic	N	%
Age (in years)		
mean: 56.1 (SD = 12.1), median: 55 (range, 27–89)		
Marital status	311	76
Married		
Education	**153**	**38**
> 12 years		
Employment status	182	45
Full-time /part-time		
Clinical stage		
0	24	6
I	142	35
II	148	36
III	24	6
IV	11	3
Recurrence	59	15
Duration since diagnosis (days)		
mean: 1040 (SD = 1353)		
25th percentile: 200		
50th percentile (median): 701		
75th percentile: 1419		
Performance status[a]		
0	369	90
1	33	8
2	4	1
3	2	1
Current anticancer treatment[b]		
Surgery[c]	34	8
Chemotherapy	68	17
Trastuzumab	18	4
Hormonal therapy	195	48
Radiation therapy	9	2

[a]Eastern Cooperative Oncology Group criteria.
[b]Multiple choice.
[c]The patient had received surgery within the previous month.

Association between patients' perceived needs and psychological distress and/or QOL

The total score of the SCNS-SF34 was significantly associated with both psychological distress (HADS total: $r = 0.63$, $p < 0.001$; HADS anxiety: $r = 0.61$, $p < 0.001$; HADS depression: $r = 0.55$, $p < 0.001$) and QOL (Global Health Status: $r = -0.52$, $p < 0.001$). All of the needs scores evaluated using the SCNS-SF34, including psychological, health system and information, physical and daily living, patient care and support, and sexuality, were significantly associated with all the types of psychological distress evaluated in the current study (anxiety, depression, and total scores of the HADS). The correlation coefficients ranged from 0.24 (the association between HADS depression and sexuality needs, $p < 0.001$) to 0.68 (the association between HADS total and psychological needs, $p < 0.001$). Regarding the relation between the patients' needs and QOL, each of the needs scores of the SCNS-SF34 were significantly associated with the Global Health Status. The correlation coefficients ranged from −0.17 (the association between the Global Health Status and sexuality needs, $p = 0.001$) to −0.61 (the association between the Global Health Status and physical and daily living needs, $p < 0.001$).

When comparing psychologically distressed patients (HADS ⩾ 11) with those without distress (HADS ⩽ 10), the distressed patients reported a higher number of total unmet needs (18.9 [SD = 9.8] vs 8.3 [SD = 8.5], $p < 0.001$). Similarly, when seriously psychologically distressed patients (HADS ⩾ 20) were compared with those without distress (HADS ⩽ 19), the seriously distressed patients experienced a much higher number of total unmet needs (26.7 [SD = 6.9] vs 11.0 [SD = 9.7], $p < 0.001$).

Characteristics of patients with a high number of unmet needs

Univariate analyses showed that employment status, duration since diagnosis, clinical stage,

Table 2. The prevalence of the ten most frequent unmet needs[a] of the study participants

Unmet needs	Needs domain	N	%
1. Fears cancer spreading	Psychological	258	63
2. Having one member of the hospital staff with whom you can talk to about all aspects of your condition, treatment and follow-up	Health system and information	225	55
3. Anxiety	Psychological	207	51
3. Being informed about things you can do to help yourself to get well	Health system and information	207	51
5. Worry that the results of treatment are beyond your control	Psychological	198	49
6. Concerns about the worries of those close to you	Psychological	197	48
7. Having access to professional counseling if you, family or friends need it	Health system and information	184	45
7. Feeling down or depressed	Psychological	183	45
9. Feelings about death and dying	Psychological	164	40
10. Being informed about cancer which is under control or diminishing (that is, remission)	Health system and information	164	40

[a]Rated 3 or more on the 5-point Likert scale on each item of the Short-form Supportive Care Needs Survey questionnaire.

performance status, surgery, current chemotherapy, and current trastuzumab usage were significantly associated with the total needs. Current hormonal therapy was a borderline significant factor. A multiple regression analysis including these eight factors demonstrated that employment status, duration since diagnosis, clinical stage, and performance status were significantly associated factors with the total needs (Table 3).

Regarding psychological needs, univariate analyses showed that employment status, duration since diagnosis, clinical stage, performance status, surgery, current chemotherapy, and current trastuzumab usage were significantly associated factors. A multiple regression analysis including these seven factors revealed that duration since diagnosis, clinical stage, and performance status were significantly associated factors (Table 4).

Univariate analyses showed that employment status, duration since diagnosis, clinical stage, performance status, current chemotherapy, and current hormonal therapy were significantly associated with health system and information needs. Current trastuzumab usage was a borderline significant factor. A multiple regression analysis including these seven factors revealed that employment status, duration since diagnosis, and clinical stage were significantly associated with health system and information needs (Table 5).

Table 3. Factors associated with the patients' total needs[a]—Multiple regression analysis

Patient characteristics	Coefficient (*B*)	Standardized coefficient (β)	*t*	*p*
Employment status (Full-time /part-time)	−8.41	−0.14	−3.12	0.002
Duration since diagnosis (less than 6 months)	15.84	0.23	4.15	<0.001
Clinical stage (IV or recurrence)	15.76	0.20	3.84	<0.001
Performance status	12.29	0.16	3.26	0.001
Surgery[b]	2.98	0.03	0.50	0.62
Current chemotherapy	3.15	0.04	0.68	0.50
Current trastuzumab usage	4.64	0.03	0.66	0.51
Current hormonal therapy	3.10	0.05	0.99	0.32
				$R^2 = 0.19$

[a]Total score of the SCNS-SF34.
[b]The patient had received surgery within the previous month.

Table 4. Factors associated with the patients' psychological needs[a]—Multiple regression analysis

Patient characteristics	Coefficient (*B*)	Standardized coefficient (β)	*t*	*p*
Employment status (Full-time /part-time)	−1.73	−0.08	−1.81	0.07
Duration since diagnosis (less than 6 months)	6.07	0.25	4.49	<0.001
Clinical stage (IV or recurrence)	5.51	0.20	3.80	<0.001
Performance status	5.40	0.20	4.04	<0.001
Surgery[b]	2.24	0.06	1.11	0.27
Current chemotherapy	−0.28	−0.01	−0.18	0.85
Current trastuzumab usage	2.86	0.06	1.16	0.25
				$R^2 = 0.20$

[a]Subscale score of psychological needs, derived from SCNS-SF34.
[b]The patient had received surgery within the previous month.

Table 5. Factors associated with the patients' health system and information needs[a]—Multiple regression analysis

Patient characteristics	Coefficient (*B*)	Standardized coefficient (β)	*t*	*p*
Employment status (Full-time/part-time)	−4.30	−0.17	−3.58	<0.001
Duration since diagnosis (less than 6 months)	4.74	0.16	3.19	0.002
Clinical stage (IV or recurrence)	6.14	0.18	3.42	0.001
Performance status	2.73	0.08	1.62	0.11
Current chemotherapy	2.06	0.06	1.04	0.30
Current trastuzumab usage	0.20	0.003	0.07	0.95
Current hormonal therapy	−0.14	−0.005	−0.10	0.92
				$R^2 = 0.13$

[a]Subscale score of the health system and information needs, derived from SCNS-SF34.

Concerning physical and daily living needs, univariate analyses showed that employment status, duration since diagnosis, clinical stage, performance status, surgery, and current chemotherapy were significantly associated factors. A multiple regression analysis including these six factors indicated that duration since diagnosis, clinical stage, and performance status were significantly associated with physical and daily living needs (Table 6).

Univariate analyses showed that employment status, duration since diagnosis, clinical stage, performance status, and current chemotherapy were significantly associated with patient's care and support needs. Surgery and current trastuzumab usage were borderline significant factors. A multiple regression analysis including these seven factors revealed that employment status, duration since diagnosis, clinical stage, and performance status were significantly associated with the patient's care and support needs (Table 7).

Finally, regarding sexuality needs, univariate analyses showed that age and education were significantly associated factors. The duration since diagnosis was a borderline significant factor. A multiple regression analysis including these three factors revealed that only age was significantly associated with sexuality needs (Table 8).

Discussion

The present findings indicated that moderate to strong associations exist between patients' needs and psychological distress and/or QOL and that the characteristics associated with patients' needs are multi-factorial.

The current study confirms our hypothesis that patients' perceived needs are significantly associated with both psychological distress and QOL. Regarding the association between patients'

Table 6. Factors associated with the patients' physical and daily living needs[a]—Multiple regression analysis

Patient characteristics	Coefficient (B)	Standardized coefficient (β)	t	p
Employment status (Full-time/part-time)	−0.79	−0.09	−1.94	0.053
Duration since diagnosis (less than 6 months)	2.08	0.20	3.63	<0.001
Clinical stage (IV or recurrence)	1.36	0.12	2.21	0.03
Performance status	2.95	0.26	5.18	<0.001
Surgery[b]	0.82	0.05	0.96	0.34
Current chemotherapy	0.26	0.02	0.41	0.69
				$R^2 = 0.18$

[a]Subscale score of the physical and daily living needs, derived from SCNS-SF34.
[b]The patient had received surgery within the previous month.

Table 7. Factors associated with the patients' care and support needs[a]—Multiple regression analysis

Patient characteristics	Coefficient (B)	Standardized coefficient (β)	t	P
Employment status (Full-time /part-time)	−1.45	−0.15	−3.17	0.002
Duration since diagnosis (less than 6 months)	1.43	0.13	2.20	0.03
Clinical stage (IV or recurrence)	2.76	0.22	3.97	<0.001
Performance status	1.78	0.14	2.77	0.006
Surgery[b]	0.25	0.01	0.26	0.80
Current chemotherapy	−0.53	−0.04	−0.72	0.47
Current trastuzumab usage	0.81	0.04	0.69	0.49
				$R^2 = 0.13$

[a]Subscale score of the patient's care and support needs, derived from SCNS-SF34.
[b]The patient had received surgery within the previous month.

Table 8. Factors associated with the patients' sexuality needs[a]—Multiple regression analysis

Patient characteristics	Coefficient (B)	Standardized coefficient (β)	t	p
Age (< 55 years)	0.89	0.19	3.63	<0.001
Education (<12 years)	−0.36	−0.08	−1.43	0.15
Duration since diagnosis (less than 6 months)	0.44	0.08	1.68	0.09
				$R^2 = 0.06$

[a]Subscale score of the sexuality needs, derived from SCNS-SF34.

perceived needs and psychological distress, the findings obtained were consistent with those of a previous study [22,23]. On the other hand, the association between patients' perceived needs and QOL is somewhat controversial. Some studies have indicated a significant association between these factors in cancer patients [23] and among psychiatric patients [24], while other studies have shown no significant association [22]. Although the current findings cannot reveal the causal association between patients' perceived needs and psychological distress and/or QOL, interventions to improve patients' perceived needs may be a promising strategy for ameliorating psychological distress and enhancing QOL among ambulatory breast cancer patients. Because the provision of medical services after the completion of a needs assessment can be adjusted to reflect the issues with which the patient desires help, this kind of intervention would be patient centered and would likely be acceptable to the patient.

Our second hypothesis was that the characteristics associated with a high number of unmet needs would be multi-factorial and that younger patients and patients with advanced cancer would have a greater number of unmet needs. The present findings partly supported these hypotheses. A general overview of the results shows that the period soon after cancer diagnosis (less than 6 months), a more advanced stage, and impaired physical functioning were associated with a higher number of unmet needs, whereas a full-time/part-time work status was associated with a lower number of unmet needs. These findings are useful for detecting potential patients with a high number of unmet needs and for developing strategies to reduce patients' psychological distress. One interesting finding may be the association between patients' needs and employment status. Because previous studies conducted in the general population have shown that work increases opportunities for adult relationships among females [25], employment may function as a resource for support for breast cancer patients. On the other hand, sexuality needs were unique, compared with other domains of needs. Sexuality needs were associated with a younger patient age, and this association was consistent with the results of previous studies [26]. Several studies have demonstrated that sexually active breast cancer patients experience various sexual problems [27] and that younger breast cancer patients (<50 years) place a greater importance on information regarding sexuality than older patients [28]. Thus, the sexuality needs of younger breast cancer patients should be carefully addressed, irrespective of other medical characteristics, including the duration since diagnosis, clinical stage, anti-cancer treatment, and physical functioning.

As mentioned above, patients with advanced stage cancer (metastatic and/or recurrent breast cancer) are likely to have a higher number of unmet needs. Clinical stage was associated with a higher number of unmet needs, and this association was independent of the period since cancer diagnosis and a lower physical function rating. Because patients with incurable cancer often confront many difficulties, including both physical and psychosocial issues, this finding is not surprising. As approximately half of breast cancer patients confronting advanced and/or recurrent disease clinically experience psychological distress [1,15], future studies are needed to clarify the types of patients' needs and the factors associated with psychological distress among breast cancer patients with advanced disease so that their distress can be ameliorated.

Although it was not the principal purpose of our study, the current study demonstrated that the number of information and psychological needs was relatively high among breast cancer patients, compared with the other needs domains, and this finding was consistent with the results of previous studies among patients with other types of cancers [29–32]. In particular, many breast cancer outpatients needed psychological help to manage their fear and/or anxiety, as shown by the number of responses to 'Fears cancer spreading' and 'Anxiety'; these results are also consistent with those of a previous study [22]. These findings suggest that the development of an interventional program for reducing fear/anxiety associated with recurrence and cancer spreading is needed for the treatment of breast cancer patients, as very few management strategies exist that specifically address these sources of distress [33]. In addition, the findings that many ambulatory breast cancer patients still experience various unmet needs after 2–3 years after diagnosis suggest that development of appropriate support system for helping survivorship may be essential to care illness trajectory of breast cancer patients.

Because a previous study has shown that simple interventions, including a needs assessment and the feedback of the resulting information to oncologists, are not effective for reducing psychological distress among cancer patients [34], the development of more comprehensive or collaborative interventions might be needed to actually improve patient outcome. Considering the applicability of interventions in many clinical settings, one promising strategy may be a collaborative care model that is structured as an intervention program mainly provided by a nurse case manager supervised by mental health professionals [35]. Furthermore, our findings suggest that interventions should often include active management strategies for reducing anxiety/fear and fulfilling information needs, based on each patient's specific needs.

Finally, we would like to comment on our findings from a cross-cultural perspective because,

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to the best of our knowledge, this is the first large Asian study to investigate breast cancer patients' need. There are many cross-cultural differences between Western and Asian countries, including differences in the expression of psychological distress (e.g. Asian depressive people are generally likely to be more somatized) and response to illness (e.g. Asian patients are more likely to respond stoically to their illness) [36,37]. On the other hand, the findings obtained in this study indicated that the most frequent need was 'Fears cancer spreading', and the psychological and health system and information domain needs were similar to findings in Western countries [38]. Considering the various differences between these two cultures, these similarities are interesting, and further studies investigating patients' perceived needs from cross-cultural perspectives are needed.

In conclusion, the present study demonstrated that moderate to strong associations exist between patients' needs and psychological distress and/or QOL and these findings suggest that interventions to respond to patients' needs may be one promising strategy for ameliorating psychological distress and enhancing QOL. We are conducting a clinical trial to investigate the effectiveness of a collaborative care program led by a nurse supervised by psychiatrists for reducing psychological distress among breast cancer patients with high levels of distress.

The present study has several limitations. First, the investigation was cross-sectional in design, precluding any conclusions from being made with regard to causality between patients' needs and psychological distress and/or QOL. Second, we did not investigate several patients' demographic data (e.g. living levels) and clinical factors (e.g. the type of breast cancer surgery [mastectomy vs breast-conserving surgery], the occurrence of acute adverse effects of chemotherapy) which are potentially relevant. While previous studies suggest that the type of breast cancer surgery and treatment does not seem to impact on patients' psychological distress [39–41], economical status can influence patients' distress [42]. Thus lack of data on patients' living levels is one of the limitation of the study and future study investigating the potential impact of economical status is promising. Third, because supportive care needs can be influenced by the patients' cultural backgrounds and each country's medical system, the findings might not be applicable to other patient populations. Fourth, since the present study was conducted at one institution, an institutional bias might exist. Finally, because this study focused on ambulatory breast cancer patients and relatively few patients with low physical functioning or advanced cancer were enrolled, the results might not be applicable to patients with other types and/or advanced stages of cancer.

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Furukawa et al. Trials 2011, 12:116
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TRIALS

STUDY PROTOCOL Open Access

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: 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: SUN(^_^)D promises to be a pragmatic large trial to answer important clinical questions that every clinician treating patients with major depression faces in his/her daily practices concerning its first- and second-line treatments.

Trial registration: ClinicalTrials.gov: 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

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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.medicine.ox.ac.uk/bandolier/index.html), 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-contradictory 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?

Methods

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 major depressive episode is the focus of the treatment and the treating physician has judged sertraline to be its appropriate 1st line drug
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 Kampo 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 central 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 its regional centre 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 Figures 1 and 2.

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

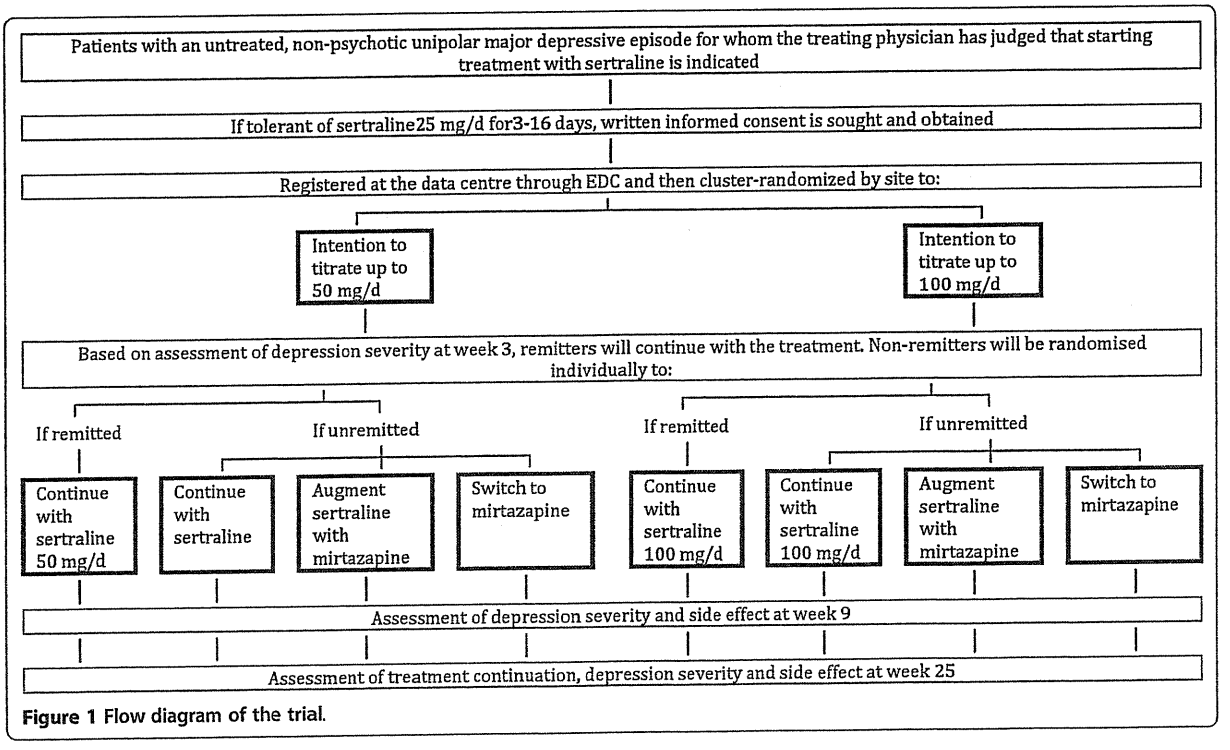

Figure 1 Flow diagram of the trial.

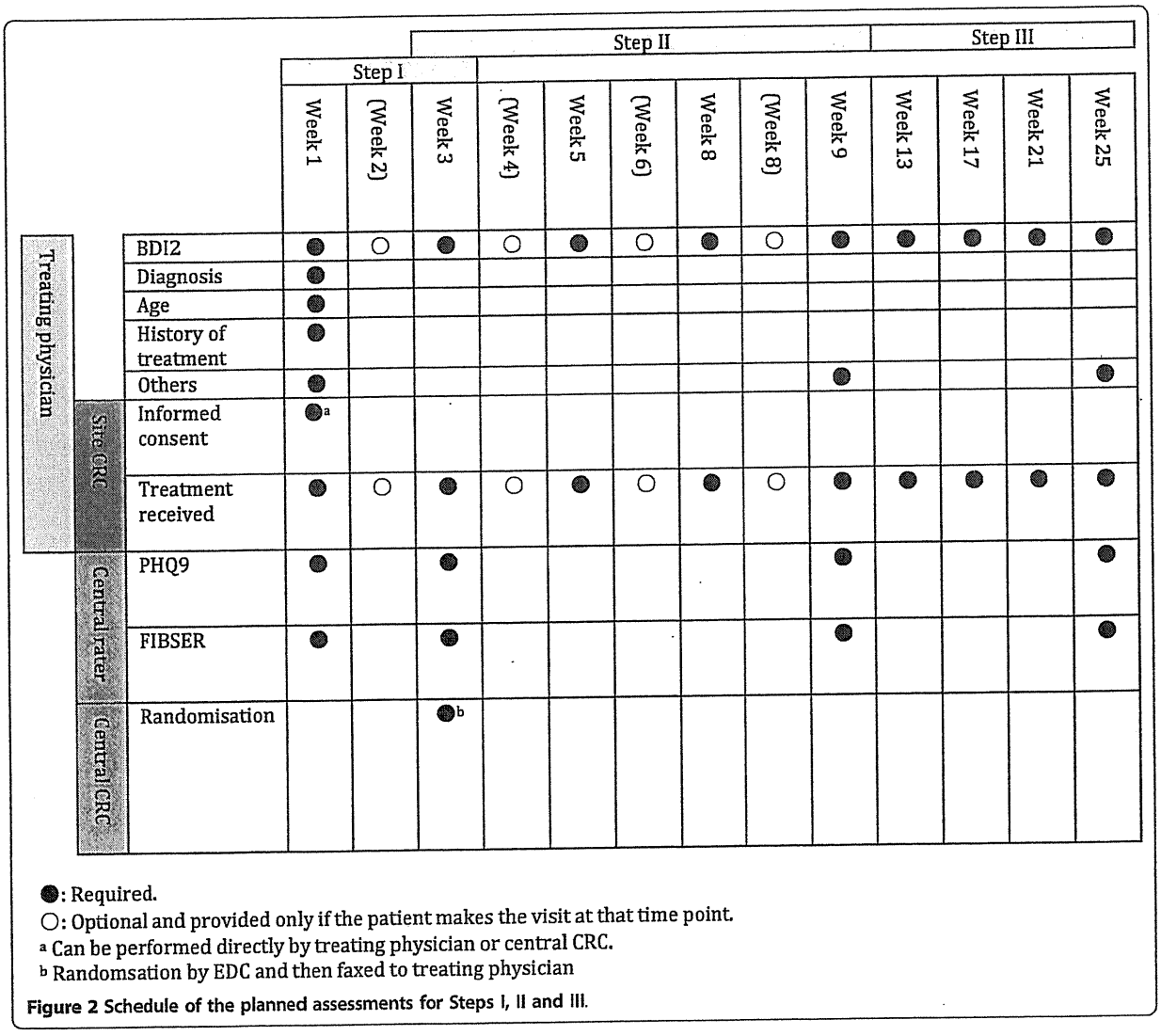

Figure 2 Schedule of the planned assessments for Steps I, II and III.

12) Suicidality as assessed with C-CASA between week 1 and week 9

13) Manic/hypomanic/mixed episode between week 1 and week 9

14) Serious adverse events between week 1 and 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

6) Suicidality as assessed with C-CASA between week 3 and week 9

7) Manic/hypomanic/mixed episode between week 3 and week 9

8) Serious adverse events between week 3 and 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 up 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) Rate of continuation of allocated treatments up to week 25
3) Change in PHQ9 at week 1 through week 25
4) Change in BDI2 at week 1 through week 25
5) Suicidality as assessed with C-CASA between week 1 and week 25
6) Manic/hypomanic/mixed episode between week 1 and week 25
7) Serious adverse events between week 1 and 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:

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) Rate of continuation of allocated treatments up to week 25
3) Change in PHQ9 at week 4 through week 25
4) Change in BDI2 at week 4 through week 25
5) Suicidality as assessed with C-CASA between week 3 and week 25
6) Manic/hypomanic/mixed episode between week 3 and week 25
7) Serious adverse events between week 3 and 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 December 2010 and October 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 reviewed 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.

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 the EDC system. The allocation will use the minimization method adjusting for 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 50-75 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 use the minimization method adjusting for (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 central CRC will enter the necessary data from PHQ9 and FIBSER into EDC. The EDC program 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 randomisation 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 within the maximum as specified by Step I cluster randomization. If the dosage has not reached this maximum (e.g. 100 mg/d) at week 3, it can be increased to this maximum (in this case, 100 mg/d) between week 3 and week 9.
2) Continue sertraline as specified by Step I cluster randomization and add mirtazapine 15 mg/d at bedtime to augment sertraline. After week 4, mirtazapine can be given in 7.5-45 mg/d at bedtime. Between week 4 and week 9, sertraline must be kept within the maximum as specified by Step I cluster randomization. If the sertraline dosage has not reached this maximum (e.g. 100 mg/d) at week 3, it can be increased to this maximum (in this case, 100 mg/d) between week 3 and week 9. Mirtazapine should usually be started at 15 mg/d but can be halved by the treating psychiatrist taking into account age etc of the patient.
3) Decrease sertraline to half the current dose and add mirtazapine 7.5-15 mg/d at bedtime in order to switch to mirtazapine. Sertraline must be halved at week 3 and stopped 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 central 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

Deviation from protocol treatment

The following cases will be considered deviation from the trial protocol. The participant, however, will not be considered to have dropped out of the study at this stage and will receive the protocol assessments.

1) Prohibited concurrent treatments were administered in Step I or II
2) The participant was not randomised within the pre-specified time frame for week 3.
3) The participant cannot take any sertraline in Step I.
4) The participant switches to manic/hypomanic/mixed in Step I.
5) The participant turns out to suffer from bipolar disorder, schizophrenia or dementia in Step II.

The treating physician is to judge whether 1) through 5) has occurred. If so judged, the physician should immediately notify the site CRC, who will notify the central office.

If 1) through 4) occurs in Step I, the randomization for step II will not be made but assessment will continue.

If 1) or 5) occurs in Step II, the patient will be analysed as randomized.

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

Assessment for week 3 must be made between -4 days to +14 days of the planned date, and that for week 9 must also be made between -4 days to +14 days of the planned date.

Data monitoring and site audit

Data monitoring The data centre will provide the following data monitoring report to the Steering Committee and the DSMB every six months. The chair of the DSMB will assess the data 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 data monitoring report will include:

1) Progress of the trial regarding trial entry and follow-up
2) Implementation of assessments (allocation will be masked)
3) Incidence of serious adverse events (allocation will be masked)