social anxiety disorder on their follow-up medical treatment.

CASE REPORTS

Several items of personal information have been modified in the following case reports to preserve the anonymity of the patients.

Case 1

Ms. A was a 48-year-old single woman. She was diagnosed as having early-stage uterine cervical cancer (stage Ib) and received a surgical resection (extensive total resection of the uterus) and subsequent chemotherapy and radiotherapy over a 10-month period beginning in April X. She developed clinical depression in April X, mainly because of communication problems with her physician (She said, "I did not confide in my doctor and his words traumatized me"). She subsequently consulted a psychiatric clinic. Her depression fluctuated and finally led to a consultation with the psychiatry department of a general hospital 2.5 years after her cancer diagnosis, at which time her depression had worsened to major depression. Her depression gradually improved with antidepressive treatment and almost remitted after about 1.5 years. However, her depression relapsed despite continued treatment, when she experienced a bloody discharge 3 years after her initial consultation with our psychiatry department. Since then, her mental status has continued to fluctuate. Three years and nine months after her initial psychiatric consultation, she confided that she had always felt strong anxiety when she met her friends, and the presence of social anxiety disorder since her teens was unexpectedly detected through an additional diagnostic interview. The patient's total score on the Liebowitz Social Anxiety Scale (Heimberg et al., 1999) was 66, indicating moderately severe social anxiety disorder. Although she was supposed to participate in a group cognitive-behavioral therapy program for social anxiety disorder offered in our department, her depression (with atypical features such as an increase in appetite and leaden paralysis) worsened and she was admitted to an inpatient unit for the treatment of depression 4 years and 4 months after her initial psychiatric consultation. Although her depression improved after 10 weeks of inpatient treatment, it relapsed soon after discharge. Since her first admission, her depression has been refractory and fluctuating despite her participation in several pharmacological trials over the 7-year period since initial psychiatric consultation. She often claims that she feels depressed and fears several social situations, including medical follow-up visits to her oncologist.

Case 2

Ms. B was a 52-year-old housewife who lived with her husband and a son. She was diagnosed as having early-stage right breast cancer (stage IIb) and received a surgical resection (partial mastectomy and axillary lymph node resection), radiotherapy, and adjuvant chemotherapy over a 10-month period starting in March Y. Because she had refused hormonal therapy because of adverse effects, including hot flashes, and had continuous insomnia and appetite loss, she was referred to our psychiatry department approximately 1 year after her cancer diagnosis. She was diagnosed as having major depression, and pharmacotherapy with antidepressants was initiated. Her depression improved slightly but remained moderately severe. Five months after her initial psychiatric consultation, she reported that she felt extremely anxious when she thought about her son's forthcoming wedding ceremony. An additional diagnostic interview clarified that she had been experiencing strong performance fear and fear of social interaction since her childhood. She was subsequently diagnosed as having comorbid social anxiety disorder. Her total scores on the Social Interaction Anxiety Scale and Social Phobia scale (Mattick & Clarke, 1998) were 74 and 55 respectively, indicating severe social anxiety disorder. Although we recommended group psychotherapy for her social anxiety disorder, she declined to participate because the group situation was too burdensome for her in her current condition. Although she said that her social anxiety disorder did not influence her breast cancer care, she also said that she had difficulty talking with a medical staff member whom she felt was coercive. Her depression has also been refractory to several pharmacotherapy trials and has been ongoing for at least 20 months, despite psychiatric treatment. Her most recent Beck Depression Inventory-II [BDI-II] (Kojima et al., 2002) score was 44, indicating severe depression.

DISCUSSION

Both of the reported cases were cancer patients whose depression occurred after cancer diagnosis, and whose preexisting social anxiety disorder was detected serendipitously during clinical follow-up interviews conducted as a part of psycho-oncology care.

Although many studies have investigated depression among cancer patients, very few studies have focused on anxiety disorders among cancer patients (Stark & House, 2000; Stark et al., 2002). The cases reported here suggest that cancer patients with social anxiety disorder can develop refractory depression and may experience communication difficulties with medical staff, including their physicians.

Therefore, comorbid social anxiety disorder should be considered when a cancer patient's depression is resistant to treatment and communication problems exist between the patient and the medical staff.

Social anxiety disorder has an early onset in most patients and tends to manifest during adolescence (Stein & Stein, 2008). However, many patients do not receive therapy until a comorbid disorder is diagnosed later in life. Both pharmacologic therapies, especially selective serotonin reuptake inhibitors, and psychotherapeutic treatments such as cognitive-behavioral therapy, are effective. However, comorbid social anxiety disorder is a well-known risk factor for refractory depression (Souery et al., 2007; Rush et al., 2008).

Although patients with cancer are bound to have greater communication opportunities and needs, not only with the medical staff but also with their families, colleagues, neighbors, and others, and although pre-existing social anxiety disorder would undoubtedly render such communication difficult, the potential impact of social anxiety disorder on cancer patients has not been previously reported. Given the high prevalence of social anxiety disorder among cancer patients, as well as in the general population, more studies regarding social anxiety disorder, especially regarding the prevalence, early detection, and potential impact on medical communication, are urgently needed to enhance cancer patients' psychological well-being.

REFERENCES

Heimberg, R.G., Horner, K.J., Juster, H.R., et al. (1999). Psychometric properties of the Liebowitz Social Anxiety Scale. *Psychological Medicine, 29*, 199–212.

Kojima, M., Furukawa, T.A., Takahashi, H., et al. (2002). Cross-cultural validation of the Beck Depression Inventory-II in Japan. *Psychiatry Research, 110*, 291–299.

Liebowitz, M.R. (1999). Update on the diagnosis and treatment of social anxiety disorder. *Journal of Clinical Psychiatry, 60*, 22–26.

Mattick, R.P. & Clarke, J.C. (1998). Development and validation of measures of social phobia scrutiny fear and social interaction anxiety. *Behavior Research and Therapy, 36*, 455–470.

Rush, A.J., Wisniewski, S.R., Warden, D., et al. (2008). Selecting among second-step antidepressant medication monotherapies: Predictive value of clinical, demographic, or first-step treatment features. *Archives of General Psychiatry, 65*, 870–880.

Souery, D., Oswald, P., Massat, I., et al. (2007). Clinical factors associated with treatment resistance in major depressive disorder: Results from a European multicenter study. *Journal of Clinical Psychiatry, 68*, 1062–1070.

Stark, D., Kiely, M., Smith, A., et al. (2002). Anxiety disorders in cancer patients: their nature, associations, and relation to quality of life. *Journal of Clinical Oncol, 20*, 3137–3148.

Stark, D.P. & House, A. (2000). Anxiety in cancer patients. *British Journal of Cancer, 83*, 1261–1267.

Stein, M.B. & Stein, D.J. (2008). Social anxiety disorder. *Lancet, 371*, 1115–1125.

Zimmerman, M. & Chelminski, I. (2003). Clinician recognition of anxiety disorders in depressed outpatients. *Journal of Psychiatry Research, 37*, 325–333.

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Patient's perceived need and psychological distress and/or quality of life in ambulatory breast cancer patients in Japan

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Abstract

***Objective*: A needs assessment can be used as a direct index of what patients perceive they need help with. The purposes of this study were to investigate the association between patients' perceived needs and psychological distress and/or quality of life (QOL) and to clarify the characteristics of patients with a high degree of unmet needs.**

***Methods*: Randomly selected ambulatory female patients with breast cancer participated in this study. The patients were asked to complete the Short-form Supportive Care Needs Survey questionnaire, which covers five domains of need (health system and information, psychological, physical, care and support, and sexuality needs); the Hospital Anxiety and Depression Scale; and the European Organization for Research and Treatment of Cancer QLQ-C 30.**

***Results*: Complete data were available for 408 patients. The patients' needs were significantly associated with both psychological distress ($r = 0.63$, $p < 0.001$) and QOL ($r = -0.52$, $p < 0.001$). A multiple regression analysis revealed that employment status (without full-time /part-time job), duration since diagnosis (less than 6 months), advanced stage, and a lower performance status were significantly associated with higher total needs. Only sexuality needs were significantly associated with a younger age, while the other domains were significantly associated with duration since diagnosis, advanced stage, and a lower performance status.**

***Conclusions*: Moderate to strong associations exist between patients' needs and psychological distress and/or QOL. The characteristics associated with patients' needs are multi-factorial, and interventions to respond to patients' needs may be one possible strategy for ameliorating psychological distress and enhancing QOL.**

Keywords: oncology; need; psychological distress; quality of life; supportive care

Introduction

Breast cancer is one of the most common cancers among women all over the world. In Japan, breast cancer is the most common cancer among women and its incidence is continuing to increase. At present, more than 40 000 women develop breast cancer annually in Japan. The psychosocial impact of breast cancer has received a good deal of attention because of the high prevalence of this disease and the severe psychological effects of both the cancer itself and its treatment. Previous studies have suggested that approximately 20–40% of breast cancer patients suffer from psychiatric morbidity, including depression and/or anxiety [1–3]. This produces not only serious suffering [4], but also worsens quality of life (QOL) [5], reduces adherence to anti-cancer treatments [6], can lead to suicide [7], is a psychological burden on the family [8], and prolongs hospitalization [9].

As psychological functioning is a key dimension of a cancer patient's QOL, dealing with patients' psychological distress is an important part of clinical practice. We have developed several types of psychosocial intervention strategies for alleviating the psychological distress of cancer patients, including a multi-faceted psychosocial intervention program [10], a pharmacological treatment algorithm [11], and a nurse-assisted screening and psychiatric referral program [12]. Based on these

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$\geqslant$11) with those without distress (HADS$\leqslant$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$\geqslant$20) were compared with those without distress (HADS$\leqslant$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.

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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.

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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, anticancer 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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References

1. Burgess C, Cornelius V, Love S, Graham J, Richards M, Ramirez A. Depression and anxiety in women with early breast cancer: five year observational cohort study. *Br Med J* 2005;**330**:702.
2. Kissane DW, Grabsch B, Love A, Clarke DM, Bloch S, Smith GC. Psychiatric disorder in women with early stage and advanced breast cancer: a comparative analysis. *Aust N Z J Psychiatry* 2004;**38**:320–326.
3. Akechi T, Okuyama T, Imoto S, Yamawaki S, Uchitomi Y. Biomedical and psychosocial determinants of psychiatric morbidity among postoperative ambulatory breast cancer patients. *Breast Cancer Res Treat* 2001;**65**:195–202.
4. Block SD. Assessing and managing depression in the terminally ill patient. ACP-ASIM End-of-Life Care Consensus Panel. American College of Physicians—American Society of Internal Medicine. *Ann Intern Med* 2000;**132**:209–218.
5. Grassi L, Indelli M, Marzola M *et al.* Depressive symptoms and quality of life in home-care-assisted cancer patients. *J Pain Symptom Manage* 1996;**12**:300–307.
6. Colleoni M, Mandala M, Peruzzotti G, Robertson C, Bredart A, Goldhirsch A. Depression and degree of acceptance of adjuvant cytotoxic drugs. *Lancet* 2000;**356**:1326–1327.
7. Henriksson MM, Isometsa ET, Hietanen PS, Aro HM, Lonnqvist JK. Mental disorders in cancer suicides. *J Affect Disord* 1995;**36**:11–20.
8. Cassileth BR, Lusk EJ, Strouse TB, Miller DS, Brown LL, Cross PA. A psychological analysis of cancer patients and their next-of-kin. *Cancer* 1985;**55**:72–76.
9. Prieto JM, Blanch J, Atala J *et al.* Psychiatric morbidity and impact on hospital length of stay among hematologic cancer patients receiving stem-cell transplantation. *J Clin Oncol* 2002;**20**:1907–1917.
10. Akechi T, Taniguchi K, Suzuki S *et al.* Multifaceted psychosocial intervention program for breast cancer patients after first recurrence: feasibility study. *Psycho-Oncology* 2007;**16**:517–524.
11. Okamura M, Akizuki N, Nakano T *et al.* Clinical experience of the use of a pharmacological treatment algorithm for major depressive disorder in patients with advanced cancer. *Psycho-Oncology* 2008;**17**:154–160.
12. Shimizu K, Akechi T, Okamura M *et al.* Usefulness of the nurse-assisted screening and psychiatric referral program. *Cancer* 2005;**103**:1949–1956.
13. Osse BH, Vernooij-Dassen MJ, Schade E, Grol RP. The problems experienced by patients with cancer and their needs for palliative care. *Support Care Cancer* 2005;**13**:722–732.
14. Bonevski B, Sanson-Fisher R, Girgis A, Burton L, Cook P, Boyes A. Evaluation of an instrument to assess the needs of patients with cancer. Supportive Care Review Group. *Cancer* 2000;**88**:217–225.
15. Okamura H, Watanabe T, Narabayashi M *et al.* Psychological distress following first recurrence of disease in patients with breast cancer: prevalence and risk factors. *Breast Cancer Res Treat* 2000;**61**:131–137.

16. Northouse LL. Breast cancer in younger women: effects on interpersonal and family relations. *J Natl Cancer Inst Monogr* 1994;183–190.
17. Okuyama T, Akechi T, Yamashita H *et al.* Reliability and validity of the Japanese version of the Short-form Supportive Care Needs Survey questionnaire (SCNS-SF34-J). *Psycho-Oncology* 2009;**18**:1003–1010.
18. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;**67**: 361–370.
19. Kugaya A, Akechi T, Okuyama T, Okamura H, Uchitomi Y. Screening for psychological distress in Japanese cancer patients. *Jpn J Clin Oncol* 1998;**28**: 333–338.
20. Aaronson NK, Ahmedzai S, Bergman B *et al.* The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;**85**:365–376.
21. Kobayashi K, Takeda F, Teramukai S *et al.* A cross-validation of the European Organization for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-C30) for Japanese with lung cancer. *Eur J Cancer* 1998;**34**:810–815.
22. Hodgkinson K, Butow P, Hunt GE, Pendlebury S, Hobbs KM, Wain G. Breast cancer survivors' supportive care needs 2–10 years after diagnosis. *Support Care Cancer* 2007;**15**:515–523.
23. Cossich T, Schofield P, McLachlan SA. Validation of the cancer needs questionnaire (CNQ) short-form version in an ambulatory cancer setting. *Qual Life Res* 2004;**13**:1225–1233.
24. Lasalvia A, Bonetto C, Malchiodi F *et al.* Listening to patients' needs to improve their subjective quality of life. *Psychol Med* 2005;**35**:1655–1665.
25. Cumming E, Lazer C. Kinship structure and suicide: a theoretical link. *Can Rev Sociol Anthropol* 1981;**18**: 271–282.
26. Thewes B, Butow P, Girgis A, Pendlebury S. The psychosocial needs of breast cancer survivors; a qualitative study of the shared and unique needs of younger versus older survivors. *Psycho-Oncology* 2004;**13**:177–189.
27. Takahashi M, Ohno S, Inoue H *et al.* Impact of breast cancer diagnosis and treatment on women's sexuality: a survey of Japanese patients. *Psycho-Oncology* 2008;**17**:901–907.
28. Degner LF, Kristjanson LJ, Bowman D *et al.* Information needs and decisional preferences in women with breast cancer. *J Am Med Assoc* 1997;**277**: 1485–1492.
29. Girgis A, Boyes A, Sanson-Fisher RW, Burrows S. Perceived needs of women diagnosed with breast cancer: rural versus urban location. *Aust N Z J Public Health* 2000;**24**:166–173.
30. Houts PS, Yasko JM, Kahn SB, Schelzel GW, Marconi KM. Unmet psychological, social, and economic needs of persons with cancer in Pennsylvania. *Cancer* 1986;**58**:2355–2361.
31. Liang LP, Dunn SM, Gorman A, Stuart-Harris R. Identifying priorities of psychosocial need in cancer patients. *Br J Cancer* 1990;**62**:1000–1003.
32. Hewitt ME, Bamundo A, Day R, Harvey C. Perspectives on post-treatment cancer care: qualitative research with survivors, nurses, and physicians. *J Clin Oncol* 2007;**25**:2270–2273.
33. Alfano CM, Rowland JH. Recovery issues in cancer survivorship: a new challenge for supportive care. *Cancer J* 2006;**12**:432–443.
34. Boyes A, Newell S, Girgis A, McElduff P, Sanson-Fisher R. Does routine assessment and real-time feedback improve cancer patients' psychosocial well-being? *Eur J Cancer Care (Engl)* 2006;**15**:163–171.
35. Aranda S, Schofield P, Weih L, Milne D, Yates P, Faulkner R. Meeting the support and information needs of women with advanced breast cancer: a randomised controlled trial. *Br J Cancer* 2006;**95**: 667–673.
36. Nilchaikovit T, Hill JM, Holland JC. The effects of culture on illness behavior and medical care. Asian and American differences. *Gen Hosp Psychiatry* 1993;**15**:41–50.
37. Nakane Y, Ohta Y, Radford M *et al.* Comparative study of affective disorders in three Asian countries. II. Differences in prevalence rates and symptom presentation. *Acta Psychiatr Scand* 1991;**84**:313–319.
38. Harrison JD, Young JM, Price MA, Butow PN, Solomon MJ. What are the unmet supportive care needs of people with cancer? A systematic review. *Support Care Cancer* 2009. DOI: 10.1007/s00520-009-0615-5.
39. Pozo C, Carver CS, Noriega V *et al.* Effects of mastectomy versus lumpectomy on emotional adjustment to breast cancer: a prospective study of the first year postsurgery. *J Clin Oncol* 1992;**10**:1292–1298.
40. Ganz PA, Schag AC, Lee JJ, Polinsky ML, Tan SJ. Breast conservation versus mastectomy. Is there a difference in psychological adjustment or quality of life in the year after surgery? *Cancer* 1992;**69**:1729–1738.
41. Bardwell WA, Natarajan L, Dimsdale JE *et al.* Objective cancer-related variables are not associated with depressive symptoms in women treated for early-stage breast cancer. *J Clin Oncol* 2006;**24**:2420–2427.
42. Ell K, Xie B, Wells A, Nedjat-Haiem F, Lee PJ, Vourlekis B. Economic stress among low-income women with cancer: effects on quality of life. *Cancer* 2008;**112**:616–625.

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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

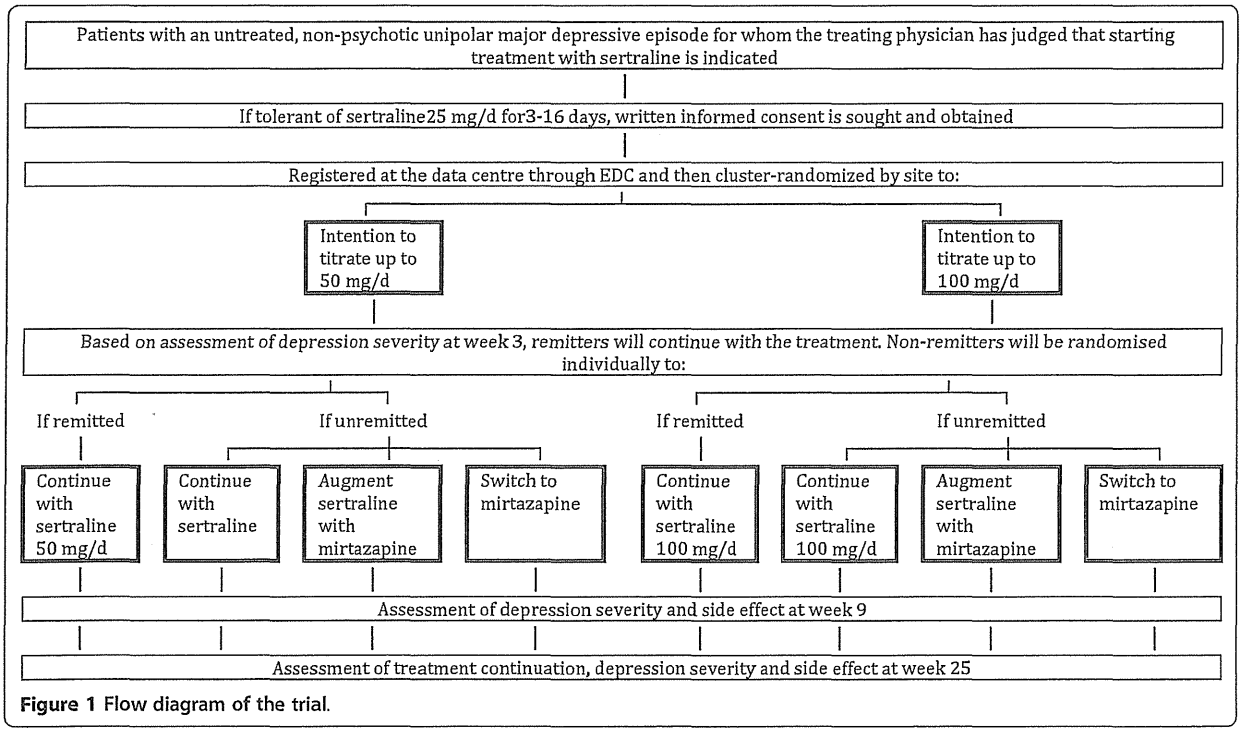

Figure 1 Flow diagram of the trial.

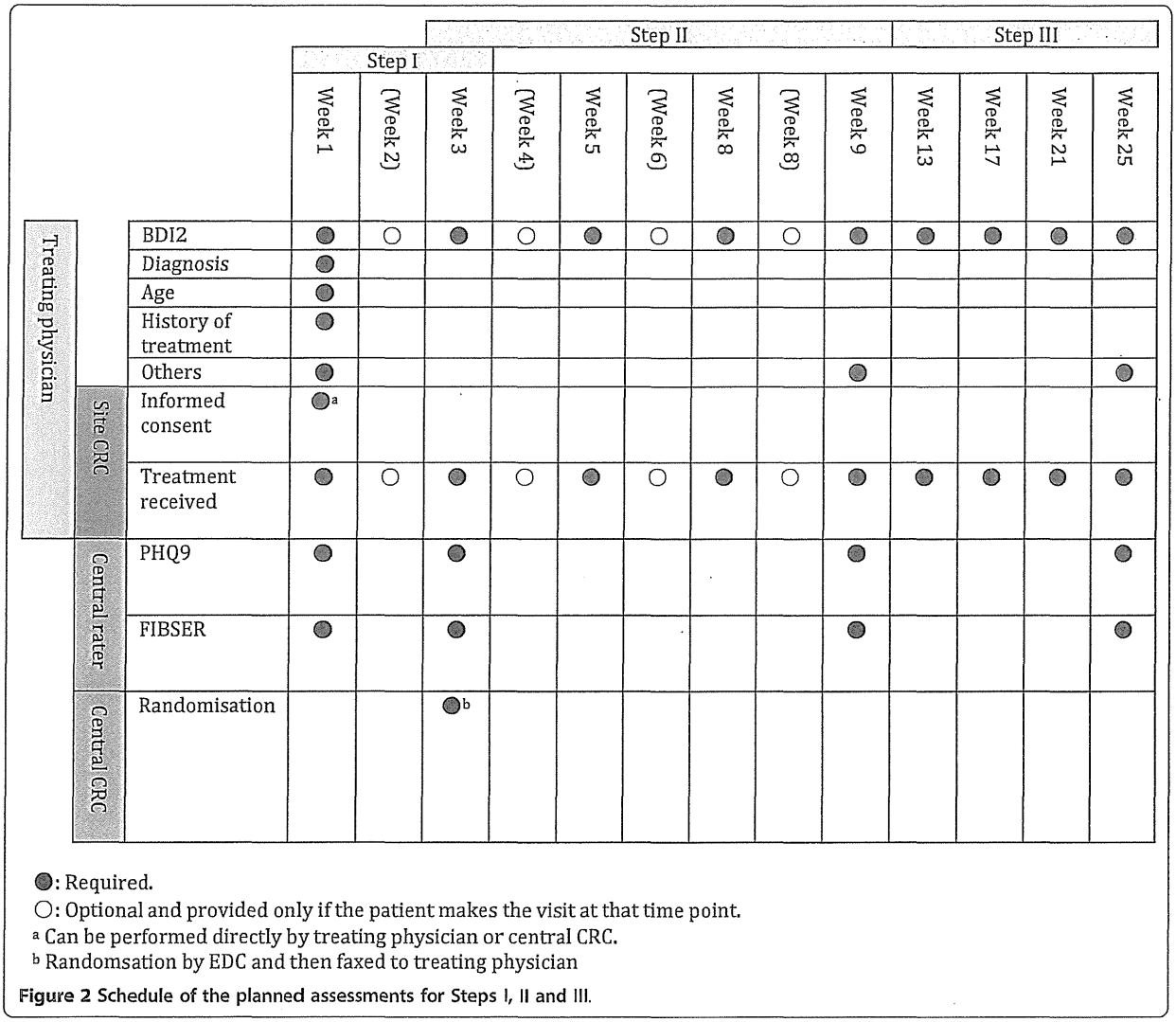

Figure 2 Schedule of the planned assessments for Steps I, II and III.

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