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**HOKKAIDO UNIVERSITY**
Development and validation of a screening questionnaire for present or past (hypo)manic episodes based on DSM-IV-TR criteria

Rie Kameyama¹, Takeshi Inoue¹*, Mai Uchida², Teruaki Tanaka¹, Yuji Kitaichi¹, Yasuya Nakato¹, Yoshiyuki Hayashishita¹, Yukiei Nakai¹, Shin Nakagawa¹, Ichiro Kusumi¹, Tsukasa Koyama¹

¹ Department of Psychiatry, Hokkaido University Graduate School of Medicine, North 15, West 7, Kita-ku, Sapporo 060-8638, Japan
² Department of Psychiatry, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114, USA

‡ Equally contributed to this paper and will be designated as co-first authors

* Corresponding author:

Takeshi Inoue, M.D., Ph.D.
Department of Psychiatry, Neural Function
Hokkaido University Graduate School of Medicine
North 15, West 7, Sapporo 060-8638, Japan
Phone: +81-11-706-5160
Fax: +81-11-706-5081
E-mail: tinoue@med.hokudai.ac.jp
Abstract

**Background:** We developed a self-reported questionnaire, the Manic Episode Screening Questionnaire (MES), based on the eight diagnostic criteria items of *DSM-IV-TR* (hypo)manic episodes. This study was designed to determine the optimal screening methods to identify bipolar disorders among mood disorder patients of a psychiatric specialty clinic.

**Methods:** In 95 mood disorder patients, we assessed the operational characteristics of the MES as a screening and diagnostic instrument using a *DSM-IV-TR* diagnosis by a trained psychiatrist as a reference standard. The reference criteria were bipolar disorders. MES was used with two methods: the diagnostic algorithm and the one-question method (question #1 only). The diagnostic algorithm was regarded as fulfilled if the answers to question #1 and three or more of questions #2 to #8 were “yes”, corresponding to the *DSM-IV-TR* (hypo)manic episode criteria. In different subjects, the test-retest reliability of the MES was examined.

**Results:** The two methods of the MES showed high specificity (0.93-0.94), high positive predictive value (0.81-0.83) and high negative predictive value (0.88-0.90), but the sensitivity scored lower (0.68-0.75). The test-retest reliability was moderate: 0.75 for the diagnostic algorithm and 0.68 for the one-question method.

**Limitations:** This study includes a small number of bipolar I patients. The findings might not be generalized to patients outside of this patient population.

**Conclusions:** The MES is useful for the screening and diagnosis of bipolar disorders among mood disorder patients in psychiatric specialty clinics. The one-question method of the MES is more convenient to use than prior questionnaires and is here recommended.

**Key words:** Manic episode screening questionnaire; Bipolar disorder; Self-report; Diagnosis; Misdiagnosis
1. Introduction

The misdiagnosis or underdiagnosis of bipolar disorders, caused by the oversight of a particular past hypomanic episode, has been noted (Ghaemi et al., 2000b; Hirschfeld et al., 2003). In some reports, the rates of bipolar disorder misdiagnosed as major depressive disorder or treatment-resistant major depressive disorder have been 37% and 59%, respectively (Ghaemi et al., 2000b; Sharma et al., 2005). A delay in the correct diagnosis inevitably leads to long-term incorrect treatment plans that are not recommended by recent treatment guidelines for bipolar disorder (Yatham et al., 2009). As a result, some bipolar disorder patients cannot receive adequate treatment for long periods of time (Hirschfeld et al., 2003), resulting in chronic and/or treatment-resistant depressive episodes (Sharma et al., 2005) or rapid cycling (Ghaemi et al., 2000b). This clinical problem is more prevalent in primary care than in psychiatric specialty clinics because the diagnosis of hypomanic or manic episodes, which is sometimes puzzling even to psychiatric specialists, can be quite challenging for primary care physicians (Smith et al., 2011). To avoid the misdiagnosis of unipolar depression for bipolar disorder cases, it is necessary not only to carefully and continuously screen through interviews regarding current or past (hypo)manic episodes but also to provide information for patients and their families based on psychoeducation (Colom and Vieta, 2006).

Three self-reported questionnaires for bipolar disorder have been developed to prevent bipolar disorders from being overlooked and to obtain sufficient information from patients. Two of these questionnaires (Mood Disorder Questionnaire, MDQ; Hypomania Checklist-32, HCL-32) were designed to screen from a lifetime history of (hypo)manic syndromes (Angst et al., 2005; Hirschfeld et al., 2000), and one (Bipolar Spectrum Diagnostic Scale, BSDS) was designed to assess mood fluctuations, such as high or low mood, and to detect the milder portions of the bipolar spectrum (Ghaemi et al., 2005). The application of these questionnaires not only to psychiatric but also to primary care clinics has been tested previously (Hirschfeld et al., 2005; Smith et al., 2011). All three questionnaires showed relatively high sensitivity (MDQ and BSDS, 0.73; HCL-32, 0.80)
and specificity (MDQ and BSDS, 0.90; HCL-32, 0.51) among mood disorder patients. Although the items of the MDQ and HCL-32 overlap with the diagnostic criteria items of a *DSM-IV-TR* (hypo)manic episode (American Psychiatric Association, 2000), the quantity of items is much larger than the eight *DSM-IV-TR* criteria items (MDQ, 13 items; BSDS, 18 items and HCL-32, 32 items). Hence, these prior questionnaires complicate the understanding of the *DSM* concept of “(hypo)manic episode” and its use for psychoeducation.

We developed a self-reported, single page, paper-and-pencil questionnaire, the Manic Episode Screening Questionnaire (MES), which is based on the eight diagnostic criteria items of a *DSM-IV-TR* (hypo)manic episode. The concept of the MES is similar to that of the PHQ-9, which is based on the nine diagnostic criteria items of a *DSM-IV-TR* major depressive episode and is widely used to screen major depressive episodes and to evaluate the severity of depression (Furukawa, 2010). The MES was designed to screen a lifetime history of (hypo)manic episodes and can be used for psychoeducation and self-evaluation due to its facilitation of understanding the concept of a *DSM-IV-TR* (hypo)manic episode. The present study was designed to determine the optimal screening methods for identifying bipolar disorders among mood disorder patients and to assess the sensitivity and specificity of those methods using a diagnosis of bipolar disorder by a mood disorder specialist as the standard criteria.

2. Methods

2.1. Subjects

From February 2008 to March 2011, 293 outpatients who visited the Department of Psychiatry, Hokkaido University Hospital as new patients were consecutively included in the study. Among them, we included 95 patients who had been diagnosed with either major depressive disorder or bipolar disorder using the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text*
Revision (DSM-IV-TR) (American Psychiatric Association, 2000) by a mood disorder specialist psychiatrist (T.I.). T.I. was blinded to the MES results and had more than 20 years of clinical experience in the field of psychiatry. The Japanese version of the MES was administered to all 293 patients during their waiting time as a routine clinical task. This study was performed in accordance with the Declaration of Helsinki and was approved by the institutional review board of Hokkaido University Hospital.

2.2. MES

The Japanese version of MES (Appendix B) was originally designed by one of the authors (T.I.) to detect current or past episodes of mania or hypomania that fulfill the DSM-IV-TR criteria in psychiatric patients. The English version of the MES (Appendix A) was translated from its Japanese version by a bilingual psychiatrist (M.U.) and approved by other authors. The validity of the English version for the screening of current or past (hypo)manic episodes has not been confirmed. The MES consists of eight yes/no items derived from the eight diagnostic criteria items of the DSM-IV-TR, namely, elevated, expansive or irritable mood, inflated self-esteem, decreased need for sleep, manic speech, flight of ideas, distractibility, increase in goal-directed activity, and excessive involvement in pleasurable activities with high potential for painful consequences. The MES was self-completed by the patient in a written form. (Hypo)manic episodes were diagnosed in two ways using the MES: the diagnostic algorithm and the one-question method. The threshold of the diagnostic algorithm for diagnosing a current or past (hypo)manic episode was regarded as fulfilled if the answers to question #1 and three or more of questions #2–#8 were “yes”. For the one-question method, a “yes” answer to question #1 was considered a positive test. Question #1 assesses “elevated, expansive or irritable mood” and represents an essential symptom for the DSM-IV-TR diagnostic criteria of (hypo)manic episodes.

2.3. Psychiatric evaluations
The *DSM-IV-TR* diagnoses of mood disorders, including major depressive disorder, minor depressive disorder and bipolar disorder, were made by a psychiatrist specializing in mood disorders (T.I.) using the *Quick Reference to Diagnostic Criteria from the DSM-IV-TR* on the same day on which the patients answered the MES. The average interview duration was 60 min. In each case, the presence of a current or past major depressive episode or a current or past (hypo)manic episode was identified.

2.4. Test-retest reliability

To assess reliability across time, a sample of 52 subjects, who were different from the 95 patients described above, was retested approximately 4-8 weeks after an initial testing from April 2011 to July 2011. All subjects had been diagnosed with major depressive disorder or bipolar disorder by trained psychiatrists using the *DSM-IV-TR* criteria before the administration of the MES.

2.5. Data analysis

With respect to the validity of the criteria, we investigated the sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio for the diagnostic algorithmic threshold and the one-question method. The *DSM-IV-TR* diagnosis of “bipolar disorder” was the criterion standard.

Test-retest reliability was measured using κ coefficients of agreement.

All continuous data are presented as the means with standard deviations or 95% confidence intervals (CIs).

3. Results

3.1. Demographic characteristics and *DSM-IV-TR* diagnoses of subjects
The demographic characteristics and DSM-IV-TR diagnoses of 95 subjects are presented in Table 1. Seventy-one percent of subjects were diagnosed with major depressive disorder, and 29% of subjects were diagnosed with bipolar disorder (5% bipolar I, and 24% bipolar II). The chief complaints of most of mood disorder subjects were depressive symptoms (89%), and most were in a current major depressive episode that fulfilled the diagnostic criteria.

3.2. Validity of the MES to screen for bipolar disorder

Table 2 (left half) presents the operational characteristics of the diagnostic algorithmic threshold of the MES for “bipolar disorder”. This threshold had a satisfactory specificity (0.94) and a positive likelihood ratio (11.37), as well as a relatively low sensitivity (0.68). The negative likelihood ratio (0.34) was a little higher than desired.

Table 2 (right half) presents the operational characteristics of the one-question method of the MES for “bipolar disorder”. The one-question method had a satisfactory specificity (0.93) and positive likelihood ratio (10.05), as well as a relatively low sensitivity (0.75). The negative likelihood ratio (0.27) was a little higher than desired. Compared with the diagnostic algorithmic threshold, the one-question method showed relatively more valid operational characteristics for bipolar disorder screening.

The DSM-IV-TR diagnoses of false-negative cases (9 for the diagnostic algorithm and 7 cases for the one-question method) were all bipolar II disorder. Conversely, the DSM-IV-TR diagnoses of false-positive cases (4 for the diagnostic algorithm and 5 cases for the one-question method) were major depressive disorder with cyclothymic disorder in 1 case and atypical depression in 1 case. However, 2 false-positive cases analyzed by both methods were converted to bipolar disorder within 1-2 years after the MES was administered. Therefore, the actual number of false positive cases was lower than that shown in Table 2; the actual values of sensitivity, specificity and positive predictive value confirmed by follow-up were higher by 1-8% than those in Table 2.
Because fewer cases were diagnosed with bipolar I disorder (5 cases), the comparison of the utility of the MES in bipolar I and bipolar II disorders was impossible. However, the operational characteristics of the MES for both disorders showed similar tendencies (data not shown).

3.3 Test-retest reliability of the MES for the screening of bipolar disorder

To assess reliability across time, a different sample of 52 subjects was retested approximately 4-8 weeks after an initial testing. All subjects had been diagnosed with major depressive disorder (29 cases, 56%) or bipolar disorder (23 cases 44%; 2 bipolar I and 21 bipolar II). The kappa values for test-retest reliability were moderate: 0.75 for the diagnostic algorithm and 0.68 for the one-question method.

4. Discussion

This study revealed that the MES has a high sensitivity (0.68-0.75), specificity (0.93-0.94), positive predictive value (0.81-0.83), and negative predictive value (0.88-0.90) for the screening of bipolar disorder among mood disorder patients in the setting of a clinic specializing in psychiatry. These values are comparable with those from the conventional self-report questionnaires, the MDQ, BSDS, and HCL-32 (Angst et al., 2005; Ghaemi et al., 2005; Hirschfeld et al., 2000). Moreover, because both the one-question method and the diagnostic algorithm of MES showed similarly excellent operational characteristics, the one-question method, which includes a single question to screen for bipolar disorders, is more advantageous and efficient than other screening methods. The test-retest reliability was excellent (0.68-0.75). Therefore, we conclude that the MES questionnaire, particularly the one-question method, is a simple, easy, and reliable screening tool for bipolar disorders.
As expected by the relatively low sensitivity of the one-question method of the MES, there were many false-negative results. This is one limitation on the use of the MES to screen for bipolar disorder. This limitation is, however, also true of the MDQ, BSDS, and HCL-32 (Angst et al., 2005; Ghaemi et al., 2005; Hirschfeld et al., 2000). One possible explanation for the low sensitivity is that reliance on patient self-reports may contribute to underawareness of mania because their insight is more impaired in mania than in depression (Ghaemi et al., 2000a).

False-negative cases were all diagnosed as bipolar II disorders, and 4 of 7 and 2 of 7 patients were depressed and hypomanic at testing, respectively. In the 2 hypomanic patients, their insight on hypomanic episodes might be impaired, but in the 4 depressed patients, not only poor insight into hypomania but also ignorance of the concept of a hypomanic episode might contribute to a false negative. Future study as to whether patients or their families are even really familiar with the concept of (hypo)manic episodes should be performed.

In this study, there were significantly fewer bipolar I patients than bipolar II patients, and this constitutes another limitation. Accordingly, we could not compare the utility of the MES for bipolar I and bipolar II patients. The utility of the MES for both bipolar disorders will be examined in the future. In addition, although such an easy-to-use questionnaire is useful in primary care as described in the introduction, one cannot extrapolate the clinical utility of the MES in primary care from the results of this study. For example, the positive predictive value may be lower in primary care, in which the prevalence of bipolar disorder is expected to be lower than that in psychiatric clinics (Akobeng, 2007). Hence, further study to test the operational characteristics of the MES using the one-question method and the diagnostic algorithm threshold is needed in primary care settings. Finally, the English version of the MES in Appendix A has been approved by us but has not been validated for the screening of bipolar disorders in native English-speaking patients. A validation of the English version of the MES will be necessary.

The MES shares some content with previous self-report questionnaires, the MDQ and the HCL-32, which ask patients about a lifetime history of (hypo)manic syndromes. As described in the
introduction, that the MES includes a smaller number of items constitutes an advantage over the MDQ and HCL-32, particularly because the 8 items of the MES correspond to the *DSM-IV-TR* criteria and can be easily used for psychoeducation on (hypo)manic episodes. Moreover, this study indicates that the first question alone is enough to screen for a lifetime history of (hypo)manic episodes. To the best of our knowledge, the MES is the first one-question case-finding instrument for the screening of (hypo)manic episodes.

In conclusion, this study clarified that question 1 alone of the simple self-reported questionnaire MES is useful for the screening of (hypo)manic episodes. The validity of the MES as a screening tool, through both the diagnostic algorithm threshold and the one-question method, needs to be confirmed in a primary care setting, and the validity of the English version of the MES needs to be examined. All eight items can be used for both screening and psychoeducation. The MES is clinically useful as a diagnostic tool to prevent the misdiagnosis or underdiagnosis of bipolar disorder and can promote the recognition of undiagnosed bipolarity. However, the gold standard for the diagnosis of bipolar disorder remains the *DSM* criteria. For this reason, caution should be exercised against overestimating the accuracy of this screening tool.

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**Conflict of interest**

The authors report no financial or other relationship that is relevant to the subject of this article.
TI has received honoraria from GlaxoSmithKline, Pfeizer, Astellas, Eli Lilly, Mitsubishi Tanabe Pharma, Mochida Pharmaceutical, Otsuka Pharmaceutical, Meiji Seika Pharma, Asahi Kasei Pharma, Shionogi, Janssen Pharmaceutical, Takeda Pharmaceutical and Yoshitomi Pharmaceutical, has received research/grant support from Otsuka Pharmaceutical, and is a member of the advisory boards of GlaxoSmithKline, Eli Lilly, Mochida Pharmaceutical and Mitsubishi Tanabe Pharma.

SN has received honoraria from GlaxoSmithKline, Eisai, Pfeizer, Daiichi-Sankyo, Meiji Seika Pharma, Ono Pharmaceutical and Eli Lilly, and has received research/grant support from Pfeizer, Eli Lilly, Eisai and Ono Pharmaceutical.

IK has received honoraria from Astellas, Eli Lilly, and Dainippon Sumitomo Pharma, and has received research/grant support from Otsuka Pharmaceutical, Astellas and Dainippon Sumitomo Pharma, and is a member of the advisory board of DainipponSumitomoPharma.

TK has received honoraria from GlaxoSmithKline, Astellas, and Eli Lilly, has received research/grant support from Astellas and GlaxoSmithKline, and is a member of the advisory boards of GlaxoSmithKline and Mitsubishi Tanabe Pharma.

The other authors declare that they have no actual or potential conflict of interest.

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**References**


Table 1. Characteristics and *DSM-IV-TR* diagnoses of 95 patients

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<tr>
<th>Characteristic</th>
<th>Value</th>
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<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female, <em>n (%)</em>; male, <em>n (%)</em></td>
<td>39 (41); 56 (59)</td>
</tr>
<tr>
<td>Age, mean ± SD (yr)</td>
<td>44.3 ± 17.4</td>
</tr>
<tr>
<td>Range</td>
<td>17–81</td>
</tr>
<tr>
<td><em>DSM-IV-TR</em> diagnosis, <em>n (%)</em></td>
<td></td>
</tr>
<tr>
<td>Major Depressive Disorder</td>
<td>67 (71)</td>
</tr>
<tr>
<td>Bipolar Disorder</td>
<td>28 (29)</td>
</tr>
<tr>
<td>Bipolar I Disorder</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Bipolar II Disorder</td>
<td>23 (24)</td>
</tr>
<tr>
<td>Current episode diagnosis, <em>n (%)</em></td>
<td></td>
</tr>
<tr>
<td>Depressive episode</td>
<td>85 (89)</td>
</tr>
<tr>
<td>Hypomanic episode</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Euthymic state</td>
<td>6 (6)</td>
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</table>
Table 2. Sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios, and overall accuracy for the diagnostic algorithm and the one-question method (item 1 only) of Manic Episode Screening Questionnaire (MES)

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<tr>
<th></th>
<th>Diagnostic algorithm of MES</th>
<th>One-question method of MES</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positive, n (%)</td>
<td>19 (20)</td>
<td>21 (22)</td>
</tr>
<tr>
<td>False positive, n (%)</td>
<td>4 (4)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>False negative, n (%)</td>
<td>9 (9)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>True negative, n (%)</td>
<td>63 (66)</td>
<td>62 (65)</td>
</tr>
<tr>
<td>Sensitivity (95%CI)</td>
<td>0.68 (0.55–0.76)</td>
<td>0.75 (0.62–0.84)</td>
</tr>
<tr>
<td>Specificity (95%CI)</td>
<td>0.94 (0.89–0.97)</td>
<td>0.93 (0.87–0.96)</td>
</tr>
<tr>
<td>Positive predictive value (95%CI)</td>
<td>0.83 (0.67–0.92)</td>
<td>0.81 (0.67–0.90)</td>
</tr>
<tr>
<td>Negative predictive value (95%CI)</td>
<td>0.88 (0.83–0.91)</td>
<td>0.90 (0.85–0.93)</td>
</tr>
<tr>
<td>Positive likelihood ratio (95%CI)</td>
<td>11.37 (4.82–28.66)</td>
<td>10.05 (4.78–21.62)</td>
</tr>
<tr>
<td>Negative likelihood ratio (95%CI)</td>
<td>0.34 (0.25–0.51)</td>
<td>0.27 (0.17–0.44)</td>
</tr>
<tr>
<td>Overall accuracy (95%CI)</td>
<td>0.86 (0.79–0.91)</td>
<td>0.87 (0.80–0.92)</td>
</tr>
</tbody>
</table>

95%CI, 95% confidence intervals
Appendix A. English version of Manic Episode Screening Questionnaire (MES)

Please answer yes or no to the following questions and circle your responses.

1. Have you ever had episodes of being extremely happy, energized or irritable, or have you felt that your condition is much better than usual for longer than a few days? Yes  No

If you answered yes to No.1, please answer the following questions.

2. During these episodes, were you more confident than usual? Yes  No
3. During these episodes, were you able to operate without getting much sleep? Yes  No
4. During these episodes, were you more talkative than usual? Yes  No
5. During these episodes, did you come up with lots of ideas, one after another? Yes  No
6. During these episodes, did your interests constantly shift? Yes  No
7. During these episodes, were you active and enthusiastic about engaging in activities? Yes  No
8. During these episodes, did you shop, gamble, make financial investments, or pursue romantic or sexual relationships more than usual? Yes  No
Appendix B. Japanese version of Manic Episode Screening Questionnaire (MES)

以下の質問があなたにあてはまりましたら「はい」に○を、あてはまらなければ「いいえ」に○をつけてください。

1. これまでの人生で、気分高揚し、ハイテンションで、怒りっぽく、普段の調子（100%）を超えた時期が数日以上続いたことがあっ
りますか？

1 で「はい」に○をつけた方は以下の質問にお答え下さい

2. その時、いつもより自信がありましたか？

3. その時、あまり寝なくても平気でしたか？

4. その時、いつもよりよくしゃべりましたか？

5. その時、いろいろな考えが次々に思いつきましたか？

6. その時、次々に関心や興味がうつりましたか？

7. その時、活発・精力的に活動できましたか？

8. その時、買い物・賭け事・投資・異性との交際などが多なくな
りましたか？