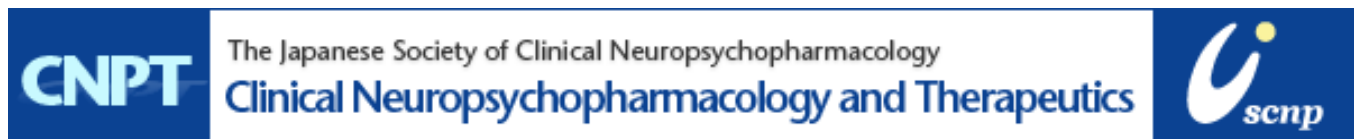This paper has been retracted from CNPT because of serious statistical errors of the data.

The 12-item self-rating questionnaire for depressive mixed state (DMX-12) in relation to categorical diagnoses of mixed depression and mixed features
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ABSTRACT

Purpose: This study aimed to investigate the relationship of the newly developed 12-item dimensional scale of depressive mixed state (DMX-12) with categorical diagnoses of mixed depression (MD) defined by Benazzi in 2008 and mixed features (MF) as a specifier for depressive and bipolar disorders by DSM-5 in 2013.

Methods: The DMX-12 questionnaire was administered to 154 patients (57males and 97 females; 13-83 years) with major depressive episode (MDE) to quantify DMX symptoms. Receiver operating characteristic (ROC) curves were applied to examine the relationship between the DMX-12 and MD or MF.

Results: Among 154 patients, 28 cases (18.2%) showed MD while 7 cases (4.5%) showed MF. Selected 6 symptoms with AUC values more than 0.6 for ROC curves differentiating both MD and MF were overreactivity, inner tension, racing/crowded thought, impulsivity, dysphoria and risk-taking behavior. The AUC of ROC curve using the sum of these 6 symptoms scores was higher (.716 for MD and .761 for MF) than those using total score (.670 for MD and .704 for MF) and disruptive emotion/behavior subscale score (.684 for MD and .714 for MF) of the DMX-12. When the cut-off value in common for both MD and MF was set at ≥14, the sensitivity and negative predictive value for prediction of MD and MF were .750 and .920 for MD and .857 and .989 for MF, respectively.

Discussion: The selected 6 symptoms of the DMX-12 may be useful for sensitive screening and negative check of clinically relevant DMX with considerable severity in patients with MDE.

Keywords: depressive mixed state, mixed depression, mixed feature, DMX-12, receiver operating characteristic

Introduction

It is not rare for clinicians to encounter depressive mixed state (DMX) in patients with major depressive episode (MDE) as temporary mixture of bipolar components with depressive psychopathology [1]. Manifestation of DMX is mainly characterized by dysphoric/irritable mood with inner agitation, racing/crowded thought despite dysfunctional thought content and impulsive/risky behavior together with restlessness [2]. However, spontaneous verbalization of DMX symptoms is usually difficult for patients whereas clinicians interview them mainly focusing on typical depressive symptoms,

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which may easily lead to underdiagnosis of DMX despite the necessity for urgent management of DMX and deliberate pharmacotherapy different from usual treatment of depression [3, 4].

The operational criteria by DSM-IV-TR [5] narrowly defined "mixed episode" as a combination of full manic and major depressive manifestations only for bipolar I disorder, which resulted in strictly limited diagnosis for mixed psychopathology during MDE. Thereafter, the newer definition of "mixed features specifier" (MF) by DSM-5 [6] was expected to provide more open opportunity for sensitive and extended diagnosis of DMX. However, prevalence of DMX still remained unexpectedly low (3.2-7.5%) during MDE even after the criteria of MF during MDE by DSM-5 was applied to clinically relevant mixed psychopathology [7, 8]. Recent reports [9-11] have also criticized underdiagnosis of DMX even after using the DSM-5 criteria due to exclusion of overlapping symptoms for both manic and depressive symptoms such as distractibility, irritability and psychomotor agitation during MDE, termed as "*dip*" into depression as fundamental symptoms defining DMX by Malhi et al [9].

Meanwhile, "mixed depression (MD)" by Benazzi [12-14] has been a well-known practical criterion for DMX, which more widely covers mild to moderate mixed states during MDE. It includes distractibility, irritability and psychomotor agitation as frequently observed manic/hypomanic symptoms for MD [15]. Benazzi defined MD as MDE concurrent with three or more manic/hypomanic symptoms including distractibility, irritability and agitation for one week or longer [12-14]. As a result, about one-third of patients with MDE are supposed to possess mixed components [8], demonstrating that the prevalence of MD is almost five to ten times higher than that of MF among individuals with unipolar and bipolar depression.

Thus, the categorical diagnoses of DMX have major limitation due to wide variability in prevalence of DMX by using different criteria for MD and MF [7, 8]. Furthermore, such criteria are unlikely to be suitable for correct assessment of severity of DMX. Recently, we proposed a postulated model for depressive psychopathology structured by static/dynamic and internalized/externalized dimensions together with its plausible treatment options and suggested the necessity of dimensional approaches to assess various types of depressive symptomatology such as melancholic depression, psychotic depression and mixed depression [3]. Thereafter, we have developed the 12-item questionnaire for screening and quantification of DMX (DMX-12), covering non-specific but frequent mixed symptoms [16].

The DMX-12 consists of 3 subscales, namely, "*spontaneous instability*" (restlessness, distractibility, racing/crowded thought, mood lability, inner tension and impulsivity), "*vulnerable responsiveness*" (hypersensitivity and overreactivity) and "*disruptive emotion/behavior*" (aggression, irritability, dysphoria and risk-taking behavior) by exploratory factor analysis (Table 1) [16]. Severity of DMX assessed by the DMX-12 was positively correlated with severity of core depressive symptoms and bipolarity while it was negatively correlated with age, suggesting that severely depressed younger subjects with potential bipolarity are more likely to develop DMX [16].

In the present study, we aimed to investigate the relationship of our dimensional scale for DMX (DMX-12) [16] with conventional categorical diagnoses of MD [12-14] and MF [6].

Subjects and Methods

Subjects

Subjects were consecutively recruited 154 patients with MDE (57 males and 97 females), who visited our clinic from June 2014 to June 2018. The mean age ($\pm$SD) was 42.6 ($\pm$17.4), and the age range was from 13 to 83 (teens: 14, twenties: 24, thirties: 31, forties: 33, fifties: 22, sixties: 20, seventies or more: 10). They were currently diagnosed as having single or recurrent MDE(s) according to DSM-5 criteria by two experienced psychiatrists and were further classified into depressive disorders (n=111) and bipolar and related disorders (n=43). Patients with substance-related/addictive disorders or neurocognitive disorders were excluded from analyses. This study used the same dataset as our previous study [16].

All subjects gave written informed consent to voluntarily participate in our research. For patients under the age of 18, we got written informed consent not only from patients themselves but also from their parents. The data were anonymously treated during the study. Only coded and grouped data

Table 1. Values of AUC for ROC curves differentiating mixed depression or mixed features

	Mixed depression (MD)	Mixed features (MF)
Vulnerable responsiveness		
Hypersensitivity	.555	.477
➡ Overreactivity	**.677**	**.706**
Spontaneous instability		
Distractibility	.499	.455
Mood lability	.533	.586
Restlessness	.576	**.613**
➡ Inner tension	**.638**	**.613**
➡ Racing/crowded thought	**.647**	**.628**
➡ Impulsivity	**.647**	**.769**
Disruptive emotion/behavior		
Irritability	.584	**.639**
Aggression	.594	**.787**
➡ Risk-taking behavior	**.622**	**.789**
➡ Dysphoria	**.678**	**.616**

* Arrows indicate 6 items with AUC values more than 0.6 for ROC curves differentiating both MD and MF

were used for analyses. Explanation for the purpose of the study, measures for protection of personal information and the right to withdraw from the study were provided to each participant. This study protocol was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of University of the Ryukyus.

Assessments and statistics

The DMX-12 questionnaire in Japanese was developed by us (Appendix 1) [16], according to previously reported core features for DMX such as distractibility, irritability and psychomotor agitation (inner tension and restlessness) and racing/crowded thought [3, 14] as well as other prevalent mixed symptoms, e.g., mood lability, overreactivity, impulsivity, aggression and risk-taking behavior, pointed out from previous researches [7, 17]. This scale was also translated into English and was again back-translated into Japanese by two native speakers for both English and Japanese, followed by confirmation from all the authors (Appendix 2) [16]. We used the original version (in the Japanese language) in the present study. Each item of the DMX-12 was scored using four-scale steps by the frequency of each symptom (0: never, 1: only occasionally, 2: often, 3: almost always) during the latest 1-week period of MDE (Appendix 1 and 2).

Prevalence of categorically-diagnosed DMX was as-

sessed by using standard criteria for MD [12-14] and MF [6] during MDE. Receiver operating characteristic (ROC) curves were applied to examine the relationship between the DMX-12 symptoms and categorical diagnoses for MD and MF. The best cut-off value was determined by the maximal Youden index (sensitivity + specificity -1). All statistical analyses were performed using EZR software version 1.27 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [18]. A two-tailed P value < .05 was regarded as statistically significant.

Results

Among 154 patients with MDE, 28 cases (18.2%) fulfilled Benazzi's criteria for MD [12-14] while 7 cases (4.5%) fulfilled DSM-5 criteria for MF [6]. As previously reported [16], only the "*disruptive emotion/behavior*" cluster out of the three DMX-12 subscales significantly differentiated both MD from non-MD (5.5 ± 2.6 versus 3.8 ± 2.9, P=.002) and MF from non-MF (6.9 ± 2.7 versus 3.9 ± 2.9, P=.013). Therefore, ROC analyses were made by using the "*disruptive emotion/behavior*" subscale score as well as total score of the DMX-12.

Values of AUC for ROC curves by the DMX-12 symptoms were summarized in Table 1. Selected 6 symptoms with AUC values more than 0.6 for ROC curves differentiating both MD and MF were over-

Table 2. Results of ROC analyses using total and cluster scores of the DMX-12 for the screening of depressive mixed state

	Cut-off	Sensitivity	Specificity	PPV	NPV	AUC of ROC
Mixed depression						
DMX-12 (total)	≥19	.714	.579	.274	.901	.670
Disruptive emotion/behavior	≥4	.750	.571	.280	.911	.684
Selected 6 symptoms	≥14	.750	.643	.318	.920	.716
Mixed features						
DMX-12 (total)	≥23	.714	.687	.098	.981	.704
Disruptive emotion/behavior	≥7	.714	.789	.139	.983	.714
Selected 6 symptoms	≥14	.857	.592	.091	.989	.761

Disruptive emotion/behavior: dysphoria, risk-taking behavior, irritability, aggression

Selected 6 symptoms: overreactivity, inner tension, racing/crowded thought, impulsivity, dysphoria, risk-taking behavior
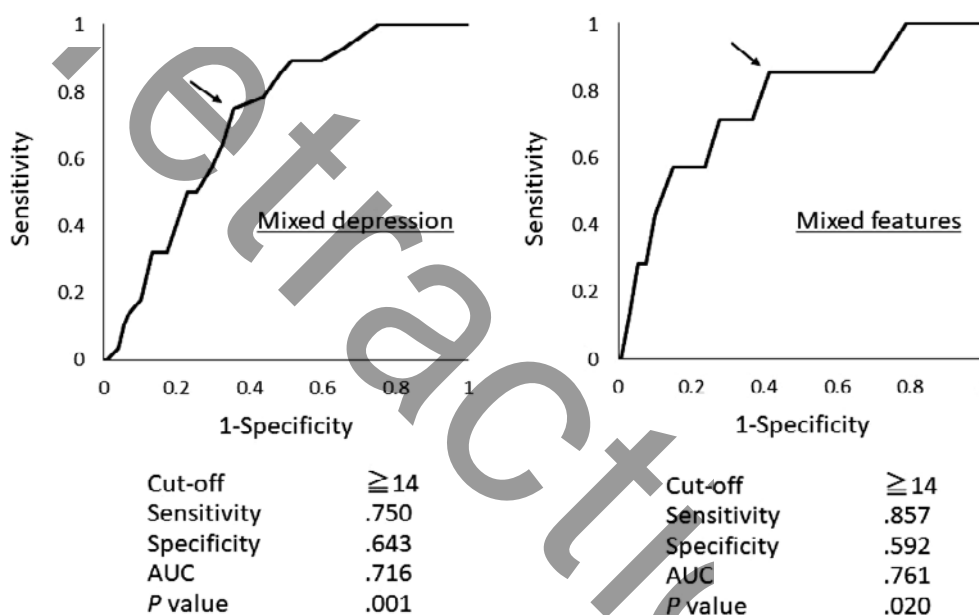

Figure 1. ROC curves differentiating mixed depression or mixed features by selective 6 mixed symptoms (overreactivity, inner tension, dysphoria, racing/ crowded thought, impulsivity and risk-taking behavior) from the DMX-12. Arrows indicate the same cut-off score at 14 for mixed depression and mixed features.

reactivity, inner tension, racing/crowded thought, impulsivity, dysphoria and risk-taking behavior (Table 1). Thus, ROC analysis was also made by using the sum of scores for these selected 6 symptoms.

The AUC of ROC curve using the abovementioned 6 symptoms was higher (.716 for MD and .761 for MF) than those using total score (.670 for MD and .704 for MF) and the "*disruptive emotion/behavior*" subscale score (.684 for MD and .714 for MF) of the DMX-12 (Table 2). When the cut-off value in common for both MD and MF was set at ≥14

(Figure 1), the sensitivity and negative predictive value for prediction of MD and MF by these selected 6 symptoms were .750 and .920 for MD and .857 and .989 for MF, respectively (Table 2).

The original versions of the DMX-12 questionnaire in Japanese and English [16] were modified according to the aforementioned advantage of use of the selected 6 symptoms in differentiating MD from non-MD and MF from non-MF (Appendix 1 and 2).

Discussion

Categorical definitions of DMX by using conventional criteria for MD and MF have resulted in confounding estimation for prevalence of clinically relevant DMX because of wide coverage of DMX by MD (overdiagnosis) and narrow selection of DMX by MF (underdiagnosis) [7, 8]. Meanwhile, Swann [10] has implied that mixed states may be a dimensional property of mood episodes. We have also suggested that categorical criteria for DMX may essentially limit sensitivity or specificity of diagnosis and consequently leave false positive or false negative cases, and that dimensional approach to DMX may become useful for quantitative assessments of real-world mixed psychopathology [3].

Recently developed dimensional scales, e.g., General Inventory of Mixed Affective Symptoms (GIMAS) [19], Multidimensional Assessment of Thymic States (MAThyS) [20] and Multiple Visual Analogue Scale of Bipolarity (MVAP-BP) [21], still include many typical but infrequent symptoms with hypomania/mania, which may not sensitively or specifically determine clinically relevant DMX. The newest scale, Koukopoulos Mixed Depression Rating Scale (KMDRS) proposed by Sani et al [22] should be noted as a well-balanced diagnostic tool for DMX although it may be rather time-consuming for clinicians to assess series of depressed cases in clinical settings due to partial adoption of objective assessments.

The DMX-12 is a compact self-rating scale by patients themselves solely for DMX, mainly consisting of nonspecific but frequently observed mixed symptoms from dimensional aspects [16]. This scale almost comprehensively covers core components from the "dip" symptoms (distractibility, irritability, restlessness and inner tension) together with other prevalent mixed symptoms like racing/crowded thought, mood lability, overreactivity, impulsivity, aggression and risk-taking behavior, which have been previously reported [3, 7, 14, 17]. Although the DMX-12 has been primarily designed for assessment of DMX severity [16], this scale is also expected as a screening tool of DMX during MDE by setting its cut-off score, especially in relation to categorical criteria for MD and MF as conventional diagnoses of DMX.

Our previous study [16] has revealed 3-factor model for symptomatological structure of the DMX-12, consisting of the "spontaneous instability", "vulnerable responsiveness" and "disruptive emotion/behavior" subscales. Among these 3 subscales, the "disruptive emotion/behavior" symptoms, featuring dysphoria, irritability, aggression and risk-taking behavior, are less frequent but are possibly helpful in distinguishing patients with DMX from those without DMX by both Benazzi's definition [12-14] and DMX- 5 criteria [6]. However, considering possibility that the "disruptive emotion/behavior" symptoms can be specific but may not be sensitive enough to detect DMX, we have reviewed usefulness of any DMX-12 symptoms in distinguishing DMX from non-DMX across the 3 subscales in the present study.

As a result, the selected 6 symptoms (overreactivity, inner tension, racing/crowded thought, impulsivity, risk-taking behavior and dysphoria) fulfilled more than 0.6 in the AUC values of ROC differentiating both MD and MF (Table 1). In fact, the sum of these 6 symptoms scores was more excellent in differentiating DMX from non-DMX than total score or the "disruptive emotion/behavior" subscale score of the DMX-12 (Table 2). In addition, it was coincidentally convenient that the abovementioned 6 symptoms could differentiate MD from non-MD and MF from non-MF by using the same cut-off score at 14 (Table 2, Fig. 1). Based on sufficient sensitivity and excellent negative predictive value (Table 2), it is concluded that the selected 6 symptoms of the DMX-12 may be useful for screening and negative check of clinically relevant DMX with considerable severity in patients with MDE.

This study is still preliminary and has several limitations. First, the results were obtained from relatively small number of Japanese subjects. Second, assessment using frequency rather than severity of DMX was conducted on the basis of self-report scales by the DMX-12. Third, the reliability and validity of the English version of the DMX-12 are not yet justified in other ethnic groups. Nevertheless, it is noted that selected 6 symptoms from the DMX-12 may be helpful for clinicians to primarily screen DMX during MDE in usual clinical settings, irrespective of different categorical diagnoses such as MD and MF.

Conclusion

The selected 6 symptoms (overreactivity, inner tension, racing/crowded thought, impulsivity, dysphoria

and risk-taking behavior) of the DMX-12 may be useful for sensitive screening and negative check of clinically relevant DMX with considerable severity in patients with MDE.

CONFLICTS OF INTEREST

ACKNOWLEDGEMENT

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抑うつ性混合状態の自記式評価票：DMX-12 (Shinzato et al, Neuropsychiatr Dis Treat 2019 より改変)

「ここ１週間のあなたの気持ちの状態がどうであったかを評価してください」		まったくない	ときにそうなる	しばしばそうなる	いつもそうである
1. 過剰反応：	ささいなことに対して、いつもと違って過剰に反応してしまう。・・・	0	1	2	3
2. 内的緊張：	気持ちがピンと張りつめていてリラックスできない。・・・・・・・	0	1	2	3
3. 思考促迫・混雑：	頭の中で急かされるように色々な考えが空回りする。・・・・・・・	0	1	2	3
4. 衝動性：	あとさきを考えずにいきなり行動に出てしまいそうになる。・・・・	0	1	2	3
5. 不快気分：	不愉快で不機嫌な気分におそわれる。・・・・・・・・・・・・・	0	1	2	3
6. 危険行為：	わざわざ危険をおかすような行動を選んでしまう。・・・・・・・・	0	1	2	3
7. 過感受性：	いつもよりも人の言葉や態度に敏感で傷付きやすい。・・・・・・・	0	1	2	3
8. 転導のしやすさ：	気が散りやすく、ひとつのことにじっくり取り組めない。・・・・・	0	1	2	3
9. 気分易変：	短時間で気分がめまぐるしく変わりやすい。・・・・・・・・・・	0	1	2	3
10. 落ち着きのなさ：	そわそわした気分でじっとしていられず落ち着かない。・・・・・・	0	1	2	3
11. 易刺激性：	なぜかイライラしてかっとなりやすい。・・・・・・・・・・・・	0	1	2	3
12. 攻撃性：	他人と意見が合わないと、すぐに口論したり、手が出そうになる。・・・	0	1	2	3

＊ 1～6 の合計点≧14 で、抑うつ性混合状態に関する詳細な問診を行うことが望ましい。

＊＊ 臨床使用の際は、項目名および脚注を除く。

Appendix 1.

The 12-item scale for depressive mixed state : DMX-12　(Shinzato et al, Neuropsychiatr Dis Treat 2019 with modification)

0: never

"Please evaluate your mental state during the latest 1 week."

1: only occasionally

2: often

3: almost always

1. Overreactivity :	"I tend to overreact to trivial things more than usual"	0	1	2	3
2. Inner tension :	"I feel so tense that I am unable to relax"	0	1	2	3
3. Racing/crowded thought :	"Many different thoughts run through my head rapidly and fruitlessly"	0	1	2	3
4. Impulsivity :	"I feel like acting impulsively with no regard for consequences"	0	1	2	3
5. Dysphoria :	"I get overwhelmed by unpleasant and displeasing feelings"	0	1	2	3
6. Risk-taking behavior :	"I tend to deliberately take risks"	0	1	2	3
7. Hypersensitivity :	"I am more sensitive and vulnerable than usual to others' comments and attitudes"	0	1	2	3
8. Distractibility :	"I am easily distracted and unable to focus completely on a task"	0	1	2	3
9. Mood lability :	"My mood changes rapidly in a short time"	0	1	2	3
10. Restlessness :	"I feel restless and unable to stay still"	0	1	2	3
11. Irritability :	"I get easily irritated for no reason"	0	1	2	3
12. Aggression :	"When someone disagrees with me, I feel like quarrelling with or hitting that person"	0	1	2	3

* Subjects at 14 or more in the sum of scores for items 1-6 may need further interview confirming depressive mixed state.

** Names of the items and footnotes need to be withdrawn for clinical use.

Appendix 2.