４．長期のフォローアップ

うつ病が慢性化したり再発したりする可能性があることはすでに説明しました。ですから、うつ病の可能性がある人には時々次のように声をかけると良いでしょう。

「眠られていますか」
「食べられていますか」
「体はだるくないですか」
「気分は重たくないですか」

うつ病の早期発見でも、長期のケアでもいわゆる不定愁訴には注意しましょう。原因がはっきりしない身体的訴えをする人がうつ病である場合が少なくありません。

参考資料

鹿児島県伊集院保健所. 地域におけるこころの健康づくり対策マニュアル～自殺防止対策を展開するために～, 平成15年３月.

資料６　うつ対策の評価例

各地域の特性に応じた「うつ対策」を効果的に推進するためには、各地域で対策のめざす方向が設定され、その達成に向けた長期・中期・短期目標が具体的に立てられることが望まれます。

その目標の達成度を確認し、めざす方向に照らし合わせて活動を評価し、活動を改善していくための「うつ対策の評価」の１例を以下に挙げます。地域の事情にあわせた評価プランを作成する際には、以下の点を参考にしてください。

評価の流れと評価項目

１．うつ対策のめざす方向を明確にします。

① 地域課題の発見：地域の状況を様々な資料から診断し、ニーズを的確にとらえます。
② 目標の設定：めざす方向を明らかにします。
③ 対象と意図の明確化：誰（何・どこ）に対して、どのような状態になることを狙っての活動かを明らかにします。
④ 結果（成果）：どのような成果を実現したいのか、明らかにします。

２．うつ対策のめざす方向にそって、実施した活動を評価します。

① うつ対策で実施した活動（健診前の教室・健診・事後指導のための教室等）ごとに、「活動内容」「連携機関」「所要時間」「参加人数・回数」等を整理します。
② 活動の結果が、目標の達成にどれだけ貢献し、成果をあげたかを評価します。
　☆ 注力度評価：うつ対策への取組姿勢や度合いを確認します。具体的には、地域診断をして地域の課題を明確にすることができたか、地域の課題をうつ対策に関わる者で共有し、組織あげての活動となっていたか等について評価し、改善策を考えます。
　☆ 協働度評価：うつ対策の各活動に関して、関係機関等との課題の共有・協働の度合いを評価し、改善策を考えます。
　☆ 組織の成熟度：うつ対策に取り組む自分たちの組織の成熟の度合いを評価し、改善策を考えます。
　☆ 地域の定着度：うつ対策が対象地域にどれほど定着しているか、その度合いを評価します。これは、地域のうつ対策実施に対する力量を評価するものです。
　☆ 総合評価：注力度・協働度・組織の成熟度・地域の定着度の評価結果をもとに、今後の課題を整理します。
③ 活動成果の評価結果を踏まえ、次に向けた改善策を提案します。

参考資料

三重県健康福祉部健康づくりチーム．三重の健康づくり総合計画「ヘルシーピープルみえ・２１」平成15年度版年次報告書，2003.

資料７：自殺未遂者への対応　青森県名川町（現：南部町）の例

これらは、一例です。プライバシーなどの倫理的側面に充分に配慮しながら、地域の状況や住民の方々の考えに応じて適切なプログラムを作成してください。

１．ケースの状態を把握します。

情報提供機関（救急隊員等）及び病院と連携できる地域システムを構築します。その際、秘密の保持には十分配慮するようにします。

２．普段から連携している精神科などの医師に報告、相談します。

ケースの状態を報告して、今後の対応の仕方のアドバイスを得ます。

３．役職者を含めて看護職でカンファレンスを開きます。

ケースについての情報を持ち寄り、精神科医師のアドバイスを参考に今後の対応策を考えます。

４．家族を援助します。

① 直接訪問して事業について説明して援助します。その際に、情報が漏れないことを伝えます。

※間接的に介入すると本題に入るタイミングを逃したり、対象者の不信感を招いたりする恐れがあります。

② 家族の精神的苦痛を受容します。

※家族の中で自殺未遂者が出たということで、本人の苦しみに気づいてあげられなかったという思いと、退院して町内に帰ってから近所の方にどう思われるかという不安が存在しているものです。

③ 自殺未遂をした本人の最近の状況を聞きます。

④ 精神科の受診を勧めます。

⑤ 困ったり悩んだりしたことがあったらいつでも連絡をしてほしいことを伝えます。

５．民生委員から家族の補助的情報も得ておくようにします。

６．本人に介入します（主治医と連絡をとり、精神状態・身体状況が安定してから面接します）。

① 事業の説明とともに情報入手経緯を話し、情報が漏れないことを伝えます。

② 本人の苦痛を受容します。

③ 主治医とも相談のうえ、必要に応じて精神科の受診を勧めます。

※家族の時と同様の対応をとるが、本人が拒否する場合は、家族の協力も得て説得します。

④ 困ったり、悩んだことがあったらいつでも連絡をしてほしいことを伝えます。

７．環境を整えます。

① 本人が退院後周囲の偏見をあまり受けないように、また、住民が影響を受けて同じ行為に走らないように民生委員へ協力を依頼します。

② 頻回に地域の巡回をします。

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資料８：我が国の 1985 年以降５年間以上継続された高齢者自殺予防活動の実績

（参考資料：大山博史著．高齢者自殺予防マニュアル．診断と治療社．2003）

	新潟県			岩手県	秋田県
	松之山町	松代町	安塚町	浄法寺町	由利町
人口規模[a]	3500-4000	4500-5000	4000-4500	5500-6000	6500-7000
65歳以上人口割合(%)[a]	27.5-30.0	25.0-27.5	22.5-25.0	20.0-22.5	17.5-20.0
高齢者自殺予防活動(施行年度)	1985-2003(継続中)	1988-1997	1991-1997	1985-2003(継続中)	1995-2003(継続中)
スクリーニングとフォローアップ					
実施期間	1986-2003(継続中)	1988-1997	1991-1997	1988-2003(継続中)	未実施
項目内容	SDS, うつ状態の既往, 自殺観念, ライフイベント	SDS	SDS	SDS	
実施頻度	年1回, 悉皆で実施	年1回, 悉皆で実施	年1回, 悉皆で実施	年1回, 30%の高齢者に実施, 5年毎に悉皆で実施	
確定診断	精神科医がRDCによりうつ状態を診断	精神科医がRDCによりうつ状態を診断	一般医がRDCによりうつ状態を診断	精神科医が臨床的にうつ状態を診断	
高危険群への介入法	一般・精神科診療, 保健師訪問	一般医診療, 精神科コンサルテーション, 保健師訪問	一般医の診療, 保健師訪問	精神科診療, 保健師訪問	
高齢者福祉活動					
活動内容	引きこもり老人へのグループ・ケアや友愛訪問	グループ・ケア 友愛訪問		精神科医による相談	保健師による相談 グループケア 友愛訪問
	リハビリ教室 特別養護老人ホーム開設	リハビリ教室 デイ・サービスセンター開設	リハビリ教室 デイ・サービスセンター開設	在宅福祉サービス	
啓発・健康教育					
テーマ	うつ病予防, 自殺の危険 自殺タブー性の強調	うつ病予防, 自殺の危険	うつ病予防, 自殺の危険	うつ病予防, 自殺の危険 自殺タブー性の強調	うつ病予防, 自殺の危険
その他				精神科医との定期連絡会	高齢住民アンケートの頻回実施
高齢者自殺死亡率(対10万) 65歳以上総計(男／女)					
1980-1984	241.9 (162.4/293.4)	226.3 (167.9/267.7)	314.1 (487.3/183.6)	330.3 (418.4/266.3)	107.3 (155.7/ 73.2)
1985-1989	319.4 (159.0/427.2)	325.7 (368.6/294.8)	224.5 (142.4/286.5)	270.3 (141.6/359.2)	219.0 (273.8/197.4)
1990-1994	95.1 (45.0/131.8)	213.3 (438.0/ 52.3)	256.5 (380.5/161.7)	67.0 (0.0/113.4)	298.0 (193.0/370.1)
1995-1999	不詳	114.2 (105.5/120.8)[b]	97.4 (149.1/57.5)	85.0 (136.8/48.4)	104.2 (222.8/22.1)

[a]1990-1994のレンジ(人口は500名区切り, 割合は2.5%区切りで表示)

[b]1995-1997の平均

SDS: Self-rating Depression Scale; RDC: Research Diagnostic Criteria

地域におけるうつ対策検討会　構成員　　(五十音順)

平成十五年八月現在

麻　原　きよみ　　聖路加看護大学　地域看護学　教授

板　波　静　一　　秋田県健康福祉部健康対策課　課長

(北のくに健康づくり推進会議代表幹事　自殺予防対策検討部会　担当)

◎今　田　寛　睦　　国立精神・神経センター　精神保健研究所　所長

宇　田　英　典　　鹿児島県伊集院保健所　所長

大　野　　裕　　慶応義塾大学保健管理センター　教授

川　上　憲　人　　岡山大学大学院医歯科学総合研究科衛生学・予防医学分野　教授

斎　藤　友紀雄　　日本いのちの電話連盟　常務理事

中　村　　純　　産業医科大学精神医学教室　教授

西　島　英　利　　日本医師会　常任理事

平　野　かよ子　　国立保健医療科学院　公衆衛生看護学部　部長

広　瀬　徹　也　　(財) 神経研究所附属晴和病院　院長

藤　臣　柊　子　　漫画家　エッセイスト

(◎　座長)

地域保健従事者向けマニュアル策定グループ　構成員名簿　(五十音順)

平成十五年九月現在

麻　原　きよみ　　聖路加看護大学　地域看護学　教授

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斉　藤　友紀雄　　日本いのちの電話連盟常務理事

野　呂　千鶴子　　三重県津地方県民局保健福祉部 (津保健所) 主査

山　下　俊　幸　　京都市こころの健康増進センター　センター長

(◎　グループ長)

地域保健従事者向けマニュアル改訂グループ　構成員名簿　（五十音順）

平成二十二年三月現在

◎大野　裕	慶應義塾大学保健管理センター　教授
秋山　剛	ＮＴＴ東日本関東病院精神神経科　部長
五十嵐　良雄	メディカルケア虎ノ門　院長
川上　憲人	東京大学大学院医学系研究科　教授
田中　克俊	北里大学大学院医療研究課　准教授
仲本　晴男	沖縄県立総合精神保健福祉センター　所長
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（◎　グループ長　）

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地域におけるうつ対策検討会　運営要綱

1．趣旨

厚生労働省患者調査によると、うつ病を含む気分障害の総患者数は、平成８年の 43 万人から、平成 11 年には 44 万人となっており、複雑な社会構造やそれに伴うストレスの増加等を背景として着実に増加している。また、うつとの関連が深い自殺死亡者についても、その数は、平成 10 年には３万人を超え、その後も横ばいの状態にある。一方、平成 14 年 12 月には、厚生労働省の「自殺防止対策有識者懇談会」の最終報告において、早急に取り組むべき実践的な自殺予防対策として、うつ対策の必要性が指摘された。
こうした状況の下、うつ対策として、保健医療従事者向けのマニュアル等を策定するなどの効果的な方策を検討するための検討会を開催し、もって国民の心の健康の保持・増進を図ることとする。

2．検討課題

① 保健医療従事者向けうつ対応マニュアルについて
② 都道府県・市町村向けうつ対策推進方策マニュアルについて　　等

3．座長

検討会に座長を置くものとする。座長は委員の中から互選により選出するものとする。

4．運営

① 検討会は、座長が必要に応じて召集する。
② 検討会は、その決定に基づき、必要に応じて作業グループで検討させることができる。

5．その他

① 検討会は、原則として公開する。
② 検討会の事務局は、障害保健福祉部　精神保健福祉課において行う。
③ この要綱に定めるものの他、検討会の運営に関し必要な事項は、座長が障害保健福祉部長と協議の上定める。

別紙４

研究成果の刊行に関する一覧表）

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Association analysis of Group II metabotropic glutamate receptor genes (*GRM2* and *GRM3*) with mood disorders and fluvoxamine response in a Japanese population

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ABSTRACT

Background: Several lines of evidence implicate abnormalities in glutamate neural transmission in the pathophysiology of mood disorders, including major depressive disorder (MDD) and bipolar disorder (BP). Preclinical antidepressant effects were also reported for group II metabotropic glutamate receptor (Group II mGluRs) antagonists show dose-dependent antidepressant-like effects in murine models of depression. Also, it has been suggested that abnormalities in the hypothalamic-pituitary-adrenal axis and serotonergic neural transmission are important mechanisms in the pathophysiology of mood disorders. Group II mGluRs play an important role in regulating the function of these mechanisms. From these results, it has been suggested that abnormalities in Group II mGluRs might be involved in the pathophysiology of mood disorders, including MDD) and BP, and may influence the clinical response to treatment with SSRIs in MDD. Therefore, we studied the association between Group II mGluR genes (*GRM2* and *GRM3*) and mood disorders and the efficacy of fluvoxamine treatment in Japanese MDD patients.
Materials and methods: Using three tagging SNPs in *GRM2* and an SNP (rs6465084) reported functional variant in *GRM3*, we conducted a genetic association analysis of case-control samples (325 MDD patients, 155 BP patients and 802 controls) in the Japanese population. In addition, we performed an association analysis of *GRM2* and *GRM3* and the efficacy of fluvoxamine treatment in 117 Japanese patients with MDD. The MDD patients in this study had scores of 12 or higher on the 17 items of the Structured Interview Guide for Hamilton Rating Scale for Depression (SIGH-D). We defined a clinical response as a decrease of more than 50% in baseline SIGH-D within 8 weeks, and clinical remission as an SIGH-D score of less than 7 at 8 weeks.
Results: We found an association between rs6465084 in *GRM3* and MDD in the allele-wise analysis after Bonferroni's correction (P-value = 0.0371). However, we did not find any association between *GRM3* and BP or the fluvoxamine therapeutic response in MDD in the allele/genotype-wise analysis. We also did not detect any association between *GRM2* and MDD, BP or the fluvoxamine therapeutic response in MDD in the allele/genotype-wise or haplotype-wise analysis.
Discussion: We detected an association between only one marker (rs6465084) in GRM3 and Japanese MDD patients. However, because we did not perform an association analysis based on LD and a mutation scan of GRM3, a replication study using a larger sample and based on LD may be required for conclusive results.

1. Introduction

Several lines of evidence implicate abnormalities in glutamate neural transmission in the pathophysiology of mood disorders, including major depressive disorder (MDD) (Hashimoto et al., 2007; Paul and Skolnick, 2003) and bipolar disorder (BP) (Hashimoto et al., 2007; Witkin et al., 2007), and in the mechanisms of therapeutic actions of antidepressants (Palucha and Pilc, 2002). Glutamate exerts its actions through activation of receptors such as *N*-methyl-d-aspartate (NMDA) receptor, metabotropic

Abbreviations: Group II mGluRs, Group II metabotropic glutamate receptors; MDD, major depressive disorder; BP, bipolar disorder; SIGH-D, Structured Interview Guide for Hamilton Rating Scale for Depression; LD, linkage disequilibrium; NMDA, *N*-methyl-D-aspartate; mGluRs, metabotropic glutamate receptors; AMPA, a-amino-3-hydroxy-5-methyl-4-isoxazole propionate; MAFs, minor allele frequencies; HWE, Hardy-Weinberg equilibrium; MDR, Multifactor Dimensionality Reduction; TSNAX-DISC1 gene, Translin-associated factor X-Disrupted-in-Schizophrenia-1 gene; GWAS, whole genome association study.

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glutamate receptors (mGluRs) and a-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA). NMDA receptor antagonists such as dizocilpine and memantine show antidepressant-like actions in mice exhibiting depressive behavior, such as in the forced swim test (Poleszak et al., 2007). Preclinical antidepressant effects were also reported for group II metabotropic glutamate receptor (mGluR2 and mGluR3) antagonists, MGS0039 and LY341495 show dose-dependent antidepressant-like effects in murine models of depression, such as the forced swim and tail suspension tests (Bespalov et al., 2008).

The mGluRs are classified into three groups (group I mGluRs: mGluR1 and mGluR5, group II mGluRs: mGluR2 and mGluR3, and group III mGluRs: mGluR4 and mGluR6-8). Postmortem study has shown decreased mGluR3 in the perirhinal cortex in MDD patients compared with control subjects (Beneyto et al., 2007). Group II mGluRs are highly expressed in brain structures apparently related to emotional states, including the forebrain and limbic areas (Tamaru et al., 2001; Wright et al., 2001). It has been suggested that abnormalities in the hypothalamic-pituitary-adrenal axis (HPA axis) (Buckley and Schatzberg, 2005) and serotonergic neural transmission (Levinson, 2006; Serretti and Mandelli, 2008) are important mechanisms in the pathophysiology of mood disorders. Group II mGluRs have been shown to regulate the function of HPA axis activity (Holsboer and Barden, 1996; Scaccianoce et al., 2003). In animal studies, MGS0039 elevated serotonin levels in the rat medial prefrontal cortex in an *in vivo* microdialysis study (Karasawa et al., 2005) and MGS0039 and LY341495 increased the activity of serotonin neurons in the rat dorsal raphe nucleus (Kawashima et al., 2005). In addition, Matrisciano and colleagues reported that reported that both the expression and function of group II mGluRs are amplified in rat hippocampus when rat was administered imipramine chronically (Matrisciano et al., 2002). From these results, group II mGluRs appear to be good candidates both for involvement in the pathophysiology of, and as therapeutic targets in, MDD.

The mGluR2 gene (*GRM2*: OMIM *604099, 7 exons in a genomic region spanning 10.466 Kb) is located on 3p21. The mGluR3 gene (*GRM3* OMIM *601115, 6 exons in a genomic region spanning 221.763 Kb) is 7q21. This genomic region has been shown to be closely related to susceptibility for BP (Detera-Wadleigh et al., 1997). Therefore, we studied the association between *GRM2* or *GRM3* and mood disorders and the efficacy of fluvoxamine treatment in Japanese MDD patients.

2. Materials and methods

2.1. Subjects

The subjects in the association analysis were 325 MDD patients (159 males and 166 females; mean age ± standard deviation 47.3 ± 14.9years), 155 BP patients (80 males and 75 females; 96 patients with bipolar I disorder and 59 patients with bipolar II disorder; 47.9 ± 14.2 years) and 802 healthy controls (351 males and 451 females; 37.2 ± 15.9 years). Of the 325 MDD patients, 117 (58 males and 59 females; 44.8 ± 16.7 years) were treated with fluvoxamine and diagnosed according to DSM-IV criteria with the consensus of at least two experienced psychiatrists on the basis of a review of medical records and assessments with the Structured Interview Guide for Hamilton Rating Scale for Depression (SIGH-D). The remaining MDD patients were diagnosed according to DSM-IV criteria with the consensus of at least two experienced psychiatrists on the basis of unstructured interviews and a review of medical records. All subjects were unrelated to each other, ethnically Japanese, and lived in the central area of Japan. All healthy controls were also psychiatrically screened based on unstructured interviews. None had severe medical complications such as liver cirrhosis, renal failure, heart failure, or other Axis-I disorders according to DSM-IV.

2.2. Data collection

The 117 MDD patients in this study had scores of 12 or higher on the 17 items of the SIGH-D (Peveler and Kendrick, 2005). We defined a clinical response as a decrease of more than 50% in baseline SIGH-D within 8 weeks, and clinical remission as a SIGH-D score of less than 7 at 8 weeks. Detailed information on data collection was described in a previous paper (Saito et al., 2006). The clinical characteristics of patients in this study, classified according to these definitions, can be seen in Table 1.

2.3. SNP selection

We first consulted the HapMap database (release#23.a.phase2, Mar 2008, www.hapmap.org, population: Japanese Tokyo: minor allele frequencies (MAFs) of more than 0.05) and included 4 SNPs covering *GRM2* (5′-flanking regions including about 6.3 Kb from the initial exon and about 1 kb downstream (3′) from the last exon: HapMap database contig number chr17: 51711684.. 51730152). Then three 'tagging SNPs' were selected with the criteria of r^2 threshold greater than 0.8 in 'pair-wise tagging only' mode using the 'Tagger' program (Paul de Bakker, http://www/broad.mit.edu/mpg/tagger), an implement of the HAPLOVIEW software (Barrett et al., 2005), for the following association analysis. In addition, we selected rs6465084 in *GRM3*, which is reported to be associated with prefrontal brain functioning, for use in the later association analysis.

2.4. SNP genotyping

We used TaqMan assays (Applied Biosystems, Foster City, CA, U.S.A.) for all SNPs. Detailed information is available on request.

Table 1
Clinical characteristics of the patients in both definition groups.

	N			Age (mean ± SD)	Baseline SIGH-D (avg ± SD)	Fluvoxamine dose at 8 weeks (mg/day) (avg ± SD)	Number of previous episode (avg ± SD)
	Total	Male	Female				
Overall	117	58	59	44.8 ± 16.7	20.1 ± 5.84	122 ± 41.0	1.38 ± 0.656
Clinical response group[a]							
Responders	60	29	31	45.1 ± 16.5	21.4 ± 6.19	119 ± 41.0	1.36 ± 0.574
Nonresponders	57	29	28	44.4 ± 17.2	18.7 ± 5.14	125 ± 41.2	1.41 ± 0.780
P-value	0.783			0.849	0.0102	0.468	0.750
Clinical remission group[b]							
Remitters	46	22	24	44.3 ± 16.2	19.5 ± 5.05	114 ± 43.7	1.37 ± 0.598
Nonremitters	71	37	34	45.2 ± 17.3	20.5 ± 6.30	127 ± 38.6	1.39 ± 0.718
P-value	0.650			0.809	0.350	0.118	0.879

[a] Clinical response was defined as a 50% or greater decrease in the baseline SIGH-D score.
[b] Clinical remission was defined as a final SIGH-D score of less than 7.

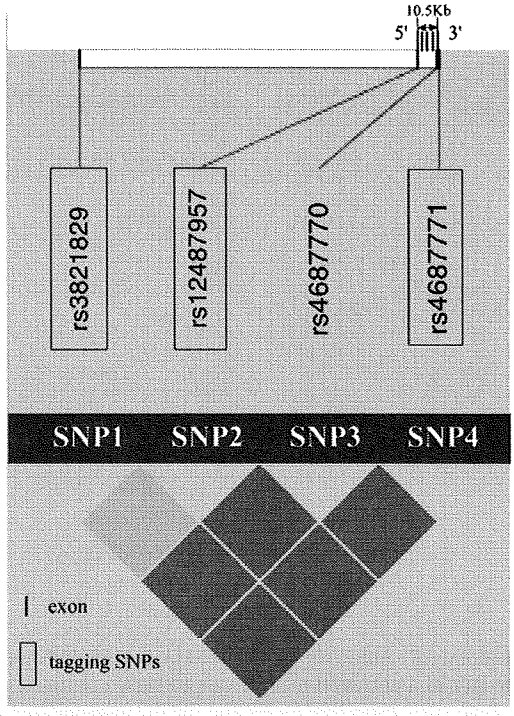

Fig. 1. LD evaluation and tagging SNPs in *GMR2*. Black bars represent exons of *GMR2*. Tagging SNPs selected from HapMap database are represented by black boxes. The color scheme is based on *D'* values. Other information can be seen at the HAPLOVIEW website.

2.5. Statistical analysis

Genotype deviation from the Hardy–Weinberg equilibrium (HWE) was evaluated by chi-square test (SAS/Genetics, release 8.2, SAS Japan Inc, Tokyo, Japan).

Marker-trait association analysis was used to evaluate allele- and genotype-wise associations with the chi-square test (SAS/Genetics, release 8.2, SAS Japan Inc, Tokyo, Japan), and haplotype-wise association analysis was done with a likelihood ratio test using the COCAPHASE 2.403 program (Dudbridge, 2003). Bonferroni's correction was used to control inflation of the type I error rate. Power calculation was performed using a statistical program prepared by Purcell et al. (2003).

3. Results

The linkage disequilibrium (LD) structure of *GRM2* can be seen in Fig. 1. Genotype frequencies were in HWE for all SNPs. In addition, regarding genotyping quality control measures, we added twenty-five randomly selected samples that were genotyped again as a measure of genotyping quality control, and the genotype consistency rates for all four SNPs were 100%. We found an association between rs6465084 in *GRM3* and MDD in the allele-wise analysis after Bonferroni's correction (*P*-value = 0.0371). However, we did not find any association between *GRM3* and BP in the allele/genotype-wise (Table 2). We also did not detect any association between *GRM2* and MDD or BP in the allele/genotype-wise or haplotype-wise analysis (MDD: *P*-value = 0.2537 and BP: *P*-value = 0.1349)(Table 2).

With regard to the clinical characteristics of patients, only one difference was detected between responders and nonresponders in baseline SIGH-D scores (*P*-value = 0.0102) (Table 1). One patient each was prescribed alprazolam, loflazepate and etizolam. Two patients each were prescribed lorazepam, brotizolm, flunitrazepam and zopiclone. We did not find any association between *GRM2* or *GRM3* and the fluvoxamine therapeutic response in MDD patients in allele/genotype-wise (Table 3) or haplotype-wise analysis (response: *P*-value = 0.2459 and remission: *P*-value = 0.3181).

Moreover, to evaluate the interactions with each SNP in these genes, we analyzed the gene-gene interactions with the use of the Multifactor Dimensionality Reduction (MDR) method (Hahn et al., 2003). In this analysis, however, no interactions were obtained with MDD and BP (data not shown).

In the power analysis, we obtained more than 80% power for the detection of association when we set the genotype relative risk at 1.31–1.63 and 1.55–2.18in MDD and BP, respectively, for *GRM2* and at 1.51 and 2.02 in MDD and BP, respectively, for *GRM3* under a multiplicative model of inheritance.

4. Discussion

We performed the first association study of *GRM2* and *GRM3* with mood disorders and fluvoxamine treatment outcome in MDD in the

Table 2
Association analysis of *GRM2* and *GRM3* with mood disorders.

Gene	SNP ID[a]	Phenotype[b]	MAF[c]	*N*	Genotype distribution[d]			*P*-value[f]			Corrected *P*-value[f,g]	
					M/M	M/m	m/m	HWE[e]	Genotype	Allele	Genotype	Allele
GRM2	rs3821829	Controls	0.0468	802	731 (91.1)	67 (8.35)	4 (0.500)	0.0751				
	C>T	BP	0.0516	155	139 (89.7)	16 (10.3)	0 (0.00)	0.498	0.501	0.713		
		MDD	0.0477	325	295 (90.8)	29 (8.92)	1 (0.308)	0.750	0.869	0.924		
	rs12487957	Controls	0.333	802	346 (43.1)	378 (47.1)	78 (9.73)	0.0834				
	T>C	BP	0.281	155	80 (51.6)	63 (40.6)	12 (7.74)	0.934	0.148	0.0719		
		MDD	0.335	325	144 (44.3)	144 (44.3)	37 (11.4)	0.912	0.579	0.910		
	rs4687771	Controls	0.376	802	300 (37.4)	401 (50.0)	101 (12.6)	0.0632				
	T>A	BP	0.332	155	66 (42.6)	75 (48.4)	14 (9.03)	0.260	0.309	0.145		
		MDD	0.378	325	121 (37.2)	162 (49.8)	42 (12.9)	0.283	0.989	0.911		
GRM3 A	rs6465084	Controls	0.0842	802	673 (83.9)	123 (15.3)	6 (0.748)	0.884				
	A>G	BP	0.0903	155	128 (82.6)	26 (16.8)	1 (0.645)	0.796	0.896	0.722		
		MDD	0.0523	325	292 (89.8)	32 (9.85)	1 (0.308)	0.901	**0.0344**	**0.00928**	0.138	**0.0371**

[a] Major allele>minor allele.
[b] BP: bipolar disorder MDD: major depressive disorder.
[c] MAF: minor allele frequency.
[d] M: major allele, m: minor allele, The number in the parenthesis showed the percentage (%).
[e] Hardy–Weinberg equilibrium.
[f] Bold numbers represent significant *P*-value.
[g] Calculated by Bonferroni correction.

Table 3
Genotype and allele distributions of *GRM2* and *GRM3* in both definition groups.

Gene	SNP ID[a]	Clinical groups	MAF[b]	N	Genotype distribution[c]			P-value[d]		
					M/M	M/m	m/m	HWE	Genotype	Allele
GRM2	rs3821829	Responders	0.0667	60	52 (86.7)	8 (13.3)	0 (0.00)	0.580		
	C>T	Nonresponders	0.0263	57	54 (94.7)	3 (5.26)	0 (0.00)	0.838	N.A.	0.145
		Remission	0.0435	46	42 (91.3)	4 (8.70)	0 (0.00)	0.758		
		Nonremission	0.0493	71	64 (90.1)	7 (9.86)	0 (0.00)	0.662	N.A.	0.837
	rs12487957	Responders	0.350	60	25 (41.7)	28 (46.7)	7 (11.7)	0.843		
	T>C	Nonresponders	0.298	57	26 (45.6)	28 (49.1)	3 (5.26)	0.190	0.462	0.398
		Remission	0.370	46	19 (41.3)	20 (43.5)	7 (15.2)	0.650		
		Nonremission	0.296	71	32 (45.1)	36 (50.7)	3 (4.23)	0.0673	0.114	0.239
	rs4687771	Responders	0.383	60	22 (36.7)	30 (50.0)	8 (13.4)	0.656		
	T>A	Nonresponders	0.333	57	23 (40.4)	30 (52.6)	4 (7.02)	0.164	0.527	0.425
		Remission	0.391	46	17 (37.0)	22 (47.3)	7 (15.2)	0.979		
		Nonremission	0.338	71	28 (39.4)	38 (53.5)	5 (7.04)	0.0989	0.361	0.407
GRM3	rs6465084	Responders	0.0667	60	52 (86.7)	8 (13.4)	0 (0.00)	0.580		
	A>G	Nonresponders	0.0614	57	50 (87.7)	7 (12.3)	0 (0.00)	0.621	N.A.	0.869
		Remission	0.0652	46	40 (87.0)	6 (13.0)	0 (0.00)	0.636		
		Nonremission	0.0634	71	62 (87.3)	9 (12.7)	0 (0.00)	0.569	N.A.	0.955

[a] Major allele>minor allele.
[b] MAF: minor allele frequency.
[c] M: major allele, m: minor allele, The number in the parenthesis showed the percentage (%).
[d] Hardy–Weinberg equilibrium.

Japanese population. We detected a significant association between *GRM3* and MDD. In this study, we selected rs6465084 in *GRM3* as the SNP. Rs6465084 has been found to be associated with decreased verbal list learning and verbal fluency (Egan et al., 2004). In addition, Egan and colleagues reported that the rs6465084 A allele predicted decreased levels of *N*-acetylaspartate in the prefrontal cortex in an *in vivo* study, and suggested that the rs6465084 A allele reduced tissue glutamate levels and synaptic abundance (Egan et al., 2004). This influence of *GRM3* on prefrontal cortex and cognitive function suggests that abnormalities in glutamate neurotransmission may be involved in the pathophysiology of MDD by altering glutamate neurotransmission. Rs6465084 was shown to have MAFs $_{controls}$: 0.0842 and MAFs $_{MDD}$: 0.0523. Tochigi and colleagues reported that with this SNP, the MAFs in the Japanese population appear to be smaller than in Caucasians (Tochigi et al., 2006). Also, the MAFs in MDD patients were smaller than in controls. Our result is similar to the results of several studies in schizophrenia (Egan et al., 2004; Mossner et al., 2008). It might be that mood disorders and schizophrenia have common susceptibility genes. In support of this hypothesis, we show recent evidence (TSNAX-DISC1 gene)(Schosser et al., in press). Two studies have also suggested that rs6465084 was associated with the cognitive function in schizophrenic patients (Egan et al., 2004; Mossner et al., 2008). Therefore, further study will be required to investigate the relationship between rs6465084 and cognitive function in MDD patients. Recently, a whole genome association study (GWAS) reported an association between rs2237554 in *GRM3* and bipolar disorder (Sklar et al., 2008). Another GWAS reported that rs2189813, which was in LD with rs2237554 according to the HapMap database ($D' = 1.00$ and $r^2 = 0.831$), was not associated with Japanese bipolar disorder patients (Hattori et al., in press)(release#23.a.phase2, Mar 2008, www.hapmap.org, population: Japanese Tokyo). Although we did not perform an association analysis of rs2237554, a replication study using larger samples than in the original studies will need to be carried out in the future. Also, Sartorius and colleagues reported that rs2228595 in *GRM3* predicted increased expression of the GRM3Delta4 splice variant (Sartorius et al., 2008). This SNP was shown to have "minor allele frequencies: 0.0330%" in the HapMap database (release#23.a.phase2, Mar 2008, www.hapmap.org, population: Japanese Tokyo). However, because our study had a small sample size, we considered it to be difficult to evaluate the association of rare variants from the viewpoint of power. Therefore, we did not include an association analysis of rs2228595.

A few points of caution should be noted in interpreting our results. First, the lack of association may be due to biased samples, such as small sample sizes, especially for BP and the fluvoxamine therapeutic response in MDD samples, or unmatched age or gender samples. Because our samples for BP and the fluvoxamine therapeutic response in MDD were small, type II errors are possible in the results of these statistical association analyses. On average, the controls were much younger than the patients. This means that a number of young controls may go on to develop one of these disorders, most likely MDD, since the incidence of major depression is as high as 5% or more. Our subjects did not undergo structured interviews. MDD patients who are not diagnosed by structured interview may develop bipolar disorder in the future (Bowden, 2001; Kishi et al., 2009; Kishi et al., 2008; Stensland et al., 2008). However, in this study patients were carefully diagnosed according to DSM-IV criteria with consensus of at least two experienced psychiatrists on the basis of a review of medical records. In addition, when we found a patient who had been misdiagnosed, we promptly excluded the misdiagnosed case to maintain the precision of our sample. Second, we could not use an LD based strategy and perform a mutation search because *GRM3* has a massive gene structure. Therefore, in future studies it will be necessary to evaluate associations between other variants and mood disorders. It will be important to replicate and confirm these findings in other independent studies using larger samples.

5. Conclusion

In conclusion, we detected an association between only one marker (rs6465084) in GRM3 and Japanese MDD patients. However, because we did not perform an association analysis based on LD and a mutation scan of GRM3, a replication study using a larger sample and based on LD may be required for conclusive results.

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Regular Article

Practice-based depression screening for psychiatry outpatients: Feasibility comparison of two-types of Center for Epidemiologic Studies Depression Scales

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Aims: The Center for Epidemiologic Studies Depression Scale (CES-D) has been validated to avoid misdiagnoses of major depression in routine psychiatric outpatient settings, but it was reported to be only marginally feasible in these specific settings. A briefer and simpler version, known as the 10-item CES-D, meant to attain adequate feasibility, has been validated in geriatric outpatient settings, but it has not yet been examined in psychiatry outpatient settings. The purpose of the present study was therefore to compare the feasibility, reliability, and validity of the two types of CES-D.

Methods: A cross-sectional analysis was conducted of 86 consecutive outpatients in a psychiatric department in a general hospital.

Results: The 10-item CES-D has a higher feasibility than the 20-item CES-D, and its internal consistency, reliability, and validity are almost identical to those of the 20-item CES-D.

Conclusions: The 10-item CES-D is the better instrument to use because of the higher feasibility than the 20-item CES-D in psychiatric outpatient settings. The different answer format used in each questionnaire (a yes or no format in the former vs a multiple-choice format in the latter) may influence the feasibility, rather than the number of items.

Key words: Center for Epidemiologic Studies Depression Scale, feasibility, major depressive disorder, receiver operating characteristic.

ACCUMULATING EVIDENCE SUGGESTS that major depression, in particular major depression comorbid with dementia,[1] is underrecognized in routine psychiatric practice.[2–4] To avoid such underrecognition and resulting under-treatment, many screening instruments have been developed to detect the presence of major depression. Few of these instruments, however, have been specifically validated for use in routine psychiatric outpatient settings.[2,5,6]

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Among these screening instruments, Schulberg *et al.* and Furukawa *et al.* examined the test characteristics of the Center for Epidemiologic Studies Depression Scale[7] (CES-D or the 20-item CES-D) in psychiatric outpatients using semistructured interviews for criterion-standard diagnoses.[2,5] Despite the demonstrated utility of the CES-D in these studies, the high CES-D incompletion rate of approximately 20–25% suggests that this tool presents problems for psychiatric patients; specifically, the CES-D utilizes a forced four-choice scale format that patients may find difficult to complete. To reduce such respondent burden and to attain an adequate response rate, a briefer and simpler version of the CES-D, known as the 10-item CES-D, has been proposed.[8] The 10-item CES-D has been reported to retain acceptable

reliability and validity in geriatric outpatients,[8–10] but its reliability and validity have not been investigated in psychiatric outpatient settings.

Furthermore, administering a questionnaire to all patients regardless of risk status in practice-based screening has significant limitations to routine use in psychiatry outpatients. The psychiatric population also tends to have a broad spectrum of cognitive impairment derived from mental disorders,[11] which may affect questionnaire feasibility. Particularly, cognitive disorders were strongly associated with the infeasibility of the CES-D.[12] Because the cognitively impaired segment of the population in psychiatry settings grows with the general aging of the population, the routine use of a screening instrument will become more prohibitive due to the decreasing feasibility related to cognitive impairment. To our knowledge, previous work has not fully investigated the feasibility of any depression screening instruments in psychiatric outpatient settings. Here, 'feasibility' is defined as the failure to complete more than a predefined threshold number of items in a screening instrument.

The first aim of the present study was therefore to compare the feasibility of the 10-item and 20-item CES-D in a psychiatric outpatient setting. The second aim was to compare the reliability and validity of the two types of CES-D in this setting.

METHODS

Subjects

We consecutively recruited all first-visit outpatients in the psychiatric department in a general hospital in Japan between 30 April 2006, and 30 March 2007. Patients were recruited regardless of whether or not they had received any psychotropic medication just before enrollment in the study. All subjects except for one agreed to participate; thus, a total of 86 subjects were included in the study. Table 1 lists demographic and diagnostic characteristics of the subjects. Those of the participants who failed to complete the two types of CES-D are also listed in Table 1. Comorbid diagnoses according to depressive status are shown in Table 2. The study protocol was approved by the ethics committees in the facility.

Measures

All patients who visited the waiting room were invited to participate in the study. After signing informed consent, they were asked to complete the

Table 1. Subject characteristics

	Total *n* (%)	20-item CES-D failed *n* (%)	10-item CES-D failed *n* (%)
No. subjects	86	10	3
Age (years) (mean ± SD)	47.0 ± 20.3	70.5 ± 16.5	79.3 ± 4.7
Sex: female (%)	56 (67%)	8 (80)	2 (67)
DSM-IV diagnosis according to MINI			
Mood disorders	51 (59.3%)	2 (20.0)	0
Depressive episode	36 (41.9%)	2 (20.0)	0
Anxiety disorders	48 (55.8%)	0	0
Substance use disorders	1 (1.2%)	0	0
Psychotic disorders†	2 (2.3%)	0	0
Eating disorders	4 (4.7%)	0	0
Antisocial personality disorder	1 (1.2%)	0	0
Cognitive disorders††	6 (7.0%)	6 (60.0)	3 (100.0)
Others	14 (16.3%)	2 (20.0)	0

Because individuals were given more than one diagnosis, the total does not agree with the number of subjects included. Similarly, the percentage of each diagnostic group does not sum to 100%.
†This term refers to schizophrenia and other psychotic disorders in the DSM-IV.
††This term refers to delirium, dementia, and amnestic and other cognitive disorders included in the DSM-IV.
CES-D, Center for Epidemiologic Studies Depression Scale; MINI, Mini International Neuropsychiatric Interview.

Table 2. Comorbid diagnoses according to depressive status[1]

DSM-IV diagnosis according to MINI	Depressive *n*	Not depressive *n*
Anxiety disorders	30	18
Substance use disorders	1	0
Psychotic disorders	0	2
Eating disorders	2	2
Antisocial personality disorders	0	1
Cognitive disorders	0	6
Others	2	12

[1]Major depressive episode according to Mini International Neuropsychiatric Interview (MINI).

two types of CES-D before seeing psychiatrists. During the course of the study, the order of administration of the two instruments was assigned randomly to eliminate ordering effects. If a subject had difficulty in completing the instrument alone, the instrument was administered in a consistent manner by trained nurses who read the items aloud to prevent deviation from the item wording. According to the previous study method,[5] we considered the instrument infeasible for the subject if more than four items of the 20-item CES-D were not completed for any reason, even with the assistance described. For the 10-item CES-D, we set the cut-off score to ≥two items, the equivalent cut-off point in the 20-item CES-D.

The CES-D score was summed to yield a total score ranging from 0 (not depressive) to 60 (most depressive) in the long form and 0 (not depressive) to 10 (most depressive) in the short form, and CES-D scores with permissible missing items were imputed based on the mean score obtained according to the conventional method.[7,8] Additionally, to measure respondent burden, we surveyed the length of time required by all subjects to complete the two types of CES-D.

On the same day of their visits, all subjects were examined using the gold standard Mini International Neuropsychiatric Interview (MINI) to identify current DSM-IV disorders.[13] The MINI is a standardized diagnostic interview according to the DSM-IV criteria, and it was developed as a short and efficient package to be used in clinical as well as research settings.[14,15] As a first step, the initial 11 consecutive subjects were independently assessed by two psychiatrists (including T.N.) using the MINI. Then, inter-rater reliability was obtained as a kappa of 0.667 for the 18 disorders included in the MINI and 0.744 for major depressive episode. With this reliability level, all subsequent subjects and, if there were, persons accompanying them were examined by one experienced psychiatrist (T.N.) who was blind to the CES-D scores.

Furthermore, diagnoses of cognitive disorders were made based on the results of the Mini-Mental State Examination,[16] neurological examination, appropriate laboratory findings, and cranial X-ray computed tomography during follow up as recommended by the Quality Standards Subcommittee of the American Academy of Neurology.[17]

Data analyses

Estimates of the internal reliability of the CES-D were computed using Cronbach's alpha.[18] When conventional operating characteristics for the criterion validity, sensitivity, and specificity of a screening instrument are applied to continuous screening scores, a great deal of information is lost. We avoided this limitation by assessing stratum-specific likelihood ratios (SSLR) for continuous scales.[19,20] Additionally, positive and negative LR, sensitivity, and specificity were also assessed for the results. Positive and negative predictive values depend on disease prevalence, but they are reported herein.

Receiver operating characteristic (ROC) analysis was also conducted. We determined whether the two correlated AUC values obtained from 76 subjects who completed both type of CES-D were statistically different using a non-parametric method.[21] Finally, a McNemar χ^2 test with continuity correction was used to assess the difference in feasibility between the two types of CES-D in a total of 86 participants. All analyses were performed in the R statistical computing environment for Windows (version 2.6).[22] All tests conducted were two tailed.

RESULTS

When the time required to complete the CES-D was surveyed, we found the 20-item CES-D to be much lengthier to administer than the 10-item CES-D (average time ± SD: 3.4 ± 2.4 min for the long form and 1.1 ± 1.0 min for the short form). On examination of the internal consistency reliability, alpha coefficients for the 20-item and 10-item CES-D were 0.92 and 0.80, respectively. ROC analysis illustrates the excellent ability of the CES-D to discriminate

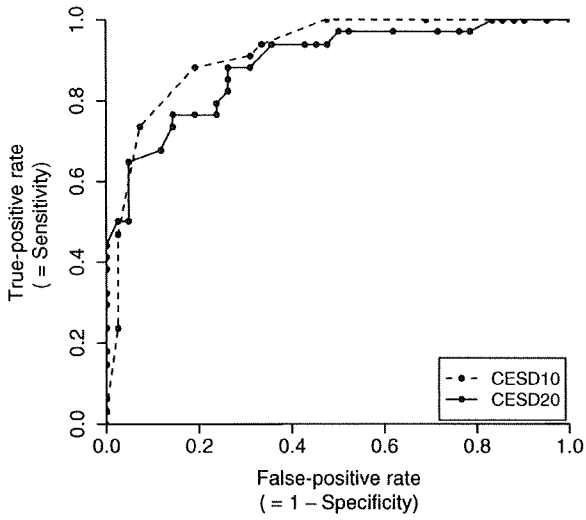

Figure 1. Receiver operating characteristic curve for the (-●-) 10-item and (-●-) 20-item Center for Epidemiologic Studies Depression Scale to screen for depressive episodes.

between depressive and non-depressive subjects. The AUC was 0.89 (95% confidence interval [CI]: 0.82–0.96) and 0.92 (95%CI: 0.86–0.98) for the 20-item and 10-item CES-D, respectively (Fig. 1). These two AUC, which were obtained from 76 subjects completing both types of CES-D, were not significantly different ($P = 0.52$). Table 3 lists the results for the sensitivity, specificity, and predictive values for the various cut-offs of the two types of CES-D. In addition, Table 4 lists the SSLR and aforementioned operating characteristics as a whole.

Finally, the number of items not completed on the 10-item CES-D were 10 items for three patients and one item for three patients, while those on the 20-item CES-D were 20 items for nine patients, six items for one patient, and one item for one patient (Fig. 2). The number of subjects who failed to complete more than a predefined threshold number of items in the 10-item CES-D was significantly lower than that in the 20-item CES-D (3/86 vs 10/86; McNemar's $\chi^2 = 5.14$, d.f. = 1, $P = 0.02$). The diagnoses assigned to the subjects who failed to complete the 20-item CES-D consisted of six cases of dementia, two of mental retardation, and two of major depression; for the 10-item CES-D, the diagnoses were three cases of dementia (Table 1).

DISCUSSION

The major findings of the present study are the following: (i) the feasibility of the 10-item CES-D is significantly and substantially higher than that of the 20-item CES-D; (ii) the 10-item CES-D's internal consistency, reliability, and validity were almost identical to those of the 20-item CES-D, and they indicate its use as a screening instrument for major depression in psychiatric outpatient settings; and (iii) the 10-item

Table 3. Validity characteristics of the 10-item and 20-item CES-D at different cut-offs

	Cut-off	Sensitivity	Specificity	PPV	NPV
10-item CES-D	3/4	0.94	0.67	0.70	0.93
	4/5	0.91	0.69	0.70	0.91
	5/6	**0.88**	**0.81**	**0.79**	**0.89**
	6/7	0.74	0.93	0.89	0.81
	7/8	0.47	0.98	0.94	0.69
20-CES-D	16/17	0.97	0.48	0.60	0.95
	19/20	0.94	0.55	0.63	0.92
	20/21	0.94	0.57	0.64	0.92
	22/23	0.91	0.71	0.72	0.91
	23/24	**0.91**	**0.76**	**0.76**	**0.91**
	24/25	0.88	0.76	0.75	0.89
	27/28	0.79	0.76	0.73	0.82
	30/31	0.76	0.86	0.81	0.82
	36/37	0.65	0.95	0.92	0.77

Bold, chosen cut-off scores.
CES-D, Center for Epidemiologic Studies Depression Scale; NPV, negative predictive value; PPV, positive predictive value.

Table 4. Validity characteristics for the 10-item and 20-item CES-D to screen for depressive episodes

	CES-D-20		CES-D-10	
AUC (95%CI)		0.89 (0.82–0.96)		0.92 (0.86–0.98)
SSLR (95% CI)	0–20	0.11 (0.03–0.37)	0–3	0.09 (0.03–0.30)
	21–36	0.73 (0.39–1.35)	4–6	0.79 (0.35–1.75)
	37–60	13.59 (3.98–46.35)	7–10	10.29 (3.70–26.63)
LR+ (95% CI)	24–60	3.83 (2.24–6.54)	6–10	4.63 (2.51–8.55)
LR– (95% CI)	0–23	0.12 (0.04–0.32)	0–5	0.15 (0.06–0.35)
Sensitivity		0.91		0.88
Specificity		0.76		0.81

AUC, area under the ROC curve; CES-D, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; LR+, positive likelihood ratio; LR–, negative likelihood ratio; SSLR, stratum-specific likelihood ratio.

CES-D can be administered in approximately 30% of the time necessary for the 20-item CES-D. To the best of our knowledge, this study is the first to evaluate the feasibility of any depression-screening instrument in psychiatric outpatient settings. The second finding is in agreement with results reported in older primary care patients, who tend to have as broad a spectrum of cognitive impairments as the psychiatric population.[9,10] With regard to administration time, the third finding is also in agreement with previous reports.[8]

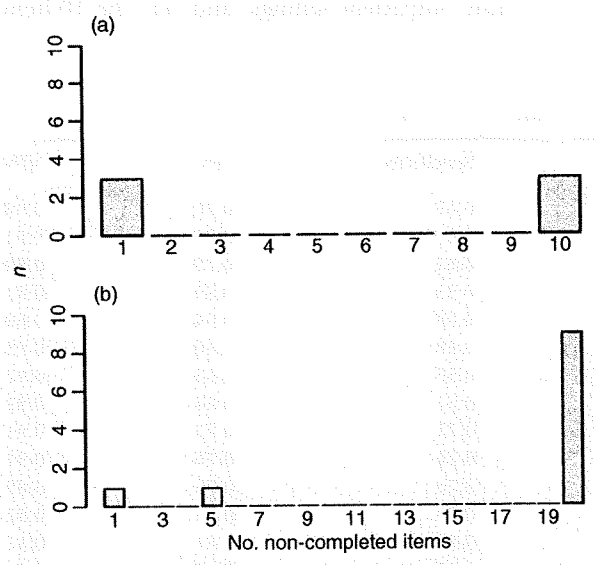

Figure 2. No. non-completed items on the (a) 10-item and (b) 20-item Center for Epidemiologic Studies Depression Scale.

Unfortunately, the psychiatric population tends to have a broad spectrum of cognitive impairments derived from their mental disorders.[11] Furthermore, major depression is a common (30–50%) complication of dementia.[23] Significant limitations thus hinder the routine administration of a questionnaire to all patients regardless of risk status in practice-based screenings. These limitations arise primarily due to patient cognitive impairment, which has been reported to reduce questionnaire acceptability and feasibility.[24] To cope with this problem, it is desirable to use questionnaires that are as feasible and acceptable as possible. The present results show that almost all of the subjects who failed to complete the 20-item CES-D were unable to answer any of the items although half of the subjects who failed to complete the 10-item CES-D were unable to answer only one item on it (Fig. 2). This suggests that the feasibility of each questionnaire may not be so much influenced by the number of items used for each questionnaire but by the answer format, where the former use a multiple-choice format but the latter uses a yes or no format. Therefore, a questionnaire with a yes or no format (e.g. the 10-item CES-D) may be more suitable for psychiatric outpatient settings than those with a multiple-choice format (e.g. the 20-item CES-D) in the light of its feasibility.

From a clinical perspective, the purpose of screening is to improve diagnostic recognition. This requires high sensitivity and a corresponding small false-negative rate so that the clinician can be confident that a negative test result indicates little need to inquire about the target disorder's symptoms. In

contrast, false positives are less of a problem for a screening instrument because their major cost is the time a clinician takes to determine that the disorder is not in fact present. Presumably, this is the time the clinician would have nonetheless spent for the same purpose.[6] This perspective is based on the situation in which the sensitivity and specificity are used to gauge test performance. If the SSLR is instead used to test performance, it is not necessary to tolerate the cost of high false positives.

Using the data in strata rather than a series of cut-offs for positive versus negative findings is a more efficient use of the information included in a test. First, a patient's pre-test probability of disease is estimated from experience, local data, or published literature. Next, the pre-test probability can be converted to the post-test probability using the formula:

$$\text{Pre-test odds} \times \text{SSLR} = \text{Post-test odds}$$

Note that these are odds, not probabilities. The conversions are simple but not intuitively obvious: odds = probability / (1 – probability) and probability = odds / (1 + odds).[19] For example, consider a patient with a pre-test probability of 30% for a major depressive episode. Those patients with a 10-item CES-D score >7 have a post-test probability of 83% for this episode, whereas those with a score <3 have a post-test probability of 4.9%. Thus, we can make our recognition sensitive and specific at the same time by using a SSLR based on a given test score.

The first limitation of the present study is the reliability of cognitive disorder diagnoses, which differ from the diagnoses of other disorders based on the MINI. It must be noted that there was no confirmation of their reliability. The second limiting issue is the relatively small size of the study sample, which did not permit the examination of variables potentially causing CES-D infeasibility. Third, because we did not check whether or not each subject had difficulty in completing the CES-D, the extent to which external help in the completion of the instrument can affect its feasibility is not clear. Each type of CES-D, however, was administered in a consistent manner and thus, the comparison of two types of CES-D should be valid at least in the present study. The fourth issue is the histogram comparison of the uncompleted item between the two types of CES-D (Fig. 2), based on which we suggested that the feasibility for each questionnaire could be influenced by their answer format, rather than by the number of items. There is a possibility, however, that the feasibility of the questionnaires may be influenced by the number of items. For example, most subjects who failed to complete the 20-item CES-D recognized it too hard to answer items on it due to their symptoms (such as lack of self-confidence, lack of concentration, or tiredness). Another explanation is the different factor structures that underlie the two types of the CES-D. There are 50% of items in the 10-item CES-D belonging to the somatic factor, but only 35% of items in the 20-item CES-D.[25] Such differences may affect the difference of the feasibility, rather than the answer format used. To eliminate this uncertainty, it is a better strategy to make a comparison between the same type of CES-D with different answer formats. One such example is the comparison between the 10-item CES-D with yes-no format and multiple-choice format. To make this comparison, we created the 10-item CES-D from the 20-item CES-D retrospectively, which is referred to as the post-hoc 10-item CES-D here. The number of items not completed on the post-hoc 10-item CES-D was 10 items for nine patients and four items for one patient, and thus, significantly more patients failed to complete the post hoc 10-item than the original 10-item CES-D (10/86 vs 3/86; $P = 0.02$). Therefore, the feasibility of the instruments seemed to be influenced by their answer format, rather than by the number of items, although there still remains the possibility that the number of items may influence the feasibility.

Despite these limitations, the present study has a higher success rate in making a diagnosis than previous studies[5,9]; this confers greater generalizability to the results.

In summary, the present data suggest that the 10-item CES-D (a questionnaire with a yes or no format) is a better instrument to use for detecting major depressive episodes in psychiatric outpatient settings because of (i) a substantial reduction of respondent burden; (ii) the resulting greater feasibility over the 20-item CES-D (a multiple-choice format test); and yet (iii) reliability and validity comparable to the 20-item CES-D. The different answer format used in each questionnaire may influence its feasibility, rather than the number of items.

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