Table 5: Prescription of psychotropic medicine by physicians.

	Major depressive disorder n = 27		Any mood disorder n = 52	
	n	%	n	%
Antidepressant (including sulpiride)	2	7.4	5	9.6
Anxiolytic/Hypnotic	16	59.3	22	42.3
No psychotropic medicine	11	40.7	29	55.8

% is in patients with depressive disorder evaluated by the PHQ.
Patients prescribed both antidepressant and anxiolytic/hypnotic: Major depressive disorder (2), any mood disorder (4).
One patient with major depressive disorder who was prescribed an antidepressant from another hospital was not included.

In addition, this is the first study reporting prescription rates of antidepressants to all consulted patients.

The present study was performed in a hospital located in a rural area where the proportion of the elderly is high. Generally, medical resources are poorer in rural areas than in urban areas, and elderly people have more chronic physical illnesses. Thus, general internal medicine in a rural area has an important primary care role in the community, especially for the elderly. In fact, most participants in the present study were geriatric patients. The findings are useful for constructing an effective intervention model to care for depressed patients in rural areas in Japan.

The rate of patients who did not participate in a similar survey performed in a rural French area using the PHQ was 14.1% (11.4% refused to participate, and 2.7% did not have enough to time to answer) [26]. The rate of patients who did not participate in the present study was half (7.1%) that of the French study. This suggests that the bias caused by refusal to participate in the present study may be smaller than that of the previous study. Furthermore, the rate of patients who did not participate in the survey using the Structured Clinical Interview for DSM-IV (SCID) was more than 40% [27]. Use of the PHQ instead of a semi-structured interview is one reason for the increased rate of participants. However, the bias from using the PHQ, which is a self-administered questionnaire, instead of a semi-structured interview may be unavoidable, as discussed in the following section.

Limitations of the study

The present study has several limitations. First, as discussed above, we used self-administered questionnaires (the PHQ and the GAD-7) to evaluate depressive disorders and comorbid psychiatric disorders. The PHQ addresses symptoms only for a two-week period and may include bereavement reactions, mood disorders caused by physical disorders or medications, and/or depressive episodes of bipolar disorders. Although the Japanese PHQ has high sensitivity and specificity for major depressive disorder, evaluation using a diagnostic interview, such as the semi-structured clinical interview for DSM-IV, will increase the validity of the results. Second, we surveyed only five physicians in one hospital. To increase the generalizability of the present results, a study including multiple hospitals or clinics is needed. Third, we judged cognitive impairment based on brief semi-structured interviews of patients or accompanying persons. Sometimes it is difficult to discriminate between depression and cognitive impairments caused by dementia in the geriatric population. A study using a screening or diagnostic tool with higher performance to exclude cognitive impairment is needed. Finally, we surveyed a history of psychotropic medicine prescription on the consultation day. However, the prescription may be reflected behavior by previous physicians rather than the one carrying out the current diagnosis.

Conclusions

The prevalence of depression at a general internal medicine outpatient clinic was higher in the present study than in the Japanese community. Thus, general internists can play a role as gatekeepers for diagnosing untreated depressed patients in the community. However, physicians did not recognize depressed patients, even in severe cases. The prescription rate of antidepressants to depressed patients and the referral rate of depressed patients to mental health specialists were also low. In addition, the prescription rate of antidepressants to patients whom physicians diagnosed as having a mood disorder was also low.

There are multiple barriers to providing appropriate care for patients with depression, such as recognition of depression, judgment of its severity, prescription of antidepressants and referral to mental health specialists. Collaborative care models developed and shown to be effective in the US and UK [5] to care for depressed patients by general practitioners and primary care physicians cannot be applied directly to the Japanese medical system.

Physicians can recognize insomnia comorbid with depression and can judge the presence of a mental disorder in depressed patients. Thus, an important step is to change physicians' attitude to depression into "it is our business" to find depression. The additional step is to perform screening and then to monitor the screening-positive patients and to refer them to mental health specialists. In addition to constructing a screening and monitoring system of depression, an educational intervention for physicians is key for improving the quality of life of depressed patients at general internal medicine outpatient clinics and of missed depressed patients in the community.

Competing interests
MI received speaking fees from Eli Lilly.

Authors' contributions
All authors have read and approved the final version of the manuscript.
MI was the principal investigator and developed the original idea for the study. TO, MI, YO, and MK designed the study. TO, MI, YO, MK, and AS performed the survey. KM developed several Japanese questionnaires used in our survey. TO and MI analyzed data and prepared the manuscript. MY was a supervisor.

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Prevalence of depression among outpatients visiting a general internal medicine polyclinic in rural Japan ☆,☆☆

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ABSTRACT

Objective: In Europe and the US, primary care has been anticipated in identifying untreated depression. Findings show a high prevalence of depression in such settings. However, the prevalence of depression in an internal medicine clinic in a rural area of Japan, which has a role in primary care, is unclear.
Method: The prevalence of depression and comorbid psychiatric disorders among outpatients of an internal medicine clinic in a rural general hospital was measured by a structured interview using the Mini International Neuropsychiatric Interview. Outpatients were recruited consecutively and stratified by Patient Health Questionnaire-9 (PHQ-9) scores. Among 598 outpatients, we interviewed 75 randomly selected patients and 29 whose results of the PHQ-9 were positive. We estimated prevalence of depressive episode using age, sex, physical findings by internal medical doctors and PHQ-9 scores as covariates.
Results: The estimated prevalence of major and minor depressive episodes were 7.4% [95% confidence interval (CI): 3.4%–11.4%] and 6.8% (95% CI: 2.6%–10.9%), respectively. Among major depressed patients, 71.4% had current suicidal ideation.
Conclusion: Given the high rate of depression and suicidality, identification of depression and collaboration between internal medical doctors in a rural area of Japan and mental health professionals are needed.
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1. Background

Depression is a prevalent, disabling disorder that has a profound influence on quality of life. It is estimated to become the leading cause of disability worldwide in 2030 and was already the leading cause of morbidity in middle- and high-income countries, including Japan, in 2004 [1].

Previous studies have invariably reported a high prevalence of depression in the general population [2–5] and in health care settings [6–8]. For example, the World Health Organization (WHO) performed a primary care mental health survey of 14 countries and found that 14% of primary care patients suffered from major depression [6]. Given the high prevalence of depression, primary care settings play an important role in identifying and treating depressed patients [9–11]. In Japan, there are few doctors specialized to primary care because its medical system has no clear definition of primary care and the specific providers responsible. Most patients, especially those in rural areas, consult an internal medical doctor for their primary care.

A previous study of patients in a general medicine clinic showed a 4.7% lifetime prevalence of major depressive episodes [12]. Another survey, also performed about 20 years ago, showed a 3.0% prevalence

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of major depressive episodes [13]. However, there are few recent studies showing depression prevalence in primary care settings.

Recently, we reported the prevalence of depression in a rural general hospital, where many of the patients were elderly [mean age (S.D.)= 72.9 (12.5) years]. Approximately 53%, 12% and 10% of the patients suffered from hypertension, hyperlipidemia and diabetes, respectively, which suggested that this rural general hospital played a role in the primary care of chronic physical illnesses of elderly patients [14]. Using the Patient Health Questionnaire-9 (PHQ-9), 8.7% [95% confidence interval (CI), 5.5%–11.8%] presented with probable major depression and, 16.7% (12.5%–20.8%), with a probable mood disorder. However, these prevalence estimates were based only on self-reports, and we did not perform any structured interviews to diagnose depression. There were also no data regarding comorbid psychiatric disorders that are commonly observed in primary care settings [15,16]. Therefore, the present study used structured psychiatric interviews to elucidate the prevalence of depression and other psychiatric disorders among patients of a general internal medicine outpatient clinic in a rural area of Japan.

2. Methods

2.1. Participants

This study was approved by the Ethics Committee of the National Center of Neurology and Psychiatry in Japan. The researchers provided all participants with detailed information using a written document and administered a battery of self-report questionnaires after the patients provided oral informed consent. After this first-stage screening, we conducted structured psychiatric interviews with patients who provided further written informed consent.

This study was conducted on nine consecutive consultation days between July 12 and 23, 2010, at a general internal medicine outpatient clinic in a general hospital having no mental health specialties. This hospital is located in a small city (population of 124,756 in 2010) in the Tohoku region of Japan. The hospital serves as a regional public hospital and is funded by the National Health Insurance Society of Oshu City. Oshu City is a typical rural area about 500 km north of Tokyo with low population influx. There are high proportions of elderly people and people engaged in primary industry [17].

We used the following inclusion criteria to define a target population that can be assessed for depression in routine clinical practice: (a) patients aged 20 years or older who visited the outpatient clinic to consult a physician for their own primary care and (b) patients who have no communication difficulties, such as hearing loss or language problems, and who have no severe cognitive impairment, such as dementia or disturbance of consciousness. Thus, we did not include visitors who came in for admission preparation or those who consulted for their family members. We also did not include patients who lived outside the catchment area of the hospital. Severe cognitive impairment was judged based on a semistructured interview, using the first two questions of the Mini-Mental State Examination concerning time and place orientation [18,19] by research staff consisted of psychiatrists (MI and MY), a research assistant (TO) having experience in survey using the Mini-Mental State Examination and PHQ-9 in internal medical clinics and nurses. All were trained for the procedure of the present study. The staff sometimes conducted an additional interview regarding patient lifestyle factors and dementia history if accompanying persons were present. Due to ethical considerations and feasibility of the survey, we also excluded patients who were too physically ill to be interviewed.

2.2. Measurements

2.2.1. PHQ-9

We used the PHQ-9 [20,21] to stratify participants. We asked patients to choose from the following options how often they had been bothered by each of nine symptoms over the last 2 weeks: "not at all," "several days," "more than half the days" and "nearly every day." Two scoring methods, a categorical algorithm and a dimensional assessment, have been proposed in the literature. In the categorical algorithm, depression screening is positive if five or more of the nine depressive symptom criteria were present at least more than half the days and one of the symptoms is depressed mood or anhedonia. One of the nine items, "thoughts that you would be better off dead or of hurting yourself in some way," was counted if present at all. In addition to the categorical algorithm, we judged depression severity using a dimensional scale, with a cutoff score of 10 reported as optimal for screening probable depression. Each item is scored from 0 to 3, with a total possible score of 27 for the nine items.

We used a categorical algorithm to screen probable depression positive. In the categorical algorithm, depression is positive if one of two items (depressed mood or anhedonia) was present. Based on the results of the PHQ-9, patients were screened as probable depression positive using either the categorical algorithm (one of the two items) or the dimensional assessment (score of more than 10).

2.2.2. Mini International Neuropsychiatric Interview (MINI)

We used the MINI [22,23] to diagnose depression and other psychiatric disorders. The interview was originally developed as a structured diagnostic interview compatible with *DSM-III-R* and *ICD-10* criteria [25,26]. The MINI focuses on current diagnoses and only explores lifetime diagnoses clinically if relevant to the present status. For most diagnostic sections, one or two screening questions are used to rule out the diagnosis when answered in the negative. The MINI includes 19 disorders chosen as most common from epidemiological data [27,28]. In the present study, we used the modules related to depression, anxiety, eating disorders and alcohol/substance dependence/abuse, which are often observed in primary care settings [16]. We evaluated current suicidality using the suicidality module (C) of the MINI, although the validity has not been completely established [22–24]. The module consists of six items that identify any suicide-related episodes or phenomena, including suicidal ideation within the last month (five items) and history of suicide attempts (one item) in the life. If any items in the suicidal ideation within the last month (five items) were relevant, we judged that current suicidality was present. In addition, we calculated the score (e.g., lifetime histories of attempting suicide=4, presence of having suicidal ideation within a month=6, planning or attempting suicide within a month=10) and showed the number of patients with a high risk (MINI suicide risk >= 10) as sever suicidality [22–24]. In addition to the current suicidality evaluated by the MINI, we investigated score of the Item 9 in the PHQ-9 (thoughts that you would be better off dead or of hurting yourself in some way: *not at all*: 0; *several days*: 1; *more than half the days*: 2; and *nearly every day*: 3, over the past 2 weeks). We confirmed that scores of the Item 9 among patients with current suicidality by the MINI (median: 1; range: 0–3) were significantly higher than those among patients without (median: 0; range: 0–1) ($U=273.5$, $P<.01$ by the Mann–Whitney U test). We also used the MINI to assess minor depressive episodes, defined as having two to four items, with one of the items being depressed mood or anhedonia in the major depressive episode module (A) of the MINI.

2.3. Procedure

We defined the target population by the inclusion criteria described in the participant section and adopted a random sampling stratified by the PHQ-9 results. Trained psychiatrists (MI or MY), who were blind to the results of the PHQ-9, conducted structured MINI interviews of patients who were screened as probable depression positive as well as randomly selected patients.

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2.3.1. Statistical analyses

We calculated the prevalence estimates of any depressive episode (major depressive episode and minor depressive episode), other psychiatric disorders and their 95% CIs using sampling weights. The weight was based on the inverse of the sampling probability for age, sex, clinical diagnosis of primary illness and PHQ-9 score. We performed multiple imputations for the missing data. We performed all statistical analyses using the statistical software packages SPSS 17.0 (IBM, Tokyo) and Statistical Analysis System (SAS) 9.2 (SAS Institute Japan, Tokyo).

3. Results

During the study period, 598 patients visited the clinic. We randomly selected 107 of the outpatients. From the selected 107 patients, we excluded 21 based on our inclusion criteria: 1 was less than 20 years old, 7 consulted for family members, 1 resided outside the area and 12 were severely cognitively impaired. Among the 86 patients, 5 patients were physically too ill, and 1 refused to participate in the study. Then we administered the PHQ-9 to 80 patients who agreed to participate in the survey.

Among the remaining 491 patients who were not selected randomly, we excluded 66 based on our inclusion criteria: 16 were less than 20 years old, 15 consulted for family members, 1 visited to prepare for admission, 2 resided outside the area and 32 were severely cognitively impaired. Among the 425 patients, 12 were physically too ill, 4 were missed and 5 refused to participate in the study. Then, we administered the PHQ-9 to 404 patients and acquired PHQ-9 data for 396 of the 404 patients, and 8 of PHQ-9 data were incomplete. As a result, 36 patients out of the 396 were screened as probable depression positive.

Among the total 116 participants (80 and 36 participants), 104 received a structured interview using the MINI. Twelve patients were not interviewed (seven were missed, one was physically ill and four refused the interview).

The target population to estimate prevalence was 511 patients (86 and 425 patients).

Table 1 shows characteristics of the target population (n=511). The median age of the population was 75 years, with more than 81.8% of participants being 65 years old or older. As shown in Table 1, chronic physical illnesses, such as hypertension, diabetes and hyperlipidemia, were frequent. The median number of visits in the past 6 months was four, which means many patients consulted the clinic approximately once every 6 weeks.

Of the 104 patients who we interviewed using the MINI, we diagnosed 21 as having experienced a major depressive episode and 15 with a minor depressive episode. One had a hypomanic episode, two had posttraumatic stress disorder (PTSD) and five had alcohol dependence. Twenty-seven patients had suicidal thoughts. No one had a high risk of suicide among 99 patients who completed the suicidality module of the MINI (five had incomplete data). Table 2 shows weighted prevalences of depression and other psychiatric disorders. The estimated prevalence of having a major depressive episode was 7.4% (95% CI: 3.4% to 11.4%). That of any depressive episode, including both major and minor depressive episode, was 14.1% (95% CI: 8.2% to 20.0%), which means that one in every seven patients was estimated to have depression. Prevalence of current suicidality was 12.7% or one in every eight patients. Alcohol dependence was also frequent (5.4%).

Table 3 shows the prevalence of comorbid psychiatric disorders and current suicidality among patients that experienced a depressive episode. Prevalence of suicidality was high in patients with a major depressive episode as well as those with any depressive episode. Among the patients with major depressive episode (n=21), median (range) of the scores of Item 9 of the PHQ-9 was 1 (0–3). Among those diagnosed as having any depressive episode (n=36), median (range) of the scores was 0 (0–3). And among those who had no depressive episode, median (range) of the scores was 0 (0–1). Proportions of patients who scored the Item 9 of the PHQ-9 as 3 (nearly every day over the past 2 weeks) were 38.1%, 22.2% and 0% among patients with major depressive episode (n=21), those with any depressive episode (n=36) and those without any depressive episode (n=68), respectively.

Table 1
Characteristics of the study participants

Median age (range) in years	75 (21–102)
Sex: female (%)	59.3
Clinical diagnosis of primary illness (%)	
Hypertension	58.7
Diabetes	16.0
Hyperlipidemia	15.9
Brain infarction	8.4
Arrhythmia	6.8
Number of visits in the past 6 months	
Median (range)	4 (0–74)

Table 2
Prevalence of depression and other psychiatric disorders

	Estimated prevalence (%)	(95% CI)
Any depressive episode	14.1	8.2–20.0
Major depressive episode (current, 2 weeks)	7.4	3.4–11.4
Minor depressive episode (current, 2 weeks)	6.8	2.6–10.9
Hypomanic episode (current)	0.8	0.0–2.4
PTSD (current, past month)	1.4	0.0–3.4
Alcohol dependence (past 12 months)	5.4	0.3–10.5
Current suicidality	12.7	6.6–18.9

4. Discussion

The present study investigated the prevalence of depression and other psychiatric disorders in a general internal medicine outpatient clinic of a Japanese rural general hospital using structured interview conducted by trained psychiatrists followed by screening of PHQ-9. Patients were elderly and had chronic physical illnesses. The prevalence of major depressive disorder was 7.4% and, that of depression including both major and minor depressive disorders, was 14.1%. The prevalence of alcohol dependence was high, and suicidality was prevalent among patients with major or minor depressive disorders.

A previous survey conducted by the WHO nearly 20 years ago reported the prevalence of depression as 3.0% in internal medicine outpatient clinics in Japan [13]. The prevalence of PTSD in the previous survey (0.2%) was also lower than that of the present study (1.4%). The prevalence of alcohol dependence in the previous survey was 6.2%, which was comparable to that of the present study (5.4%). In contrast, the prevalence of generalized anxiety disorder was 5.0% in

Table 3
Rate of comorbid psychiatric disorders in patients with depression

	Number	%
Major depressive episode (n=21)		
Current suicidality	15	71.4
PTSD	1	4.8
Alcohol dependence	0	0
Any depressive episode (n=36)		
Current suicidality	18	50.0
PTSD	2	5.6
Alcohol dependence	1	2.8

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the previous survey, while no patients had generalized anxiety disorders in the present study.

These discrepancies may be explained by differences in participants and methods between the previous survey and the present study. The previous survey was conducted in a hospital located in a medium-sized city, whereas we examined prevalence of psychiatric disorders in a rural hospital. The previous survey excluded patients older than 65 years old, while the majority of participants in the present study were older than 65 years old. In addition, we need to consider that the previous survey was performed nearly 20 years ago.

A previous study performed in the US showed that the prevalence of major depression in rural primary care (8.3%) was lower than that in urban primary care settings (14.8%) [29]. The internal medicine clinic in the present study was located in a rural area, and the prevalence of major depression (7.4%) was similar to that previously reported [29]. However, the prevalence of depression in an urban clinic in Japan may be different.

Our previous study using the PHQ-9 to identify probable depression in the same clinic showed that prevalence of probable major depressive disorders (8.7%, 95% CI: 5.5%–11.8%) [14] was similar to that of the present study, suggesting that the results are reproducible.

The present study showed a high prevalence of current suicidality. In addition to the high prevalence, there was a higher rate of current suicidality among patients with major depressive episodes. Thus, current suicidality should be considered in addition to depression in patients evaluated at internal medicine clinics of rural general hospitals. In particular, referral of depressed patients with suicidal thought more than several days in the past 2 weeks to mental health professionals is required.

Previous studies in other countries showed that the prevalence of major depression in primary care settings for people aged 65 or older is 19.5% [30], which is higher than the prevalence found in the present study. The prevalence of depression in the general Japanese population is 2.9% [31], which is lower than that in other countries [32]. The lower prevalence in the general population may reflect the lower prevalence of depression in general internal medicine outpatient clinics.

The prevalence of depression in the internal medical outpatient clinic shown in the present study was higher than that previously reported for the general population in Japan [31]. This is similar to findings from other countries where the prevalence of depression in primary care settings is higher than in the community [30,33]. These results suggest that depressed patients more frequently consult internists. Thus, it is important that physicians appropriately identify, treat and/or refer untreated depressed patients that consult the clinic to mental health specialists.

The study has two major limitations. First, we selected only a single hospital for convenience. A survey of multiple, randomly selected sites from across Japan should be performed to generalize the findings. Second, the number of participants in the study was too small to effectively investigate comorbidities.

The present study showed a high prevalence of depression in an internal medicine outpatient clinic of a rural general hospital that plays a role in primary care for residents of its catchment area. We also showed a high prevalence of suicidality and its higher comorbidity rate with depression. Given the high rate of depression and suicidality, identification of depression and collaboration between internal medical doctors and mental health professionals, such as psychiatrists, are needed.

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大うつ病に対する新規抗うつ剤の最適使用戦略を確立するための大規模無作為割り付け比較試験　研究プロトコル

Strategic Use of New generation antidepressants for Depression (SUN ☺ D) Study Protocol

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略語および用語の定義一覧

5-HT	5-hydroxytryptamine	セロトニン
BDI2	Beck Depression Inventory-II	ベック抑うつ質問票第2版
C-CASA	Columbia Classification Algorithm of Suicide Assessment	コロンビア自殺評価分類アルゴリズム
CRC	Clinical Research Coordinator	臨床研究コーディネータ
CRO	Contract Research Organization	開発業務受託機関
CYP	Cytochrome pigment	シトクロム色素
DALY	Disability-Adjusted Life Years	障害調整生命年
DSMB	Data Safety Monitoring Board	データ・安全性管理委員会
EDC	Electronic Data Capturing	電子的臨床検査情報収集システム
FIBSER	Frequency, Intensity, and Burden of Side Effects Rating	副作用総合評価票
IMS	IMS	アイ・エム・エス
MANGA	Meta-Analyses of New Generation Antidepressants	新規抗うつ剤のネットワークメタアナリシス研究
MAO	Monoamine oxidase	モノアミン酸化酵素
NICE	National Institute of Clinical Excellence	英国国立医療技術評価機構
NaSSA	Noradrenergic and Specific Serotonergic Antidepressant	ノルアドレナリン作動性・特異的セロトニン作動性抗うつ剤
NNT	Number needed to treat	治療必要症例数
PHQ9	Personal Health Questionnaire-9	こころとからだの質問票
RCT	Randomized controlled trial	無作為割り付け比較試験
SMO	Site Management Organization	治験施設支援機関
SNRI	Serotonin & Noradrenalin Reuptake Inhibitor	セロトニン・ノルアドレナリン再取り込み阻害剤
SSRI	Selective Serotonin Reuptake Inhibitor	選択的セロトニン再取り込み阻害剤
STAR*D	Sequenced Treatment Alternatives to Relieve Depression	うつ病軽減のための治療選択肢配列に関する大規模無作為割り付け比較試験
SUN☺D	Strategic Use of New generation antidepressants for Depression	大うつ病に対する新規抗うつ剤の最適使用戦略を確立するための大規模無作為割り付け比較試験

目次

別添資料 1	「うつ病に対して新規抗うつ剤をどのように組み合わせればもっとも速くかつ飲みやすく治療が出来るかを明らかにするための、大規模無作為割り付け比較試験」の説明同意文書
別添資料 2	ジェイゾロフト®添付文書、レメロン®添付文書
別添資料 3	初診患者スクリーニング名簿
別添資料 4	選択基準確認用紙 [EDC ひな形]
別添資料 5	第 3 週の割付連絡用紙 [EDC ひな形]
別添資料 6	第 9 週追跡調査時調査項目[EDC ひな形]
別添資料 7	第 25 週追跡調査時調査項目[EDC ひな形]
別添資料 8	PHQ9
別添資料 9	BDI2
別添資料 10	FIBSER(副作用総合評価尺度)
別添資料 11	自殺性対処マニュアル
別添資料 12	SUN☺D 重篤な有害事象報告手順書および SUN☺D 重篤な有害事象に関する報告書テンプレート
別添資料 13	医薬品安全性情報報告書
別添資料 14	被験者負担軽減費受領証
別添資料 15	C-CASA 報告用紙

0. 臨床試験の概要

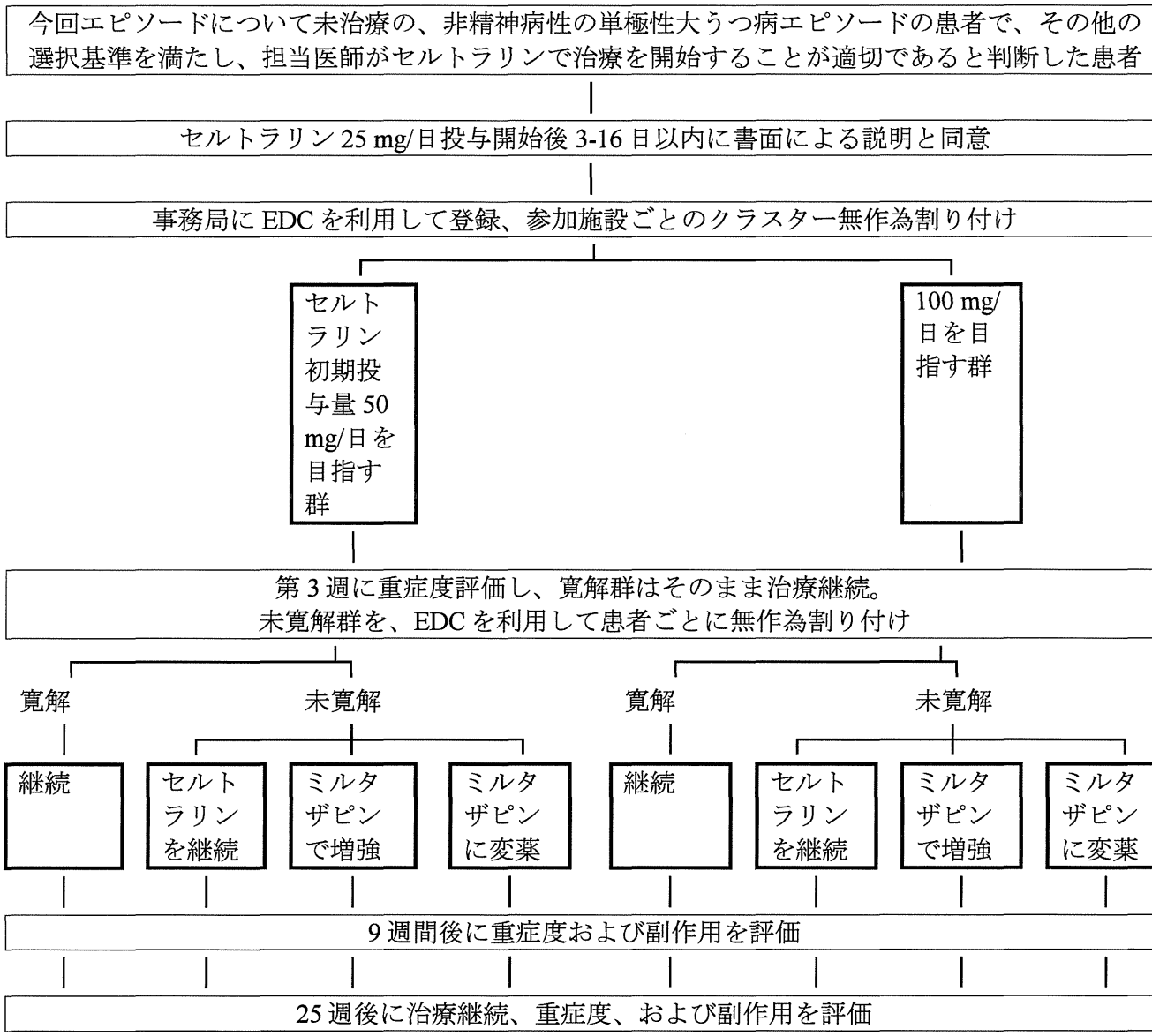
0.1. 目的

単極性大うつ病の急性期治療について、ファーストラインおよびセカンドラインでの抗うつ剤の最適治療戦略を確立する

0.2. 試験デザイン

評価者盲検化(医師患者非盲検化)、並行群間比較、多施設共同、無作為割り付け比較試験

0.3. 試験のフローチャート



0.4. 試験薬の名称

セルトラリン
一般名：セルトラリン錠
商品名：ジェイゾロフト錠

ミルタザピン

一般名：ミルタザピン錠
商品名：レメロン錠、リフレックス錠

0.5. 試験の対象

今回エピソードについて未治療の、非精神病性の単極性大うつ病エピソードの患者

0.6. 試験薬の投与方法

セルトラリンは初期投与量25 mg/日から開始し、50 mg/日まで漸増、または50→75→100 mg/日と漸増する。
ミルタザピンは7.5~15 mg/日から開始し、45 mg/日まで漸増可能とする。
9週以降の継続、変更、中止は担当医師の判断とする。

0.7. 検査スケジュール

評価スケジュールは下記の通り

			ステップI		ステップII							ステップIII			
担当者①	担当者②		第1週	(第2週)	第3週	(第4週)	第5週	(第6週)	第7週	(第8週)	第9週	第3ヶ月 (第13週)	第4か月 (第17週)	第5ヶ月 (第21週)	第6ヶ月 (第25週)
担当医師		BDI2	●	○	●	○	●	○	●	○	●	●	●	●	●
		診断	●												
		年齢	●												
		治療歴	●												
		その他	●								●				●
	サイトCRC	説明同意と補助	● 医師でも中央CRCでも可												
		治療データ	●	○	●	○	●	○	●	○	●	●	●	●	●
	中央CRC	PHQ9	●		●						●				●
		FIBSER	●		●						●				●
		割り付け			● Webで確認しFAX										

●：必須

○：患者が来院した場合のみ収集する

0.8. 評価項目

主要評価項目はPHQ9

副次評価項目はBDI2、副作用総合評価尺度(FIBSER)、治療継続

0.9. 目標症例数

計2000例

0.10. 試験実施期間

2010年12月1日～2015年10月31日（症例登録期間は2010年12月1日～2015年3月31日）

1. 試験の背景

1.1. 日本国民の健康にとって大うつ病の負担はきわめて大きい

WHO推計によると、大うつ病は人類にとって死亡を含めないDALY*損失、すなわち健康損失の最大の原因であり、死亡を含めたDALY損失、すなわち健康および生命損失の3番目に大きな原因であり、さらに今後20年間その損失は増加傾向にあると推定されている[1]。同じ推計によると、日本では、前者についてはやはり最大の原因であり、後者については脳血管疾患に次いで2番目に大きな原因となっており、国民全体の健康および生命損失の実に約6%を占めている。

* DALY (disability-adjusted life years)は「障害調整生命年」と訳され、WHOの定義によれば「死が早まることで失われた生命年数」と「健康でない状態で生活することにより失われている生命年数」の合計である

実際、うつ病は日本人においてももっとも頻度の高い精神疾患であり、女性では12人に1人(8.5%)、男性では29人に1人(3.5%)が生涯に一度はうつ病に罹患すると推定されている[2]。厚労省の患者調査でも気分障害の推計受療患者数は大きく伸びており、過去20年間で6倍にもなっている。日本では1998年から自殺者数が3万人以上に急増し、以後減少していない（1日に換算すると平均およそ85～95人）。10万人当たりの自殺率は日本は米国の約2倍英国の約3倍に達する。自殺既遂者に対する心理学的剖検研究では、既遂者の9割は自殺直前に何らかの精神疾患に罹患しており、その半分がうつ病であると考えられている[3]。

うつ病の治療には、薬物療法も精神療法も同等に有効である[4]が、入手可能性と品質管理と費用の面から、医療現場では抗うつ剤が治療の中心となっている。抗うつ剤には、異環系抗うつ剤(HCA)、モノアミン酸化酵素阻害剤(MAOI)、選択的セロトニン再取り込み阻害剤(SSRI)、セロトニン・ノルアドレナリン再取り込み阻害剤(SNRI)、その他の新規抗うつ剤(ミルタザピン、bupropion)*などがあるが、先進国では過去20年間抗うつ剤の使用量が劇的に増加し、これは主にSSRI、SNRIなどの新規抗うつ剤の増加に由来し、今や新規抗うつ剤がもっとも一般的に処方される抗うつ剤となった[5]。日本ではSSRIが登場する1999年までは抗うつ剤の市場規模150億円程度で推移していたが、SSRIとSNRIの発売後に年20%以上の伸び率で急成長し、2008年には1200億円にせまり、10年間で約8倍に市場が拡大したことになる。現在新規抗うつ剤の市場シェアは89%に達している[IMS Japan]。

* 以下、日本で未承認の薬剤はアルファベット表記、日本で承認済みの薬剤はカタカナ表記とする。

1.2. 抗うつ剤のファーストライン選択についての最新のエビデンス

うつ病の治療に際しては、抗うつ剤の具体的かつ適切な使用指針が必要であることは論を俟たない。しかるに、2008年に至るまで、アメリカ精神医学会のガイドライン[6]、カナダ精神医学会のガイドライン[7]、アメリカ内科医学会のガイドライン[8]、イギリス保健省のNICEガイドライン[9]、日本のガイドライン[10]のいずれにおいても、種々の抗うつ剤の間では副作用プロフィールに差があるだけで、有効性には差がない[11]ので、「副作用プロフィール、費用、および患者の好みに基づいて新規抗うつ剤の中から選択をする」ことが推奨されている[8]。

しかし、2009年、日本・イタリア・イギリスの合同チームが、大うつ病の急性期治療において12個の新規抗うつ剤同士を比較したRCT全117件(25928人)の系統的レビューの結果がLancet誌に発表された[12]。このMeta-analyses of New Generation Antidepressants (MANGA)研究は、コクラン抑うつ不安神経症グループのデータベースを利用して現時点で考えられるもっとも網羅的なデータセットに基づいているうえに、抗うつ剤Aと抗うつ剤Bとの直接比較だけではなく、別の抗うつ剤CやDやE他とAおよびBとの比較も統計学的に合算させるネットワークメタアナリシスという手法を用いている。これらにより、①今までででもっとも精密な（つまり95%信頼区間の狭い）効果推定を、②可及的に出版バイアスを排除する（抗うつ剤AならAを扱った研究にはどうしてもAを販売している会社のデータが多くAに有利な出版バイアスがかかっている可能性があったがここにBもCもDも他の薬剤も統合することで出版バイアスの影響が小さくなる）形で行うことが出来た。

結果、12個の新規抗うつ剤の間にはいくつもの統計学的に有意で臨床的に有意味な差異が観察された。有効性efficacyにおいては、ミルタザピン、escitalopram、venlafaxine、セルトラリンが優れ

ており、受容性 acceptability においては escitalopram、セルトラリン、bupropion、citalopram が優れていた。コストも勘案し、原著者らはセルトラリンをファーストライン選択の候補と結論している。

1.3. 抗うつ剤のセカンドライン選択についての最新のエビデンス

大うつ病治療の困難点の一つは、十分量の抗うつ剤の十分期間の治療でも、反応（うつ病重症度が治療開始時の半分以下になる）率は約 50%、寛解（ほぼ正常気分になる）率は約 30%に過ぎない点である[13]。ファーストラインの治療に対して患者が無ないし部分反応である時に、セカンドラインの治療戦略が用意されなくてはならない。種々のガイドラインで推奨されているものには、①増量 dose escalation、②変薬 switching、③増強 augmentation がある[9, 14]。しかし、多くの RCT が薬剤の認可あるいはその後のマーケティング戦略の中で計画される中、セカンドライン治療についてのエビデンスはファーストラインのそれに比してかなり乏しい。

まず、増薬のストラテジーについては、前薬の継続を対照群とした RCT について系統的レビューが 3 本発表されているが、すべて、ファーストラインの治療に無ないし部分反応であった場合に、同じ投与量を続けるよりも、増量した方が有効性が高くなるというエビデンスはないと結論している[15-17]。次に、変薬については、系統的レビューが 2 本[18] [19]あるが、これらによると、前薬の継続と変薬のストラテジーを比較した RCT は 1 本しかなく、これによると fluoxetine 20 mg/日による 6 週間の治療後も無反応であった者 104 人を、さらに 6 週間そのまま継続するか、ミアンセリン 60 mg/日に変薬するかで比較したところ、寛解率は 18%と 36%であった（p=0.10) [20]。また、変薬する薬の間での差異を検討すると、ファーストラインが SSRI であるときに SNRI の venlafaxine への変薬は同じ SSRI への変薬よりも有効であるようだが、それ以外に異なった薬理学的クラスへの変薬を推奨する根拠は強くなかった[19]。最後に、増強戦略については多数の RCT と系統的レビューが発表されている。もっともエビデンスが揃っているのがリチウム増強[21]、甲状腺ホルモン増強[22]、非定型抗精神病剤による増強[23]である。ほかに、ミルタザピン／ミアンセリンによる増強の RCT が 3 本[20, 24, 25]、ピンドロールによる増強の RCT が 11 本ある[26]。

増量、変薬、増強の 3 戦略それぞれの効果も問題であるが、さらにそれらの間での優劣を比較したエビデンスはほとんど存在しない。例えば、米国 NIMH が 30 億円をかけて実施した実践的大規模 RCT の Sequenced Treatment Alternatives to Relieve Depression (STAR*D)では、それまでの治療で寛解に達しなかった患者に、変薬については計 5 選択肢と増強については計 4 選択肢を検討したが、変薬と増強の間の優劣については変薬と増強のいずれに割り付けられても構わないという同意をした患者が少なくて比較すら出来なかった[27, 28]。

1.4. 新規抗うつ剤の最適使用戦略を確立するために

こうしてみると、最新のエビデンスを踏まえた上でも、日本の臨床家がうつ病の薬物療法を組み立てて行く上で解決されていない、切実かつ重要な臨床疑問がいくつも存在する。切実とは、実地臨床家がほぼ毎日のように遭遇する臨床疑問であるという意味である。重要とは、実際に患者の日常生活に直結する臨床疑問であるという意味である。イギリスの独立エビデンスレビュー誌 Bandolier (http://www.bandolier.com) は MANGA 研究のレビューを「このメタアナリシスが提供しているのは、次のステップのための原材料である。すなわち、最も速く最も安価に最も多くの患者に良い結果をもたらす、うつ病の治療戦略を作成し検証するための原材料である」と締めくくった。うつ病治療研究の次の世代の研究はここから始まる。

1.4.1 ファーストライン治療

まず、ファーストラインについては、MANGA 研究の結果から、有効性と受容性のバランスを考えれば日本ではセルトラリンを第一選択と考えて良いだろう。しかし、すでにこの段階から実地臨床家は選択を迫られる。初期投与量の設定である。日本に於けるセルトラリンの標準投与量は 50-100 mg/日であるが、臨床家はまず 50 mg/日を目標に投与スケジュールを組むべきであろうか、それとも 100 mg/日を目指して投与を開始すべきであろうか。Papakostas ら[29]が SSRI について複数の固定投与量を比較した RCT の系統的レビューを行ったところ、標準投与量の下限（セルトラリ

ンなら 50 mg/日）を投与するのに比して、その 2 倍を投与した場合、有効性は高くなるかもしれない(RR=1.12, 95%CI: 0.99 から 1.27)が受容性が低くなる(RR=0.74, 0.54 から 1.00)ことを見いだしている。反応率（うつ病重症度が 50%以上減少）で言うと 51% から 55%に 4%増えるかもしれないが、脱落率が 10%から 17%に 7%増えてしまう。ただし、Papakostas らが検討した研究は、セルトラリン 200mg, 100mg, 50mg, プラセボの 4 群を比較した Fabre ら[30]の研究も含めて、すべて最初から固定用量を投与するデザインとなっている。

果たして、患者の副作用に留意しながらも最大投与量まで増量するという、多くのガイドライン[6, 7, 10]で推奨される戦略は、まずは標準投与量の最低限を狙うべしという戦略よりも、本当に患者の抑うつ症状を軽減しかつ副作用を増やすことはないのか。誰も知らない。大うつ病患者の治療を開始するすべての臨床家が直面する、これほど切実な臨床疑問への回答がないのはきわめて奇妙にして残念なことである。したがって、我々はこれに回答する RCT を計画した。

1.4.2. セカンドライン治療

次に、ファーストライン薬による治療を最適化しても、現在の知見では患者の半数以上は寛解に達することが出来ない[31]。ならば、セカンドラインでは、何を使えば良いのだろうか、そして、それをいつ判断するのが良いのだろうか。

増薬というストラテジーにはこれに効果があるとする系統的レビューがないので、今回は検討の対象としない。増強については上述のように複数の増強戦略について RCT が行われているが、このうち、現在の日本の保険制度で使用可能なのはミルタザピンおよびミアンセリンによる増強のみである。さらに、増強と変薬といずれがより効果と受容性のバランスでまさっているかは、やはり上述のように、誰も知らない。いつファーストラインに見切りを付けてセカンドラインを考慮すると良いのかも、分かっていない。複数の選択肢について一挙に回答を出す臨床研究を行うことは不可能であるので、われわれは今回の研究では SSRI を継続する選択肢と比較して、MANGA 研究でもっとも有効性が高かったミルタザピンへの変薬と、複数の RCT が有効性を示唆している SSRI のミルタザピンによる増強とを比較検討することにした。

ミルタザピンへの変薬がセカンドラインの候補となる理由は以下の通りである。①MANGA 研究で、ミルタザピンは有効性が最も高い新規抗うつ剤であった。受容性においてやや劣るためファーストラインとはならなかったが、ファーストラインの抗うつ剤に対して無ないし部分反応の患者に対し、より有効性が高いミルタザピンを考慮するのは当然であろう。②2 剤の併用による増強療法は単剤による治療よりも既知および未知の副作用のリスクが大きくなるので、単剤治療をまず考慮すべきであるという議論が成立する。

ミルタザピンによる SSRI の増強もセカンドラインの候補となる。その理由は以下の 3 つである。①ミルタザピン増強の先行研究が有望な結果を出している。1 つの RCT では SSRI, bupropion または venlafaxine に反応しなかった患者 26 人を、ミルタザピン 15-30 mg/日を追加する群とプラセボを追加する群に無作為割り付けして比較したところ、寛解率は 46%と 13% (p=0.068)であった[25]。別の RCT は、大うつ病の治療当初から fluoxetine のみを投与する群と fluoxetine+ミルタザピンを投与する群を比較したところ、寛解率は 25%と 52%(p=0.053)であった[32]。②SSRI に NaSSA（ノルアドレナリン作動性・特異的セロトニン作動性抗うつ剤）のミルタザピンを併用することは薬理学的に理にかなっている。ミルタザピンは、まずノルアドレナリンニューロンのα2 自己受容体を阻害することにより、ノルアドレナリンの放出を増加させる。ノルアドレナリンはセロトニンニューロンを刺激し、またミルタザピン自体がセロトニンニューロンのα2 ヘテロ受容体を阻害するので、併せてセロトニンの放出を促進する。ところが、ミルタザピンは 5-HT2A, 2C, 3 受容体の遮断効果を持っており、抗うつ効果に直結する 5-HT 1A 受容体を特異的に刺激することができる。SSRI と併用した場合、2A の遮断により SSRI で見られる性機能障害や不眠の抑制、2C の遮断により不安の抑制、3 の遮断により消化器症状の抑制が期待される。③ミルタザピンは肝薬物代謝酵素を阻害せず、併用薬との相互作用のリスクが少ない。セルトラリンは CYP2D6 や 3A4 を軽度阻害するが、これとの併用の場合も、他の SSRI よりも安全であると見なされる。

セカンドラインの治療を考慮する際に忘れてはならない臨床疑問は、いつセカンドラインに切り替えるのが適切であるかという臨床疑問である。この問題も、実地臨床家の立場からすれば初期投与量と同じくらい切実な臨床疑問であるのに、筆者らが知る限りこの問題を明示的に扱ったRCTが存在しない上に、ガイドラインはなおざりな推奨でお茶を濁している。アメリカ内科医学会のガイドラインは「6−8週後に十分な反応が得られなかったときには治療を変更する」としているが、その根拠は薬物の治験の平均持続期間であるという[8]。論理的に説得力のない根拠である。改訂NICEガイドラインに至っては、ガイドライン内に不一致があって、ある箇所では3-4週間でセカンドラインを考慮するが、別の箇所では6-8週間でセカンドラインを考慮することとなっている[9]。そこで我々は、ファーストライン薬の投与開始から3週間後という比較的早期にセカンドラインを考慮する群と、ファーストライン薬を継続する群を設けることにより、早期からセカンドラインを検討することに意味があるか否かを検証できるデザインを採用した。

1.4.3. 継続治療

急性期のファーストラインおよびセカンドライン治療を考えるに当たり、もう一つ非常に重要な視点がある。それは継続治療へのスムーズな移行である。急性期治療のみで薬物療法を中断すると再発率が倍増することは、われわれの系統的レビューによって実証されており[33]、現行のすべてのガイドラインが少なくとも数ヶ月の継続治療を推奨している。しかし、実際には多くの患者はガイドラインで推奨されるだけの継続治療を受けていない[34]。従って、急性期治療後3-6ヶ月にわたり抗うつ剤治療を継続できるかは、急性期治療における効果と受容性に加えて、急性期治療を選択する上でもう一つ重要な要因である。そこで、われわれはコホートを治療開始後6ヶ月の時点までフォローすることにより、どの治療戦略がもっとも継続されやすくかつ症状寛解につながるかも検討する。

以上により、われわれは急性期治療から継続治療にわたり、「最も速く最も安価に最も多くの患者に良い結果をもたらす、うつ病の治療戦略」(Bandolier 2009)を組み立てるデザインのRCTを計画した。

2. 試験の目的

今回エピソードについて未治療の、非精神病性の単極性大うつ病エピソードの患者を対象に、
①ファーストライン選択薬をセルトラリンとしたときに初期投与戦略として標準投与量の下限を目標とするのか、上限を目標とするのかいずれが急性期治療として有効性および安全性(即ち、副作用と治療継続)において優れるのか、
②ファーストライン選択薬を3週間服用しても寛解しなかった大うつ病患者を対象に、さらに同じ抗うつ剤を続けるのか、ミルタザピンで増強するのか、ミルタザピンに変薬するのか、いずれが急性期治療として有効性および安全性に優れるか、
③ファーストラインからセカンドラインに至る以上の治療戦略のうちいずれが、急性期治療から継続治療にかけて、もっとも有効性および安全性に優れるか、
を検討する

3. 試験薬の情報

セルトラリンおよびミルタザピンの医薬品添付文書を別添

3.1. セルトラリン

一般名：セルトラリン錠
商品名：ジェイゾロフト錠25mg、50mg
剤型：白色フィルムコート錠
含有量：1錠中にセルトラリンとして25 mgまたは50 mg
発売元：ファイザー株式会社