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Reliability and validity of the Japanese version of the Short-form Supportive Care Needs Survey Questionnaire (SCNS-SF34-J)

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Abstract

***Purpose*: Provision of supportive care to meet patients' individual needs is instrumental to enhancing their quality of life. We therefore need an appropriate assessment tool to measure such needs. The purpose of this study was to examine the psychometric property of the Japanese version of the Short-form Supportive Care Needs Survey questionnaire (SCNS-SF34-J).**

***Subjects and methods*: The forward–backward translation method was used to develop the Japanese version of SCNS-SF34, originally developed by Boyes *et al.* in Australia. Randomly selected ambulatory female patients with breast cancer participated in this study. They were asked to complete the SCNS-SF34-J and the European Organization for Research and Treatment of Cancer QLQ-C 30. The validity and the reliability of SCNS-SF34-J were evaluated statistically.**

***Results*: Complete data were available from 408 patients. A five-factor solution that accounted for 74.6% of the total variance was reproduced. The results confirmed the five-factor structure found in the original SCNS development study, consisting of Health system and Information needs, Psychological needs, Physical needs, Care and Support needs, and Sexuality needs. Cronbach's alpha coefficients, which are the measures of the internal consistency, were above 0.85 for all of five subscales. Significant correlations were also found for corresponding subscales in each of the instruments. The anticipated differences in supportive care needs between groups divided by the patient characteristics, such as the disease stage, were found to be significant.**

***Conclusion*: The results indicated that SCNS-SF34-J is a valid and reliable tool for assessing the supportive care needs of Japanese cancer patients.**
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Keywords: oncology; need; psychometric properties; quality of life; supportive care

Introduction

Quality of life (QOL), as much as survival, has been one of the prime goals in oncology. Numerous studies have reported many aspects of QOL, including physical, psychological, social, and spiritual, being diminished across the cancer trajectory [1–3]. Integration of supportive care into cancer therapeutics is crucial to enhance the patients' QOL [4].

Supportive care has been provided based on the patients' reporting of how often a problem occurred or how severe the problem was. But each patient experiences each problem individually, making the severity alone of a problem not the best or only indicator of a patient's supportive care needs. Alternatively, a patient's perception of the need for supportive care can be an important indicator [5]. Assessment of the patient-perceived needs would enable us to recognize what kind of help each of our patients requires directly, and to provide care meeting such requirement. We therefore need an appropriate assessment tool to measure such needs.

Various kinds of needs' assessment scales have been developed. A recent review compared the contents of 15 scales to assess patients' needs [6]. The domains generally covered by these scales were composed of needs related to the health status (symptoms and side effects, physical functioning, psychological well-being, spiritual well-being, cognitive, social occupational and global well being) and those related to satisfaction with health care (participation in care, information, accessibility

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and flexibility, continuity of care, and so on). The review concluded that none of the scales appears to cover all the relevant domains, and that each of the scales had been subjected to some, but not comprehensive, validity and reliability testing. To the best of our knowledge, none of the scales had been validated in Japanese subjects.

One of the promising tools identified by us is the Supportive Care Needs Survey (SCNS) questionnaire developed by Girgis' group in Australia [7]. One of the major advantages of this scale over others is its comprehensiveness with respect to the health status. SCNS has been identified to be one of the most comprehensive tools among the scales reported [6]; it provides, in particular, a broader coverage of domains related to satisfaction with health care. Another advantage is its robustly established validity and reliability. The review cited above also reported that SCNS is one of the two tools that has been subjected to empirical validation beyond that undertaken at the time of its initial construction by the original developers [6]. More recently, a 34-item short form survey (SCNS -SF34) has been developed, which covers the same five domains as those covered by the longer version described above [8].

The purpose of this study was to investigate the validity and the reliability of this scale in Japanese female outpatients with breast cancer, in order to develop new psycho-social interventions tailored to the patient-perceived needs.

Methods

Subjects

The study subjects were ambulatory female patients with breast cancer attending the outpatient clinic of the Oncology, Immunology and Surgery of Nagoya City University Hospital. We chose this population as the subjects, since breast cancer has been the most frequently diagnosed cancer in Japanese women since the mid-1990s [9] and it has been recognized that these patients frequently have unmet psychosocial care needs [10], and we are planning to examine the efficacy of a psychosocial intervention to be provided according to the patient-perceived needs on the patients' QOL.

The eligibility criteria for inclusion in the study were women (a) with a breast cancer diagnosis (b) 20 years of age or older, (c) informed of the cancer diagnosis, and (d) well enough to complete the survey questionnaire (0–3 on the Eastern Cooperative Oncology Group (ECOG) performance status). The exclusion criteria were patients with (a) severe mental or cognitive disorders or (b) inability to understand the Japanese language. We selected participants at random using a visiting list and a random number table for logistic reasons (to control the number of patients enrolled per day).

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 provision of a thorough explanation of the purpose and method of the study.

Procedure

After informed consent had been obtained, the patients were asked to complete the self-administered questionnaires described below at home and return them at the next day. In the case of inadequate answers, clarifications were sought over the telephone.

The Short-form Supportive Care Needs Survey questionnaire (SCNS-SF34)

SCNS is a self-administered instrument for assessing the perceived needs of patients with cancer. The original questionnaire, the Cancer Needs Questionnaire (CNQ), was developed in the early 1990s [11]. Based on a review of the CNQ and further testing with cancer patients, the long form of the SCNS (SCNS-LF59) was developed [7]. This included 59 items mapped to five domains of need: Psychological, Health system and information, Physical and daily living, Patient care and support, and Sexuality. Respondents are asked to indicate their level of 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]) [12]. SCNS-SF34 is the short form of the SCNS-LF59, consisting of 34 items covering the same five domains. The validity and reliability of the original SCNS-SF34 have been established [8]. Subscale scores are obtained by summing the individual items. This study was conducted with permission from the original authors.

The forward–backward translation method was used to develop the Japanese version. In the translation process, the items were first translated into Japanese by two translators and then back-translated into English by two other translators who had not seen the original English version. Bilingual fluency was required of all the translators to complete the translation. Next, the English back-translated items were compared with the originals. If a back-translated item did not agree with the original, the first translator performed a second translation and the second translator performed a second back-translation; this process

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was repeated until satisfactory agreement was reached.

EORTC QLQ-C 30

The European Organization for Research and Treatment of Cancer Quality of Life-C30 (EORTC QLQ-C 30) was used for comparative measurement; this is one of the most frequently used self-rating questionnaires to assess cancer patients' QOL [13]. It consists of 30 items and five multi-item function subscales plus global health status/ QOL subscales (physical, role, emotional, cognitive, and social function), four multi-item symptom subscales (fatigue, pain, nausea, and vomiting), and six separate items to assess the symptoms (dyspnea, sleep disturbance, appetite loss, diarrhea, and constipation) and the financial impact. The Japanese version of the EORTC QLQ-C 30 has been established [14].

Sociodemographic and biomedical factors

An *ad hoc* self-administered questionnaire was used to obtain information on the sociodemographic status, including the marital status, level of education, and employment status. Performance Status, as defined by theECOG, was evaluated by the attending physicians. All other medical information (clinical stage and anti-cancer treatment) was obtained from the patients' medical records.

Statistical analysis

The validity and the reliability of SCNS-SF34-J were evaluated statistically.

Factor validity was evaluated using principal components factor analysis with varimax rotation. The number of subscales was identified by Keiser's criterion (eigenvalue of 1.0 or greater). Representation of the same factor structure found in the original scale was expected. Coefficients of congruence were calculated to measure both the pattern and magnitude of similarities between the factor loading pattern in the original study conducted in Australia and that obtained in this study. The coefficient of congruence was calculated by summing the products of the paired loadings divided by the square root of the product of the two sums of the squared loadings. The possible range is 0–1, and higher scores indicated greater similarity. The factor loading pattern data in Australian cancer patients were provided by the developer and will be published elsewhere [8]; therefore, that information is not placed in this manuscript.

Convergent validity was explored by calculating Spearman's Rank correlation between the SCNS-SF34-J domains and EORTC QLQ-C 30 subscales. The consensus meeting was held in the study group to determine the hypothesis for convergent validity, during the study protocol development. As a result, predictions of the effect size of inter-instrument correlations between the scales made based on the results of the validation study for the short form of CNQ [15]. Although SCNS differs from its predecessor in several ways (some CNQ items are not included in the SCNS, some are rephrased, and some new items were included), these two scales assess many common domains of patient needs: both the scales share the Health information domain, Psychological domain, Physical and daily living domain, and the Patient care and support domain subscale. Thus, we predicted that the effect size of the correlations between each of the four common domains of CNQ, which are shared by SCNS and EORTC QLQ-C 30 would be replicated in this study. Therefore, we predicted that the Health system and information domain in SCNS-SF34-J would be moderately correlated with the EORTC QLQ-C 30 emotional function subscale, that the Psychological domain would be strongly correlated with the EORTC QLQ-C 30 emotional function subscale, and moderately correlated with the EORTC QLQ-C 30 subscales of global QOL, cognitive function, social function, fatigue, insomnia, appetite, and that the Physical and daily living domain would be strongly correlated with the EORTC QLQ-C 30 subscales of global QOL, physical function, fatigue, and moderately correlated with pain and insomnia subscales. Finally Patient care and support domain moderately correlated with EORTC QLQ-C 30 emotional function subscale. Strong and moderate correlations were defined as *Spearman's rank correlation coefficients* of over 0.50 and 0.30–0.50, respectively.

The dicriminant validity, that is, the ability of each of the SCNS-SF34-J domains to discriminate between subgroups of patients, was investigated. We hypothesized that patients with a poor physical condition (poor performance status score or advanced cancer) and those currently receiving aggressive anti-cancer treatment would express higher supportive care needs in all of the domains, except the Sexuality domain, than those in a better physical state. Also, younger patients may be expected to have more Sexuality needs than elderly patients. These hypotheses were examined using Mann–Whitney U tests.

The reliability of the scale was evaluated by calculating Cronbach's alpha coefficient, a measure of the internal consistency of the responses to a group of items. The minimum acceptable value for internal consistency is thought to be 0.70 [16].

A p value of less than 0.05 was adopted as the significance level in all of the statistical analyses, and all p values reported are two-tailed. All the statistical

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procedures were conducted using the SPSS 13.0J version software for Windows (SPSS Inc., 2004).

Results

Patient characteristics (Table 1)

A pool of 420 potential participants was identified for the study. Twelve patients were excluded: seven for refusing to participate, two because of cognitive disturbance, one because of very advanced disease, and two 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 (±SD) and median age of the study population was 56.1 (±12.1) and 55 years, respectively. The breast cancer registry developed by the Japanese Breast Cancer Society, the year 2004 report of which included 14 805 newly diagnosed patients throughout Japan, described the characteristics of the patients with primary breast cancer in Japan: 99.6% were female, the mean age of the patients was 57.1 years, and the most frequent clinical stage was I (33.1%), followed by II (41.1%) and III (8.5%); the characteristics of our present study population were similar. Thus, we consider that this population can be thought of as being representative of Japanese breast cancer patients.

Utility: missing data on the SCNS-SF34-J

For all questions on the SCNS-SF34-J, 75 responses were missing. Thus, we missed only 0.5% of the total data points (408 patients answering 34 items).

Factor validity (Table 2)

Factor analysis indicated a five-factor solution, which accounted for 74.6% of the total variance. The number of factors was consistent with the original, and the factor loading pattern almost replicated the original results, with the exception of only two items: 'Hospital staff attending promptly to your physical needs' and 'Hospital staff acknowledging, and showing sensitivity to, your feelings and emotional needs,' originally involved in the Patient care and Support need, loaded evenly on both Factors 1 and 2. The first 13 variables comprising needs related to treatment and information showed significant loading on Factor 1. The next 10 items related to emotional and coping needs loaded onto Factor 2. Five items related to needs associated with coping with physical symptoms and performing usual tasks and activities loaded on Factor 3. Another three items to assess needs related to health-care providers loaded on Factor 4. The remaining three items representing sexuality needs showed high loading on Factor 5. The coefficients of congruence ranged from 0.99 for the Health system and information domain to 0.95 for the Sexuality domain. Based on these results, we applied the same factor structure as that obtained in Australia to conduct the validation analysis. The name of each subscale is shown in Table 2.

Reliability (Table 3)

The Cronbach's alpha coefficient for the subscale ranged from 0.87 for Sexuality needs to 0.96 for Information needs.

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

Characteristic		N	(%)
Age	Mean: 56.1 (SD = 12.1) median: 55 (range, 27–89)		
Sex	Female	408	100.0
Marital status	Married	311	76.2
Job	Employed (full-time/part-time)	182	44.6
Clinical stage	0	24	5.9
	I	142	34.8
	II	148	36.3
	III	24	5.9
	IV	11	2.7
	Recurrence	59	14.5
ECOG performance status[a]	0	369	90.4
	1	33	8.1
	2	4	1.0
	3	2	0.5
History of anticancer treatment	Surgery	381	93.4
	Chemotherapy	180	44.1
	Radiation therapy	157	38.5
Days after diagnosis	Mean: 1039.8 (SD = 1352.7) median: 701 (range, 11–17915)		

[a]Eastern Cooperative Oncology Group.

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Table 2. Factor pattern for the items of the SCNS-SF34-J. Loadings after orthogonal rotation. ($n = 408$)

		Factor name and factor loadings[a]					
	Item number in the questionnaire and Item	Health system and information	Psycho-logical	Physical and daily living	Patient care and support	Sexuality	% patients endorsing[b]
28	Being informed about cancer which is under control or diminishing (that is, remission)	0.84					40.2
26	Being adequately informed about the benefits and side-effects of treatments before you choose to have them	0.84					35.8
27	Being informed about your test results as soon as feasible	0.83					37.5
25	Being given explanations of those tests for which you would like explanations	0.81					35.5
29	Being informed about things you can do to help yourself to get well	0.81					50.7
33	Being treated in a hospital or clinic that is as physically pleasant as possible	0.80					31.4
23	Being given written information about the important aspects of your care	0.77					34.6
32	Being treated like a person not just another case	0.76					39.5
24	Being given information (written, diagrams, drawings) about aspects of managing your illness and side-effects at home	0.73					35.0
34	Having one member of hospital staff with whom you can talk to about all aspects of your condition, treatment and followup	0.71					55.1
30	Having access to professional counselling (e.g. psychologist, social worker, counsellor, nurse specialist) if you, family or friends need it	0.66					45.1
21	Hospital staff attending promptly to your physical needs	0.57		0.37	0.48		24.3
22	Hospital staff acknowledging, and showing sensitivity to, your feelings and emotional needs	0.56		0.36	0.43		27.5
9	Fears about the cancer spreading		0.78				63.2
6	Anxiety		0.76				50.7
14	Feelings about death and dying		0.75				40.2
7	Feeling down or depressed		0.73				44.9
11	Uncertainty about the future		0.73				39.5
10	Worry that the results of treatment are beyond your control		0.71				48.5
8	Feelings of sadness		0.71				39.2
13	Keeping a positive outlook		0.69				34.6
12	Learning to feel in control of your situation		0.69				32.6
17	Concerns about the worries of those close to you		0.69				48.3
4	Work around the home			0.76			25.2
3	Feeling unwell a lot of the time			0.75			20.3
2	Lack of energy/tiredness			0.74			33.6
1	Pain			0.67			30.6
5	Not being able to do the things you used to do		0.50	0.55			29.4
19	More choice about which hospital you attend				0.76		24.0
18	More choice about which cancer specialists you see	0.43			0.72		24.0
20	Reassurance by medical staff that the way you feel is normal	0.42	0.39		0.63		33.3
15	Changes in sexual feelings					0.91	15.4
16	Changes in your sexual relationships					0.90	13.7
31	To be given information about sexual relationships					0.76	14.5
	Variance	26.08	21.43	11.65	7.92	7.49	
	Eigenvalue	17.51	3.47	1.96	1.29	1.12	
	Coefficients of congruence	0.99	0.98	0.96	0.96	0.95	

[a]Factor loadings for each item for main loading and for the items where a cross-loading >0.3 were demonstrated.
[b]Defines patients who rated 3 or more on the 5-point Likert scale (1 [No Need (Not applicable)], 2 [No Need (Satisfied)], 3 [Low Need], 4 [Moderate Need], 5 [High Need])).

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Table 3. Reliability and descriptive data of the SCNS-SF34-J ($n = 408$)

SCNS domain	♯ of items included	Cronbach's alpha coefficient	Number of unmet need patients endorsed in each domain[a]	
			Mean	Median
Health system and information	11	0.96	4.4	3
Psychological	10	0.96	4.4	4
Physical and daily living	5	0.90	1.4	0
Patient care and support	5	0.92	1.3	0
Sexuality	3	0.87	0.4	0

[a]Defines patients who rated 3 or more on the 5-point Likert scale (1 [No Need (Not applicable)], 2 [No Need (Satisfied)], 3 [Low Need], 4 [Moderate Need], 5 [High Need])).

Table 4. Convergent validity: correlation between SCNS-SF34-J and EORTC QLQ-C 30 examined using Spearman Rank Correlation ($n = 408$)

EORTC QLQ-C30[a]	SCNS domain				
	Health system and information	Psychological	Physical and daily living	Patient care and support	Sexuality
Global health status/QoL		−0.48	−0.54		
Physical functions			−0.56		
Role functions					
Emotional functions	−0.39	−0.59		−0.40	
Cognitive functions		−0.39			
Social functions		−0.55			
Fatigue		0.48	0.60		
Nausea/vomiting					
Pain			0.53		
Dyspnoea					
Insomnia		0.37	0.41		
Appetite loss		0.38			
Constipation					
Diarrhoea					
Financial problems					

Statistical results corresponded to only those hypothesized previously were shown. If the hypothesis was supported, the number was underlined. All of correlations between the scales were statistically significant.
[a]European Organization for Research and Treatment of Cancer (EORTC) Quality of Life-C30.

Convergent validity (Table 4)

Results of Spearman's rank correlation between SCNS-SF34-J subscales and the corresponding EORTC QLQ-C 30 scores are shown in the Table 4. Most of the hypotheses were supported by the results. Only two coefficients (between the Psychological domain in the SCNS SF34-J and the EORTC QLQ-C30 Social function, and between the Physical and daily living domain in the SCNS SF34-J and EORTC QLQ-C30 Pain subscale) were found to be strong, against our prediction.

Discriminant validity (Table 5)

Patients in poor physical condition perceived significantly higher supportive care needs in all of the domains, except Sexual needs, than those in better physical condition, as we had expected. Younger patients expressed needs related to sexual issues significantly more frequently than elderly patients, again as expected.

Prevalence of unmet need

Percentage of patients with each unmet needs was shown in Table 2. The most common unmet needs (rated 3 or more on the 5-point Likert scale) was 'Fears about the cancer spreading' (63.2%), following 'Having one member of hospital staff with whom you can talk to about all aspects of your condition, treatment, and follow-up' (55.1%). The prevalence of top 10 unmet needs was over 40%, and all of these unmet needs were related to Health system and information domain or Psychological domain. The mean and median number of unmet needs was demonstrated in Table 3.

Discussion

Provision of supportive care to meet patients' individual needs is instrumental in enhancing their QOL. An appropriate assessment tool should be used to measure such needs in both research and clinical practice. The results of this study proved

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Table 5. Discriminant validity: differences in SCNS-SF34-J scores between patient subgroups examined using Mann–Whitney *U*-test

Group			SCNS domain									
			Health system and information		Psychological		Physical and daily living		Patient care and support		Sexuality	
		N	*U*[a]	*p*[b]	*U*	*p*	*U*	*p*	*U*	*p*	*U*	*p*
Age	>66	90									11296	< 0.01
	≤65	318										
Performance Status	≥1	39	4289.0	< 0.01	3731.0	< 0.01	3352.0	< 0.01	3975.0	< 0.01		
	0	369										
Treatment	Some	115	12423.5	< 0.01	11396.5	< 0.01	11429.5	< 0.01	13083.0	< 0.01		
	None	293										
Disease stage	Advanced	70	7844.5	< 0.01	7314.0	< 0.01	8919.0	< 0.01	7613.0	< 0.01		
	Non-advanced	338										

Statistical results corresponded to only those hypothesized previously were shown.
[a]Mann–Whitney *U* value.
[b]*p* value.

the sufficient reliability and validity of the Japanese version of SCNS-SF34-J.

The factor analysis reproduced an almost identical factor loading pattern as that of the original version developed in Australia. The high coefficients of congruence proved the applicability of the five-factor structure found in the SCNS SF-34 development study, consisting of Health system and Information needs, Psychological needs, Physical needs, Care and Support needs, and Sexuality needs, to this study population. High Cronbach's alpha coefficients, above 0.85 in all domains, indicated the structural reliability of each subscale in the Japanese version.

Construct validity of these five subscales was also supported by the results of this study. Convergent validity was proved by the findings that corresponding symptom items in each of the instruments were significantly correlated. The results of the discriminant validity testing proved our hypotheses that, in general, patients in poor physical condition would perceive higher needs in all of domains except sexual needs, and that the sexual needs would be associated with patients' age. Domains included in the SCNS were so unique that we could not investigate the concurrent validity, as no gold standard instruments exist.

We shall report on the factors correlated with each supportive care need using current dataset elsewhere. Further research should be conducted to examine whether assessment of the supportive care needs of patients using this scale might contribute to better patient outcomes. Some randomized controlled trials conducted to investigate the efficacy of provision of psychosocial support based on needs questionnaires have been reported [17,18]. These studies indicate that psychosocial intervention provided according to the patients' needs may be beneficial, particularly in patients with high need or high distress levels.

Cautions must be exercised in interpreting the results of this study due to the following reasons. Supportive care needs can be influenced by the cultural background. We did not investigate whether there might be any other supportive care domains that might be specific to Japanese patients that were not included in the SCNS developed in Australia. Since this study was conducted on patients with specific characteristics, care must be taken when applying the study results to those with other characteristics. Third, the sensitivity to the changes in supportive care needs was not investigated in this study.

These limitations notwithstanding, this study has laid the foundation for better care based on patients' perceived supportive care needs in Japanese cancer patients.

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This study was approved by the Institutional Review Board and Ethics Committee of Nagoya City University Graduate School of Medical Sciences, Japan.

Written informed consent was obtained from each of the patients after provision of a thorough explanation of the purpose and method of the study.

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Cancer patients' reluctance to discuss psychological distress with their physicians was not associated with underrecognition of depression by physicians: A preliminary study

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ABSTRACT

Objective: To investigate the association between cancer patients' reluctance for emotional disclosure to their physician and underrecognition of depression by physicians.

Methods: Randomly selected ambulatory patients with lung cancer were evaluated by the Hospital Depression and Anxiety Scale (HADS), and those with scores over the validated cutoff value for adjustment disorder or major depressive disorder were included in this analysis. The data set included the responses to the 13-item questionnaire to assess four possible concerns of patients in relation to emotional disclosure to the treating physician ("no perceived need to disclose emotions," "fear of the negative impact of emotional disclosure," "negative attitude toward emotional disclosure," "hesitation to disturb the physician with emotional disclosure"). The attending physicians rated the severity of depression in each patient using 3-point Likert scales (0 [*absent*] to 2 [*clinical*]). Depression was considered to be underrecognized when the patients had a HADS score above the cutoff value, but in whom the depression rating by the attending physician was 0.

Results: The HADS score was over the cutoff value in the 60 patients. The mean age was 65.1 ± 10.0, and 82% had advanced cancer (Stage IIIb or IV or recurrence). Depression was underrecognized in 44 (73%) patients. None of the four factors related to reluctance for emotional disclosure was associated with the underrecognition of depression by the physicians. None of the demographic or cancer–related variables were associated with depression ‡ underrecognition by physicians.

Significance of results: The results did not support the assumption that patients' reluctance for emotional disclosure is associated with the underrecognition of depression by physicians.

KEYWORDS: Oncology, Communication, Psycho-Oncology, Depression, Quality of life

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INTRODUCTION

Cancer patients frequently experience psychological distress, especially depression (McDaniel et al., 1995). Because depression interferes with the quality

Depression Rating by Patients

The Hospital Anxiety and Depression Scale (HADS) was used to evaluate the level of depression (Zigmond & Snaith, 1983). This questionnaire consists of a seven-item anxiety subscale and a seven-item depression subscale. It assesses the patients' mental status over the preceding week. We have previously established the reliability and validity of the Japanese version of this questionnaire in cancer patients (Kugaya et al., 1998). The optimal cutoff point for screening of patients with adjustment disorder or major depressive disorder and with major depressive disorder was >10 and >20, respectively (Kugaya et al., 1998).

Sociodemographic and Medical Factors

An *ad hoc* self-administered questionnaire was used to obtain information on the sociodemographic status, including marital status, level of education, and employment status. Performance status as defined by the Eastern Cooperative Oncology Group (ECOG) was evaluated by the attending physicians. All other medical information (clinical stage and anti-cancer treatment) was obtained from the patients' charts.

Depression Rating by the Attending Physicians

An attending physician rated the severity of depression in each patient using a 3-point Likert scale (0 [*absent*], 1 [*present but not interfering with daily life (care not needed)*], 2 [*present and interfering with daily life (care needed)*]) during or just after the patients' visit to the outpatient clinic.

Definition of Underrecognition of Depression

Depression was considered to be underrecognized when the patients had a HADS score above the cutoff value for screening of patients with adjustment disorder or major depressive disorder but in whom the depression rating by the attending physician was 0.

Statistical Analysis

The presence or absence of underrecognition was entered into the analyses as the dependent variable. Univariate analyses were carried out to determine the potential correlated factors. Intergroup comparisons of categorical and continuous variables were conducted using the chi-squared test, Fisher's exact test, and the unpaired *t* test, respectively.

RESULTS

Patient Characteristics

Data were available for 60 cancer patients (Table 1). The mean age was 65.1 years (*SD*, 10, range, 43–83) and the mean number of days after the diagnosis was 263 (*SD*, 380, range, 24–2,226). Of all the patients, 78% were male, and 82% had advanced cancer (Stage IIIb or IV or recurrence).

Prevalence of Underrecognition of Depression

Depression was underrecognized by the physicians in 44 (73%) patients (Table 2). There were no significant difference in rate of depression underrecognition by physicians between patients with adjustment disorder level distress and those with major depression level distress ($\chi^2 = 0.09$, $df = 1$, $p = .76$).

Factors Correlated with Underrecognition of Depression by the Physicians

Univariate analyses revealed that none of the factors related to the reluctance for emotional disclosure was associated with the underrecognition of depression by the physicians (Table 3). None of the demographic and cancer–related variables were associated with the underrecognition of depression.

Table 1. *Demographical and Clinical Characteristics of Patients (N = 60)*

Sample characteristic	*N*	%	
Age (year)			mean: 65.1 ± 10 (range, 43–83), median: 65.5
Sex			
Male	47	78	
Clinical stage			
I-IIIA	11	18	
IIIB	22	37	
IV	26	43	
Recurrent	1	2	
Days after diagnosis			mean: 263 ± 380 (range, 24–2226), median: 140
Performance status			
0	47	78	
1	9	15	
2	4	7	
Anti-cancer treatment within a month			
Surgery	0	0	
Chemotherapy	43	72	
Radiation therapy	7	12	

factors, system and environmental factors, and interactions between these factors might be play a role in depression recognition. These should be taken into account in future studies.

We acknowledge that the results must be interpreted with caution for several reasons. First, although the questionnaire used to investigate the reluctance for emotional disclosure has been validated, there remains the possibility that the attitudes assessed using the questionnaire in this study might not be concordant with the actual behavior of the patients. Second, depression was not assessed by psychiatric interviews, such as the Structured Clinical Interview for DSM-IV-TR, which is thought to be a gold standard to diagnose depression in patients. Also the definition of underrecognition of depression in the patients was *post hoc*. Third, only two physicians were included in this study. Fourth, this was conducted in a university hospital and included Japanese outpatients with lung cancer. These facts may limit the generalizability.

This study indicated, consistent with the many previous reports, a high prevalence and frequent underrecognition of depression among cancer patients. Because of these limitations, we should still be cautious in assuming that the reluctance of patients for emotional disclosure may not contribute significantly to underrecognition of depression in clinical practice. To resolve this critical problem, further investigation into this phenomenon and its associated factors and barriers is warranted.

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Efficacy, tolerability and side-effect profile of fluvoxamine for major depression: meta-analysis

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on behalf of the Meta-Analysis of New Generation Antidepressants (MANGA) Study Group

Abstract

Fluvoxamine, one of the oldest selective serotonin reuptaking inhibitors, is commonly prescribed to patients with major depression. Several studies have reviewed the efficacy and tolerability of fluvoxamine for the treatment of major depression. However, these reviews are outdated, have not been systematic and/or suffered from several methodological weaknesses. We conducted a systematic review to synthesize the best available evidence on the efficacy of fluvoxamine for adult patients suffering from major depression in comparison with other active antidepressive agents. Relevant randomized controlled trials were identified through a comprehensive search. The primary outcome was a relative risk of response, and the secondary outcome was a relative risk of remission. Tolerability and side-effect profile were also examined. Fifty-three trials were included. There were no large differences between fluvoxamine and any other antidepressants in terms of efficacy and tolerability. There is evidence of differing side effect profiles, especially when comparing gastrointestinal side effects between fluvoxamine and tricyclics. Clinicians should focus on practically or clinically relevant differences including those in side-effect profiles.

Key words

fluvoxamine; antidepressive agents; major depressive disorder; meta-analysis

Introduction

Major depression is the third leading cause of burden among all diseases of mankind after lower respiratory infections and HIV/AIDS in the year 2002, accounting for 4.5% of the total human suffering. Moreover, it is expected to show a rising trend during the coming 20 years (WHO, 2006). This condition is associated with a marked personal, social and economic morbidity, loss of functioning and productivity and creates significant demands on service providers in terms of workload (NICE, 2004). In the United States, Greenberg, *et al.* (2003) estimated the economic burden of depression to be just over $83 billion in 2000, of which $26 were direct treatment costs, $5 billion were suicide-related costs and $52 billion were workplace costs (Greenberg, *et al.*, 2003). They also suspect that these figures are still underestimates of the true economic burden of the disease, such as burden on family members and caregivers, cost of lost productivity while at work and cost associated with those who remain untreated (Greenberg and Birnbaum, 2005).

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Although a number of effective interventions are available for the treatment of major depression including pharmacotherapy and psychotherapy, antidepressants (ADs) play an important role in its treatment (American Psychiatric Association, 2000; Ellis, 2004). Following the introduction of tricyclics (TCAs) in the 1950s, the number of available ADs has increased, such as heterocyclics, monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs: venlafaxine, duloxetine and milnacipran) and other newer agents (mirtazapine, reboxetine and bupropion).

In many Western countries, during the last 20 years, ADs consumption has dramatically risen, mainly because of the increasing consumption of SSRIs and newer ADs, which have progressively become the most commonly prescribed ADs (Ciuna, *et al.*, 2004; Guaiana, *et al.*, 2005). SSRIs are generally better tolerated than TCAs (Barbui, *et al.*, 2000), and there is evidence of similar efficacy (Anderson, *et al.*, 2000; Geddes, *et al.*, 2000; Williams, *et al.*, 2000). However, head-to-head comparison provided contrasting findings. Amitriptyline, for example, may have an edge over SSRIs in terms of efficacy (Guaiana, *et al.*, 2003), and individual SSRIs and SNRIs may differ in terms of efficacy and tolerability (Cipriani, *et al.*, 2006; Gartlehner, *et al.*, 2007; Puech, *et al.*, 1997; Smith, *et al.*, 2002).

Given that the most recent available evidence refers to the SSRIs as a homogeneous group (Arroll, *et al.*, 2005; Geddes, *et al.*, 2000; Hansen, *et al.*, 2005), it is still unclear how each of SSRIs or newer agents compares with other ADs in terms of effects and side effects.

Fluvoxamine is a potent and specific SSRI, which has been available since 1983 in many countries including Europe and Japan as ADs (87 countries and regions as of 2006). It is well absorbed after oral administration and is widely distributed in the body. Plasma protein binding of fluvoxamine (77%) is low, compared with that of other SSRIs. Not only is fluvoxamine structurally quite different from the TCA, heterocyclics and other class of ADs, considerable chemical differences exist between the various SSRIs. For example, fluvoxamine is the only monocyclic SSRI and belongs to the 2-aminoethyloximethers of aralkylketones (Claassen, *et al.*, 1977; Fuller and Wong, 1987). Therefore, some differential clinical potency may be expected not only between the drugs classes but also among the SSRIs.

A group of researchers, therefore, agreed to join forces under the rubric of the Multiple Meta-Analyses of New Generation Antidepressants (MANGA) Study to systematically review all available evidence for each specific newer antidepressant. We have till now completed an individual review for fluoxetine (Cipriani, *et al.*, 2006).

There exist in the literature two systematic reviews on fluvoxamine, but they are already outdated, suffer from several methodological weaknesses and did not attempt meta-analytic summaries (Burton, 1991; Ware, 1997). Burton (1991) reviewed 17 double-blind comparative studies between fluvoxamine and other ADs in depressed patients. The review, however, was limited to published materials (publication bias not eliminated) and study inclusion criteria, data sources and validity assessment were not reported. Ware (1997) reviewed 31 controlled trials of fluvoxamine in the pharmacotherapy of depression. However, the review was limited to published materials and English language articles, and validity assessment of the included studies was not reported. Neither has provided meta-analytic summaries.

In this article, we report a systematic quantitative review of randomised controlled trials (RCTs) concerning the effectiveness and tolerability of fluvoxamine in the acute phase treatment of major depression in comparison with tricyclic or heterocyclic ADs, SSRIs (fluoxetine, sertraline, paroxetine, citalopram and escitalopram), SNRIs (venlafaxine, duloxetine and milnacipran) and MAOIs or newer agents (mirtazapine, bupropion and reboxetine).

Methods

This review was conducted within the overall collaboration framework of the MANGA study and according to the same agreed-on methodology, the details of which have already been given in Cipriani, *et al.* (2006).

Study inclusion criteria

The trials we included in the review conducted a random assignment procedure of study participants to intervention or control group and compared fluvoxamine with all other active ADs in the acute phase treatment of major depression in patients aged 18 or older. The diagnosis must have been made based on established operationalised diagnostic criteria such as DSM-IV(American Psychiatric Association, 1994). Trials in depressive patients with primary diagnosis of other Axis I or Axis II disorders or a serious concomitant medical illness were excluded. We excluded the studies including depression with psychotic features and those in which more than 20% of the participants suffered from bipolar depression. We did not include trials in which fluvoxamine was used as an augmentation strategy.

Study quality was assessed by appraisal of method of concealment of allocation and blinding based on the criteria described in the Cochrane Handbook (Higgins and Green, 2005). The processes of trial selection and quality assessment were each performed by two independent reviewers. Where disagreement occurred this was resolved by discussion.

Data sources

RCTs were initially identified on June 2, 2006 by searching the Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Registers (CCDANCTR-Studies and CCDANCTR-References), which contains the results of regularly updated searches of the Cochrane Central Register of Controlled Trials on the Cochrane Library, MEDLINE, EMBASE, CINAHL, sycINFO, PSYINDEX and LILACS and hand searches of major psychiatric, medical journals and conference proceedings. Trial databases (e.g., the Medicines and Healthcare products Regulatory Agency in the United

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Kingdom) and ongoing trial registers (e.g., http://www.clinicaltrials.gov in the United States) in North America, Europe, Japan and Australia, were hand searched for published, unpublished and ongoing RCTs. Pharmaceutical companies and experts in this field were asked if they knew of any study which possibly met our inclusion criteria. Reference lists of the included studies, previous systematic reviews and major textbooks of affective disorder were checked for published reports and citations of unpublished research. The review was not limited to English language articles. Search terms used were as follows: Diagnosis or Keyword = Depress* or Dysthymi* or 'Adjustment Disorder*' or 'Mood Disorder*' or 'Affective Disorder' or 'Affective Symptoms' and Intervention or Free-text = fluvoxamine.

Outcome measures

The trial phase was subdivided as early phase (between 1 and 4 weeks) and acute phase treatment (between 6 and 12 weeks) because one systematic review suggested that SSRIs begin to have observable beneficial effects in depression during the first week of treatment (Taylor, *et al.*, 2006). We set response at the end of acute phase as the primary outcome of this systematic review, defined as a reduction of at least 50% on the Hamilton Rating Scale for Depression (HAM-D; Hamilton, 1960) or Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979). We included remission as the secondary outcome, which showed a score of 7 or less on the 17-item HAM-D (Furukawa, *et al.*, 2007a) and of 8 or less for all the other longer versions of HAM-D. The original authors' definitions of response and remission were not used in this review to avoid possible outcome reporting bias (Furukawa, *et al.*, 2007b).

Tolerability of the treatment was evaluated using the number of patients dropping out of the trial for any reason and because of side effects. Descriptive data regarding side-effect profile were extracted from all available studies.

Two reviewers independently extracted data. When disputes arose resolution was attempted by discussion.

Statistical analysis

Data were entered into Review Manager 4.2 software (The Nordic Cochrane Centre, 2003) twice using the duplicate data entry facility. All comparisons were performed between fluvoxamine and the comparator ADs as a class and each individual ADs as well.

For dichotomous outcomes of response and remission, relative risks (RRs) were calculated using random effects model because random effects model RR has been shown to be superior in clinically interpretability and external generalisability than fixed effects models and odds ratios or risk differences (Furukawa, *et al.*, 2002). If a statistically significant difference was found, a number needed to treat (NNT) was calculated. Heterogeneity between studies was assessed by the I-squared statistics and Q-statistics (I-squared equal to or more than 50% and were considered indicative of heterogeneity and P values smaller than 0.1) and by visual inspection of the results in the forest plots. If significant heterogeneity was suspected, sources were investigated. We performed intention-to-treat analysis assuming that those who dropped out – from whatever group – had an unfavourable outcome (e.g., failure to respond to treatment). When data on dropouts were included, usually by way of the last-observation-carried-forward (LOCF) method, the LOCF data were used. When dichotomous outcomes were not reported, we converted continuous outcome data expressed as mean and standard deviation (SD) into response and remission rates using the validated imputation methods (Furukawa, *et al.*, 2005). When RCTs failed to provide SDs of their continuous outcome measures, we substituted them by those reported in other studies in the review (Furukawa, *et al.*, 2006). Data from all included studies were entered into a funnel plot (trial effect against trial size) in an attempt to investigate the likelihood of overt publication bias (Egger, *et al.*, 1997).

For the primary outcome, we performed subgroup analyses for treatment settings (e.g., psychiatric inpatients or outpatients or primary care patients) because it is possible that results obtained from either of these settings may not be applicable to the other settings (US Department of Heath and Human Services: Agency for Health Care Policy and Research, 1993).

A small number of sensitivity analyses were also planned *a priori*: excluding studies funded by or with at least one author affiliated with a pharmaceutical company marketing fluvoxamine because it has been reported that funding strongly affects outcomes of clinical trials (Buchkowsky and Jewesson, 2004; Perlis, *et al.*, 2005). Examination of 'wish bias' was done by comparing fluvoxamine as investigational drug versus fluvoxamine as a comparator as there is evidence to suspect that a new antidepressant might perform worse when used as a comparator than when used as an experimental agent (Barbui, *et al.*, 2004) and excluding trials for which the response and remission rates had to be calculated based on the imputation method.

With regard to response and remission, a P value less than 0.01 and a 99% confidence interval (CI) were considered statistically significant to place more emphasis on type I error than type II error because the robust differences between ADs were considered valuable for clinical practice (Cipriani, *et al.*, 2006). However, we set the α-level to 0.05 and calculated a 95% CI for outcomes of tolerability because we should be alert to any probable existence of harmful effects.

Descriptive data regarding side-effect profile were extracted from all available studies. Only studies reporting the number of patients experiencing individual side effects were retained. Because of variety in description of side effects, terms describing similar side effects were combined, such as 'dry mouth', 'reduced salivation' and 'thirst' which were combined into 'Dry mouth'. All side effect categories were then grouped by organ system, such as neuropsychiatric, gastrointestinal, respiratory, sensory, genitourinary, dermatological and cardiovascular in accordance with the advice of the previous study (Mottram, *et al.*, 2006).

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Results

Description of studies

Initially, we identified 152 references considered to be relevant for our review (Figure 1). Of these, five trials were unpublished, and one trial written in Finnish was not retrieved and has been placed in the list of studies awaiting assessment. The remaining 146 references were retrieved for more detailed evaluation. Of these trials, 40 references were excluded because of not meeting the inclusion criteria; 53 because of multiple publications. Finally, 53 RCTs (59 comparisons) meeting the inclusion criteria were included. Table 1 summarises descriptive information on these trials.

Of the 53 included studies, 48 RCTs (50 comparisons) contributed usable data for the efficacy analysis and 49 RCTs (53 comparisons) for the tolerability analysis. Four studies only reported the non-clinical data that lacked adequate information for meta-analysis, and we were not able to obtain further data because the authors were not contactable by any means. There were 29 studies comparing fluvoxamine with TCAs, five studies with heterocyclics, 10 with SSRIs, three with SNRIs, four with newer ADs, and one study comparing fluvoxamine with sulpiride and one with amitriptyline, doxepine and paroxetine. The majority of the studies (38 RCTs) recruited less than 100 participants. Duration of treatment was relatively brief with a mean of 5.5 weeks (range 2–10 weeks). In total, 18 trials enrolled inpatients, six both inpatients and outpatients, 21 outpatients, two at general practice setting, whereas the remaining studies were unclear. In 24 studies, some elderly subjects (over 65 years old) were included, but the actual number of elderly persons was not reported in most of the trials. One trial was for elderly patients only, whereas seven studies did not include any elderly patients.

The great majority of the identified studies (43) used the HAM-D as a primary or secondary outcome measure, whereas a minority of studies used the MADRS and Clinical Global Impression scale. Among the studies reporting the total number of dropouts because of any reason (49), 42 reported the number of dropouts because of side effects. In all, 40 studies reported the number of patients experiencing individual side effects.

Description of concealment of allocation was unclear in all studies. The majority of studies were reported to be double blind. For six studies the blinding was unclear, and five were open-label trials. Outcomes concerning response and remission were available in 16 and nine studies, respectively, without using the imputation method.

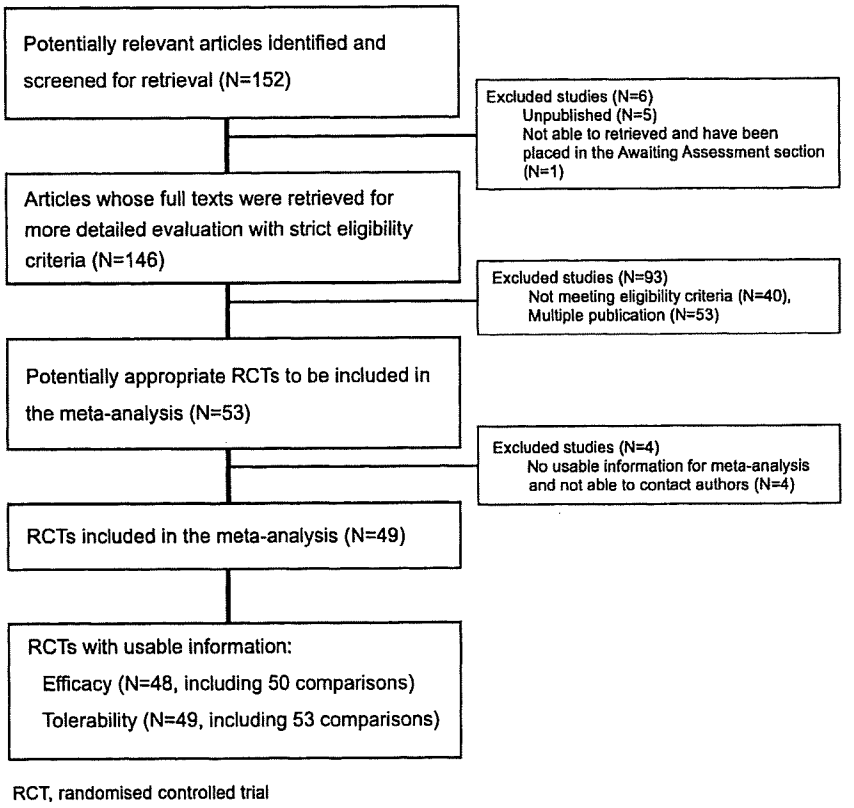

Figure 1 Trial flowchart for the included studies.

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Table 1 Summary of included Studies

Randomized Controlled trial[a]	Comparator	Follow up (wk)	Treatment setting	Diagnostic Criteria	Sample Size FLVX	Sample Size Comp.	Baseline score (SD) Outcome measure	Baseline score (SD) FLVX	Baseline score (SD) Comp.	Dose (mg) FLVX range	Dose (mg) FLVX mean (SD)	Dose (mg) Comp. range	Dose (mg) Comp. mean (SD)	Quality[b] allocation concealment	Quality[b] Double blind	Imputing for dicholomous data at acute phase response	Imputing for dicholomous data at acute phase remission	Funded by the company marketing	FLVX as Investigational or comparator drug
Berge-Schaapveld et al, 1995	Amitriptyline	8	GP	DSM-III-R	13	10	HAMD-17	25.7 (1.7)	24.4 (2.8)	100		150		B	C	No	No	FLVX	unclear
Harris et al, 1991	Amitriptyline	6	Out	DSM-III	35	34	HAMD-17	22.7 (5.0)	22.8 (4.5)	50-150	115 (n.s.)	50-150	99 (n.s.)	B	A	Yes	Yes	FLVX	Investigational
Kostiukova et al, 2003	Amitriptyline	6***	In	ICD-10	30	30	HAMD-17	26.3 (3.3)	25.7 (9.9)	50-300	187.8 (56.0)	50-250	200.0 (47.5)	B	B	Yes	Yes	Unclear	Investigational
Murasaki et al, 1998	Amitriptyline	4	In and Out	DSM-III-R	113	122	HAMD-17	22.9 (6.1)	23.6 (5.9)	50-150	86.0 (38.4)	50-150	76.3 (33.2)	B	A	No	Yes	FLVX/Comp.	Investigational
Rechlin, 1994	Amitriptyline	2	In	DSM-III-R	8	8	n.s.	n.s.	n.s.	150		150		B	B	—	—	Unclear	Unclear
	Doxepin					8			n.s.			150							
	Paroxetine					8			n.s.			20							
Remick et al, 1994	Amitriptyline	7	Out	DSM-III-R	16	17	HAMD-17	23.8 (2.7)	23.5 (2.6)	50-300	175 (n.s.)	50-300	135.0 (n.s.)	B	A	Yes	Yes	FLVX	Investigational
Rota et al, 2005	Amitriptyline	6	In	DSM-IV	n.s.	n.s.	n.s.	n.s.	n.s.	200		150		B	B	—	—	Unclear	Unclear
Coleman & Block, 1982	Chlorimipramine	4	In	Feighner	50	48	HAMD-17	25.4 (n.s.)	24.6 (n.s.)	150-300	n.s.	150-300	n.s.	B	A	Yes	Yes	FLVX	Investigation al
De Wilde et al, 1983	Chlorimipramine	6	Out	Feighner	22	21	HAMD-17	23.4 (n.s.)	24.2 (n.s.)	100-300	300 (n.s.)	50-150	144.0 (n.s.)	B	A	Yes	Yes	FLVX	investigational
Dick & Ferrero, 1983	Chlorimipramine	4	In	Feighner	17	15	HAMD-15	26.4 (4.8)	24.4 (3.0)	150	130.9 (19.0)	150	132.8 (16.8)	B	A	No	No	Unclear	investigational
Ottevanger, 1995	Clomipramine	4	In	Feighner	20	20	HAMD-17	26.4 (4.7)	25.7 (3.6)	100-300	204 (n.s.)	50-150	106.0 (n.s.)	B	A	Yes	Yes	FLVX	Investigational
Zoher et al, 2003	Clomipramine	8	In	DSM-III-R	44	42	HAMD-17	30.6 (4.8)	30.5 (3.8)	100-250	185.5 (55.1)	100-250	147.7 (57.5)	B	A	No	Yes	FLVX	investigational
Nathan et al, 1990	Desipramine	4	In	DSM-III	20	20	HAMD-17	24.8 (5.8)	24.3 (3.9)	n.s.	203.0 (70.0)	n.s.	206.0 (82.0)	B	A	Yes	Yes	FLVX	investigational
Tourigny Rivard et al, 1996	Desipramine	10	Unclear	DSM-III-R	22	25	HAMD-17	24.1 (n.s.)	24.3 (n.s.)	-150	135 (n.s.)	-150	121.0 (n.s.)	B	A	Yes	Yes	Unclear	Investigational
Mullin et al, 1986	Dothiepin	6	Out	DSM-III	37	36	HAMD-17	21.3 (n.s.)	21.1 (n.s.)	100-300	n.s.	75-225	n.s.	B	A	Yes	Yes	FLVX	Investigational
Rahman et al, 1991	Dothiepin	6	In	DSM-III	26	26	MADRS	35.6 (4.6)	34.9 (3.8)	100-200	157.0 (n.s.)	100-200	159.0 (n.s.)	B	A	Yes	Yes	FLVX	Unclear
Amore et al, 1989	Imipramine	4	In	DSM-III	15	15	HAMD-21	25.7 (n.s.)	28.8 (n.s.)	100-150	123.3 (25.8)	100-150	128.7 (25.8)	B	A	Yes	Yes	FLVX	Investigational
Bramanti et al, 1988	Imipramine	4	Unclear	DSM-III	30	30	HAMD-21	30.5 (7.5)	27.2 (6.8)	100-150	n.s.	100-150	n.s.	B	A	Yes	Yes	FLVX	Investigational
Brown et al, 1986	Imipramine	6	Out	DSM-III	33	17	n.s.	n.s.	n.s.	200-300	214.0 (63.8)	150-225	n.s.	B	A	—	—	Unclear	Investigational
Cassano et al, 1986	Imipramine	4	In and Out	DSM-III	169	161	HAMD-17	25.6 (n.s.)	25.9 (n.s.)	50-300	134.6 (n.s.)	50-300	144.2 (n.s.)	B	A	Yes	Yes	FLVX	Investigational
Claghorn et al, 1996	Imipramine	6	Out	DSM-III-R	50	50	HAMD-21	26.1 (3.5)	25.9 (3.5)	50-150	92.7 (46.9)	80-240	136.4 (71.7)	B	A	Yes	Yes	FLVX	Investigational
Fabre et al, 1996	Imipramine	6	Out	DSM-III-R	50	50	HAMD-21	27.7 (n.s.)	26.5 (n.s.)	50-150	117.0 (n.s.)	80-240	160.0 (n.s.)	B	A	No	Yes	FLVX	Investi gational
Feighner et al, 1989	Imipramine	6	In	DSM-III	31	36	HAMD-17	25.0 (n.s.)	27.2 (n.s.)	150-300	145; median	150-300	159; median	B	A	Yes	Yes	Unclear	Inv estigational
Guy et al, 1984	Imipramine	6	In	DSM-III	17	19	HAMD-17	24.6 (n.s.)	25.1 (n.s.)	150-225	n.s.	150-225	n.s.	B	A	Yes	Yes	Unclear	Investigational
Itil et al, 1983	Imipramine	4	Out	RDC	22	25	HAMD-16	20.3 (3.0)	21.9 (4.2)	50-300	101.0 (45.0)	50-300	127.0 (46.0)	B	A	Yes	No	FLVX	Investigational
Koetsier et al, 2002	Imipramine	4	In	DSM-IV	27	25	HAMD-17	27.0 (5.4)	27.7 (5.1)	n.s.	201.0 (86.5)	n.s.	220.7 (93.4)	B	A	Yes	Yes	Unclear	Unclear
Lydiard et al, 1989	Imipramine	6	Out	DSM-III	18	18	HAMD-17	24.5 (n.s.)	26.4 (n.s.)	100-300	240.0 (80.5)	100-300	160.0 (97.5)	B	A	Yes	Yes	FLVX	investigational
March et al, 1991	Imipramine	8	Out	DSM-III	18	18	HAMD-17	25.0 (n.s.)	25.5 (n.s.)	100-300	n.s.	100-300	n.s.	B	A	Yes	Yes	FLVX	Investigational
Miller et al, 2001	Imipramine	8	Out	DSM-III-R	13	11	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	B	A	No	No	No	Unclear
Otsubo et al, 2005	Nortriptyline	8	Out	DSM-IV	36	38	HAMD-17	21.4 (6.2)	23.7 (7.8)	25-150	106.0 (n.s.)	25-150	114.0 (n.s.)	B	C	No	No	No	Investigational
Brunner, 1994	Amineptine	4	In	Feighner	20	20	HAMD-17	24.3 (2.6)	24.8 (3.2)	100-300	220.3 (n.s.)	100-200	155.2 (n.s.)	B	C	Yes	Yes	Unclear	Investigational
Kasper et al, 1990	Maprotiline	4	In	DSM-III	21	21	HAMD-21	25.8 (3.2)	26.6 (5.1)	100-300	229.0(47.0)	100-300	236.0 (32.0)	B	A	Yes	Yes	Unclear	Unclear
Mendonca Lima et al, 1997	Maprotiline	4	Unclear	DSM-III-R	20	20	MADRS	30.4 (4.0)	31.1 (4.8)	100		75		B	C	Yes	Yes	Unclear	Unclear
Moon & Jeainger, 1991	Mianserin	8	GP	DSM-III	31	31	n.s.	n.s.	n.s.	100-300	n.s.	60-180	n.s.	B	A	No	No	FLVX	Investigational
Perez & Ashford, 1990	Mianserin	6	Out	DSM-III	30	33	MADRS	35.8 (n.s.)	37.2 (n.s.)	100-300	176.0 (n.s.)	60-180	100 (n.s.)	B	A	Yes	Yes	FLVX	Unclear
Haffmans et al, 1996	Citalopram	6	Out	DSM-III-R	109	108	HAMD-17	24.5 (n.s.)	24.7 (n.s.)	150-200	n.s.	30-40	n.s.	B	A	No	No	Comp.	Unclear
Dalery & Honig, 2003	Fluoxetine	6	Out	DSM-III-R	90	94	HAMD-17	22.3 (n.s.)	22.2 (n.s.)	100		20		B	A	No	Yes	FLVX	Unclear
Gonul et al, 1999	Fluoxetine	4	Unclear	DSM-IV	40	40	n.s.	n.s.	n.s.	150		20		B	A	—	—	Unclear	Unclear
	Paroxetine					40			n.s.			20							
	Sertraline					40			n.s.			50							
Kavoussi et al, 1999	Fluoxetine	8	Out	DSM-IV	n.s.	n.s.	n.s.	n.s.	n.s.	100-150	102.0 (35.0)	20-80	34.0 (19.0)	B	A	—	—	FLVX	Unclear
Rapaport et al, 1996	Fluoxetine	7	Out	DSM-III-R	51	49	HAMD-21	25.2 (n.s.)	25.6 (n.s.)	100-150	101.9 (25.2)	20-80	34.2 (18.8)	B	A	Yes	Yes	FLVX	Unclear
Annseau et al, 1994	Paroxetine	6	In and Out	DSM-III-R	64	56	HAMD-21	26.5 (4.5)	26.0 (4.2)	50-200	151.6 (59.1)	20-30	25.4 (5.0)	B	A	No	Yes	Comp.	Unclear
Kato et al, 2006	Paroxetine	6	Unclear	DSM-IV	49	52	HAMD-21	23.9 (8.0)	21.5 (5.1)	50-150	90.5 (35.0)	20-40	22.3 (5.6)	B	C	No	Yes	FLVX/Comp.	Unclear
Kiev & Feiger, 1997	Paroxetine	7	Out	DSM-III-R	30	30	HAMD-21	24.4 (n.s.)	24.4 (n.s.)	50-150	102.0 (44.0)	20-50	36.0 (13.0)	B	A	Yes	Yes	FLVX	Unclear
Nemeroff et al, 1995	Sertraline	7	Out	DSM-III	49	48	HAMD-21	24.6 (3.7)	23.2 (2.8)	50-150	123.8 (n.s.)	50-200	137.1 (n.s.)	B	A	Yes	Yes	FLVX	Unclear
Rossini et al, 2005	Sertraline	7	In	DSM-IV	40	48	HAMD-21	31.2 (5.1)	29.2 (3.5)	200		150		B	A	Yes	No	Unclear	Investigational
Annseau et al, 1991	Milnacipran	4	In	RDC	41	42	HAMD-24	32.5 (7.6)	33.8 (6.7)	200		300		B	A	No	Yes	Comp.	Comp.
						44			31.7 (9.6)			200							
Clerc et al, 2001	Milnacipran	6	In and Out	DSM-III-R	56	57	HAMD-24	31.4 (7.7)	32.8 (7.9)	200		100		B	B	No	Yes	Comp.	Comp.
Hackett et al, 1999	Venlafaxine	6	Out	DSM-III-R	34	37	MADRS	31.6 (5.1)	32.7 (6.2)	200		100		B	B	Yes	No	Comp.	Comp.
						40			31.7 (4.9)			100							

[a] Only one main paper for each of the studies is cited; b Cochrane criteria for quality (Higgins et al, 2005) were used. Studies were given a quality rating of A (adequate), B (unclear) or C (inadequate).

(*Continued*)

Table 1 Summary of Included Studies *(Continued)*

Randomized Controlled trial[a]	Comparator	Follow up (wk)	Treatment setting	Diagnostic Criteria	Sample Size FLVX	Sample Size Comp.	Baseline score (SD) Outcome measure	Baseline score (SD) FLVX	Baseline score (SD) Comp.	Dose (mg) FLVX range	Dose (mg) FLVX mean (SD)	Dose (mg) Comp. range	Dose (mg) Comp. mean (SD)	Quality[b] allocation concealment	Quality[b] Double blind	Imputing for dichotomous data at acute phase response	Imputing for dichotomous data at acute phase remission	Funded by the company marketing	FLVX as investigational or comparator drug
Schoemaker et al, 2002	Mirtazapine	6	Out	DSM-IV	207	205	HAMD-17	23.8 (4.0)	24.0 (3.8)	50-150	78.5 (26.2)	15-45	20.9 (7.7)	B	A	No	No	Comp.	Comp.
Barrelet et al, 1991	Moclobemide	4	In and Out	DSM-III	30	31	HAMD-17	26.4 (3.0)	24.7 (4.2)	100-200	116.0 (n.s.)	300-450	323.0 (n.s.)	B	A	Yes	Yes	Comp.	Comp.
Bocksberger et al, 1993	Moclobemide	4	In	DSM-III	20	20	MADRS	43.3 (8.5)	41.9 (8.1)	100-200	165.0 (49.0)	300-450	435.0 (46.0)	B	A	Yes	Yes	Comp.	Comp.
Bougerol et al, 1992	Moclobemide	6	In and Out	DSM-III	63	67	HAMD-17	25.1 (3.8)	24.4 (4.8)	100-200	121.0 (n.s.)	300-450	336.0 (n.s.)	B	A	Yes	Yes	Comp.	Comp.
Ueda et al, 2002	Sulpiride	4	Unclear	DSM-IV	24	24	HAMD-17	21.2 (3.9)	21.3 (3.5)	n.s.	108.8 (39.1)	n.s.	155.0 (35.9)	B	B	Yes	Yes	No	Unclear

HAMD, Hamilton Rating Scale for Depression; MADRS, Montgomery-Asberg Depression Rating Scale.

[a]Only one main paper for each of the studies is cited.

[b]Cochrane criteria for quality (Higgins and Green, 2005) were used. Studies were given a quality rating of A (adequate), B (unclear) or C (inadequate). FLVX, Fluvoxamine; Comp., Comparator; In, Inpatients; Out, outpatients; GP, general practice; DSM, The Diagnostic and Statistical manual of Mental Disorders; RDC, the Research Diagnostic Criteria; Feighner, the Feighner criteria; HAMD-17, the 17 item Hamilton Rating Scale for Depression; HAMD-21, the 21 item Hamilton Rating Scale for Depression; HAMD-24, the 24 item Hamilton Rating Scale for Depression; HAMD-18, one item of the HAMD 17 were excluded from analysis by original authors; HAMD-15, the HAMD 17 items 'genital symptoms' and 'loss of weight were excluded from analysis by original authors; MADRS, Montgomery-Asberg Depression Rating Scale; SD, standard deviation; n.s., not stated.

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Most of the included studies (37 studies) were funded by industry. Amongst the 29 trials comparing fluvoxamine with TCAs, a great majority (19 trials) was sponsored by or had at least one author affiliated with a pharmaceutical company marketing fluvoxamine, and almost all the trials (24 trials) set fluvoxamine as an investigational drug. On the contrary, amongst the 24 trials comparing fluvoxamine with ADs other than TCAs, eight trials were sponsored by a pharmaceutical company marketing fluvoxamine, nine trials by a company marketing comparator drug and only three trials set fluvoxamine as an investigational drug.

Treatment effectiveness

At early phase of treatment Forty-five comparisons involving 3961 patients compared fluvoxamine to other ADs. The percentage of response and remission of fluvoxamine group at early phase were 25.9% (500 of 1932 participants) and 9.4% (173 of 1842 participants) respectively.

We found no significant differences in response and remission rates between fluvoxamine and other ADs as a class (TCAs, heterocyclics, etc.). These results were consistent when fluvoxamine was individually compared with each AD (Table 2). From a subgroup analysis, there was no evidence that the RRs significantly varied except for response rate in favour of amitriptyline over fluvoxamine in outpatients setting (RR 0.28, 99% CI 0.10–0.82, $P = 0.002$, NNT 4) based on only two trials.

There was significant statistical heterogeneity for the response between trials comparing fluvoxamine to amitriptyline based on four trials (I-squared = 71.2%, $P = 0.02$). Visual inspection showed that, amongst these studies, three smaller ones using the imputation methods for response (Harris, *et al.*, 1991; Kostiukova, *et al.*, 2003; Remick, *et al.*, 1994) reported results favourable to amitriptyline. However, because of the small number of trials, sources of the heterogeneity cannot be further explained. Statistical heterogeneity was also observed for the response between trials comparing fluvoxamine to fluoxetine (I-squared = 72.6%, $P = 0.06$), but this heterogeneity was based on only two trials.

At end of acute phase of treatment Thirty-one comparisons involving 2663 patients compared fluvoxamine to other ADs. The percentage of response and remission of fluvoxamine group at acute phase were 53.5% (698 of 1305 participants) and 29.0% (379 of 1305 participants) respectively.

There were no significant differences for dichotomous outcomes when fluvoxamine was compared with other ADs as a class or individually (Table 2). From a subgroup analysis, there was no evidence that the RRs significantly varied according to treatment settings.

No difference was found between fluvoxamine and other ADs in sensitivity analyses excluding the studies using the imputation methods for response or remission. A sensitivity analysis to investigate the effect of commercial funding, excluding studies sponsored by pharmaceutical companies, showed the uncertainty about the true effect because almost all of the included trials had been funded by the industry. For example, among 30 trials compared fluvoxamine with TCAs, there were only two trials free from commercial funding. In a similar way, examination of 'wish bias' was impossible because no trials compared fluvoxamine with TCAs set fluvoxamine as a comparator, and amongst studies compared fluvoxamine with ADs other than TCAs, only three trials set fluvoxamine as an investigational drug. Neither significant heterogeneity nor publication bias (Egger regression statistics: $P = 0.50$ for all studies; $P = 0.91$ for studies against TCAs only) was observed in every comparison. Visual inspection of funnel plots also did not suggest any small study effects.

Tolerability

The total number of dropouts for any reason, a proxy measure of total acceptability of fluvoxamine, was not significantly different between fluvoxamine and other ADs as a class and between fluvoxamine and individual comparator ADs (Table 3).

In terms of patients who dropped out because of side effects, again there was no class difference.

Side-effects profile of each drug group by body system

For each individual side effect, data of fluvoxamine in comparison with TCAs as a class and with each control ADs other than TCA were pooled (Table 4).

Cardiovascular side effects As a class, TCAs were associated with more hypotension or bradycardia than fluvoxamine. Hypertension or tachycardia was more frequent in patients treated with milnacipran than in patients treated with fluvoxamine.

Dermatological side effects Sweating was more frequent in paroxetine-treated patients than in fluvoxamine-treated patients.

Gastrointestinal side effects The experiences of nausea or vomiting were more common in fluvoxamine recipients than in TCAs, mianserin, milnacipran and mirtazapine-treated patients. In addition, weight loss or anorexia was more common in fluvoxamine-treated patients than in TCAs recipients.

However, constipation and dry mouth were less frequent in fluvoxamine-treated patients than in TCAs recipients.

Neuropsychiatric side effects As a class, TCAs were associated with more tremor and dizziness or vertigo than fluvoxamine. Anxiety or agitation and somnolence or drowsiness were more common in mirtazapine-treated patients than in fluvoxamine recipients. Some ADs, in particular SSRIs, have been pointed out to cause the emergence or worsening of suicidal ideas in vulnerable patients (Barbui, *et al.*, 2008; Hammad,

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Table 2 Summary of efficacy data of fluvoxamine

Comparator agent	N of comparisons	N of participants	Response RR [a]	Response 99% CI	N of comparisons	N of participants	Remission RR [a]	Remission 99% CI
At early phase of treatment (at 2 weeks)								
TCAs	**24**	**1829**	**0.95**	**0.80, 1.14**	**24**	**1829**	**0.94**	**0.69, 1.26**
Amitriptyline	4	397	0.50	0.16, 1.58	4	397	0.45	0.08, 2.65
Chlorimipramine	3	173	0.99	0.69, 1.42	3	173	0.82	0.45, 1.48
Clomipramine	2	126	1.01	0.49, 2.07	2	126	0.79	0.16, 3.91
Desipramine	1	40	0.83	0.22, 3.15	1	40	1.00	0.09, 11.51
Dothiepin	2	125	0.97	0.31, 2.98	2	125	0.97	0.13, 7.30
Imipramine	11	894	0.97	0.72, 1.30	11	894	0.97	0.54, 1.74
Nortriptyline	1	74	1.45	0.51, 4.09	1	74	2.11	0.38, 11.79
Heterocyclics	**3**	**122**	**0.97**	**0.60, 1.56**	**3**	**122**	**1.18**	**0.47, 2.95**
Amineptine	1	40	1.00	0.29, 3.47	1	40	1.00	0.09, 11.51
Maprotiline	2	82	0.96	0.58, 1.62	2	82	1.21	0.45, 3.26
Mianserin	-	-	-	-	-	-	-	-
SSRIs	**8**	**967**	**0.98**	**0.68, 1.40**	**7**	**783**	**0.78**	**0.39, 1.58**
Citalopram	1	217	0.62	0.15, 2.58	1	217	0.99	0.03, 33.22
Fluoxetine	2	284	1.18	0.43, 3.22	1	100	0.82	0.22, 3.14
Paroxetine	3	281	0.79	0.47, 1.30	3	281	0.67	0.21, 2.12
Sertraline	2	185	1.23	0.50, 3.05	2	185	0.88	0.25, 3.06
SNRIs	**5**	**352**	**0.80**	**0.51, 1.25**	**5**	**352**	**0.82**	**0.30, 2.24**
Milnacipran	3	241	0.75	0.45, 1.25	3	241	0.64	0.18, 2.27
Venlafaxine	2	111	1.01	0.38, 2.63	2	111	1.48	0.14, 15.32
Newer AD	**5**	**643**	**0.78**	**0.56, 1.08**	**5**	**643**	**0.65**	**0.34, 1.25**
Mirtazapine	1	412	0.79	0.53, 1.19	1	412	0.71	0.34, 1.52
Moclobemide	3	231	0.71	0.34, 1.48	3	231	0.50	0.14, 1.83
Other AD (Sulpiride)	**1**	**48**	**0.05**	**0.00, 1.84**	**1**	**48**	**0.33**	**0.01, 20.99**
At the acute phase treatment (most commonly at 6 weeks)								
TCAs	**16**	**935**	**0.99**	**0.86, 1.14**	**16**	**935**	**0.98**	**0.71, 1.35**
Amitriptyline	4	185	0.91	0.61, 1.38	4	185	0.74	0.42, 1.30
Chlorimipramine	1	43	0.90	0.62, 1.31	1	43	0.81	0.40, 1.63
Clomipramine	1	86	0.99	0.68, 1.44	1	86	0.72	0.20, 2.56
Desipramine	1	47	1.44	0.90, 2.31	1	47	2.27	0.90, 5.73
Dothiepin	2	125	1.05	0.65, 1.69	2	125	1.05	0.48, 2.25
Imipramine	6	375	0.95	0.67, 1.36	6	375	1.03	0.53, 2.00
Nortriptyline	1	74	0.96	0.57, 1.62	1	74	1.48	0.61, 3.57
Heterocyclics	**2**	**125**	**1.09**	**0.86, 1.40**	**2**	**125**	**1.16**	**0.93, 1.44**
Amineptine	-	-	-	-	-	-	-	-
Maprotiline	-	-	-	-	-	-	-	-
Mianserin	125	2	1.09	0.86, 1.40	125	2	1.16	0.93, 1.44
SSRIs	**8**	**967**	**0.99**	**0.85, 1.16**	**8**	**967**	**1.01**	**0.77, 1.34**
Citalopram	1	217	0.93	0.54, 1.60	1	217	0.59	0.21, 1.66
Fluoxetine	2	284	1.00	0.78, 1.28	2	284	1.15	0.72, 1.82
Paroxetine	3	281	0.92	0.70, 1.21	3	281	0.83	0.52, 1.31
Sertraline	2	185	1.10	0.71, 1.70	2	185	1.16	0.63, 2.15
SNRIs	**3**	**224**	**0.76**	**0.56, 1.04**	**3**	**224**	**0.73**	**0.45, 1.20**
Milnacipran	1	113	0.81	0.56, 1.18	1	113	0.76	0.37, 1.59
Venlafaxine	2	111	0.65	0.37, 1.15	2	111	0.70	0.36, 1.37
Newer AD	**1**	**412**	**0.95**	**0.78, 1.16**	**1**	**412**	**1.10**	**0.83, 1.45**
Mirtazapine	1	412	0.95	0.78, 1.16	1	412	1.10	0.83, 1.45
Moclobemide	-	-	-	-	-	-	-	-
Other AD (Sulpiride)	-	-	-	-	-	-	-	-

a RRs over 1 indicate an advantage to fluvoxamine. AD, antidepressant; CI, confidence interval; RR, relative risk; TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-noradrenaline reuptake inhibitor.

et al., 2006), but among the trials included in this review only four trials recorded completed suicide, with three events among patients taking fluvoxamine and one among those taking control agents, and suicide attempts or ideation were reported in only seven trials, with nine events among patients taking fluvoxamine and seven among those taking control agents.

Genitourinary side effects Only five trials reported genitourinary side effects, such as sexual dysfunction. Although some previous trials have reported that fluvoxamine was associated with relatively low prevalence of sexual dysfunction compared with other SSRIs (Mackay, *et al.*, 1997; Montejo-Gonzalez, *et al.*, 1997), we could not find any significant differences in these side effects between fluvoxamine and control ADs.

Discussion

The results of our study indicate that no substantial difference exists in the effectiveness between fluvoxamine and any of the

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Table 3 Summary of tolerability of fluvoxamine

Comparator agent	N of comparisons	N of participants	RR [a]	95% CI
Drop out due to any reason				
TCAs	**27**	**1949**	**0.99**	**0.87, 1.12**
Amitriptyline	5	420	0.85	0.66, 1.10
Chlorimipramine	3	173	1.30	0.60, 2.83
Clomipramine	2	126	0.92	0.45, 1.89
Desipramine	2	87	1.50	0.28, 8.04
Dothiepin	2	125	1.03	0.61, 1.74
Imipramine	12	944	1.07	0.91, 1.26
Nortriptyline	1	74	0.68	0.37, 1.25
Heterocyclics	**5**	**247**	**0.67**	**0.33, 1.35**
Amineptine	1	40	0.67	0.12, 3.57
Maprotiline	2	82	0.33	0.01, 7.74
Mianserin	2	125	0.62	0.17, 2.24
SSRIs	**11**	**1126**	**1.20**	**0.96, 1.51**
Citalopram	1	217	1.31	0.80, 2.12
Fluoxetine	3	337	1.12	0.72, 1.75
Paroxetine	4	334	1.05	0.73, 1.52
Sertraline	3	238	1.11	0.32, 3.82
SNRIs	**5**	**386**	**1.04**	**0.71, 1.54**
Milnacipran	3	241	1.17	0.70, 1.94
Venlafaxine	2	145	0.88	0.47, 1.63
Newer AD	**4**	**643**	**1.00**	**0.74, 1.35**
Mirtazapine	1	412	0.86	0.60, 1.25
Moclobemide	3	231	1.30	0.79, 2.16
Other AD (Sulpiride)	**1**	**48**	**1.00**	**0.28, 3.54**
Drop out due to side effects				
TCAs	**24**	**1772**	**0.82**	**0.66, 1.03**
Amitriptyline	5	420	0.65	0.43, 1.00
Chlorimipramine	1	32	1.76	0.18, 17.56
Clomipramine	2	126	0.66	0.20, 2.11
Desipramine	2	87	1.00	0.16, 6.42
Dothiepin	2	125	1.20	0.54, 2.66
Imipramine	11	908	0.94	0.69, 1.28
Nortriptyline	1	74	0.45	0.13, 1.62
Heterocyclics	**5**	**247**	**0.84**	**0.39, 1.81**
Amineptine	1	40	3.00	0.13, 69.52
Maprotiline	2	82	0.33	0.01, 7.74
Mianserin	2	125	0.79	0.26, 2.37
SSRIs	**10**	**942**	**1.17**	**0.66, 2.06**
Citalopram	1	217	1.61	0.92, 2.83
Fluoxetine	2	153	0.87	0.21, 3.58
Paroxetine	4	334	0.96	0.32, 2.84
Sertraline	3	238	1.25	0.17, 9.28
SNRIs	**3**	**241**	**2.18**	**0.67, 7.11**
Milnacipran	3	241	2.18	0.67, 7.11
Venlafaxine	-	-	-	-
Newer AD	**5**	**643**	**0.89**	**0.54, 1.40**
Mirtazapine	1	412	0.63	0.35, 1.19
Moclobemide	3	231	1.43	0.67, 3.03
Other AD (Sulpiride)	-	-	-	-

[a] RRs below 1 indicate an advantage to fluvoxamine

AD, antidepressant; CI, confidence interval; RR, relative risk; TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-noradrenaline reuptake inhibitor

ADs including TCAs, such as amitriptyline or clomipramine, in terms of response or remission in any clinical settings. This was somewhat surprising because TCAs are sometimes believed to be more effective than SSRIs, in particular, among hospitalised depressive patients (Anderson, 1998).

Another surprising finding was that in terms of patients acceptability, there was no difference in dropouts for any reason or for side effects between fluvoxamine and other ADs as a class (TCAs, SSRIs, etc.) or individually. The general statement across the class that SSRIs are better tolerated by patients than old TCAs needs to be moderated. In addition, in our review, 10 trials involving fluvoxamine was included, and from the pooled data, we could not find any difference in total dropouts and dropouts because of side effects between fluvoxamine and other SSRIs. Edwards and Anderson conducted a well-designed systematic review and meta-analysis of RCTs involving direct comparisons between five SSRIs in the treatment of patients with major depressive illness (Edwards and Anderson, 1999). They reported in the review that significantly more patients on fluvoxamine stopped treatment because of any reason and because of side effects compared with other SSRIs. However, they included only five trials involving fluvoxamine, and their review is now outdated. The clinical guideline released by the same authors (Anderson and Edwards, 2001) suggested that fluvoxamine was not the best choice of SSRI in routine practice because of relatively high discontinuation rate, but this statement needs to be moderated. It is, therefore, very hard for us to speculate why fluvoxamine is less popular than the other SSRIs (Kadusevicius, *et al.*, 2006; Lawrenson, *et al.*, 2000). Perhaps because of the earlier review that happened to be less favourable to fluvoxamine or perhaps because of the difference in marketing strategies used by the pharmaceutical company in different countries.

Therefore, the initial selection of an antidepressant medication will and should largely be based on the anticipated side-effect profile and patient's preference. The analysis of individual side effects generated the findings that there is evidence of differing side-effects profiles, especially when comparing gastrointestinal side effects between fluvoxamine and TCAs. Nausea or vomiting and weight loss or anorexia were experienced significantly more frequently with fluvoxamine than with TCAs and some of other ADs (mianserin, milnacipran and newer ADs). On the contrary, constipation and dry mouth were more common with TCAs than with fluvoxamine.

SSRIs are chemically different from the TCAs, heterocyclics and other Ads, and considerable structural differences also exist between the various SSRIs. Therefore, some differential pharmacology between the drugs in the same class may be expected. However, we found no evidence to suggest differences of side-effect profile between fluvoxamine and other SSRIs except for sweating, which was found to be more common in paroxetine- than fluvoxamine-recipients in a single trial.

This systematic review is not without methodological problems. First, although neither the funnel plot nor the Egger's test detected small study effects, we still cannot rule out the possibility of publication bias. For example, we have concerns that some eligible RCTs report only the laboratory data. One RCT reported prolactine response to d-fenfluramine for depressive patients before and after medication but no clinical outcome at all (Kavoussi, *et al.*, 1999). This trial formed part of an industry drug trial sponsored by Solvay, marketing fluvoxamine. We were unable to locate a trial that matched the description in this report elsewhere, and we strongly suspect that we are missing one large trial sponsored by this company. Second, amongst the trials comparing fluvoxamine with TCAs,

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