

# Validity of the Shahin Mixed Depression Scale: A Self-Rated Instrument Designed to Measure the Non-DSM Mixed Features in Depression

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**Background:** The DSM5-defined mixed features in depression do not include psychomotor agitation, irritability or distractibility because they are considered overlapping symptoms. A growing number of modern psychiatrists have expressed dissatisfaction with this and proposed alternative sets of mixed symptoms that are much more common and clinically relevant. Among such alternative criteria were those proposed by Koukopoulos. He utilized the research diagnostic criteria of agitated depression (RDC-A) as a mixed depression subtype, and validated another form of mixed depression, the Koukopoulos criteria for mixed depression (K-DMX).

**Purpose:** This study provides psychometric validation for the first self-rated scale designed to measure the most common mixed symptoms in depression as proposed by Koukopoulos.

**Patients and Methods:** We conducted a multicenter cross-sectional study of 170 patients with unipolar depression. They completed the Shahin Mixed Depression Scale (SMDS) and underwent expert interviews as a gold standard reference. SMDS' psychometric properties were assessed, including Cronbach's alpha, factor analysis, sensitivity, specificity, predictive value and accuracy.

**Results:** We found significant association and agreement between mixity according to SMDS and the gold standard (K-DMX and RDC-A according to expert interview) with good internal consistency (Cronbach's alpha=0.87), high sensitivity (=91.4%), specificity (=98.0%), positive predictive value (=96.9%), negative predictive value (= 94.2%) and accuracy (=95.2%). Factor analysis identified one factor for psychomotor agitation and another for mixity without psychomotor agitation.

**Conclusion:** SMDS was a reliable and valid instrument for assessing the frequently encountered and clinically relevant mixed features in depression.

**Keywords:** mixed depression, mixed depression scale, major depressive disorder, psychomotor agitation, agitated depression, unipolar depression

## Introduction

Irritability, psychomotor agitation and distractibility were considered overlapping symptoms and excluded from the DSM-5 definition of mixed depression (DMX).<sup>1</sup> Such a definition is poorly adjusted to the reality. Moreover, there is no mention in the earlier scientific literature of the DSM5-defined mixed symptoms (excluding pressured speech and flight of ideas).<sup>2</sup>

Including the overlapping symptoms, and psychomotor agitation is one of them, recent studies have reported a high prevalence of mixed depression both in samples of patients with bipolar disorder (BD) and major depressive disorder (MDD); for

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instance, Koukopoulos et al<sup>3</sup> reported a prevalence of 27% with both of their definitions of mixed depression (i.e. either motor or psychic agitated depression) among 361 patients with bipolar and unipolar depression. In the same line, Maj et al<sup>4</sup> found 19.5% agitated depression defined by the research diagnostic criteria<sup>5</sup> (RDC) in 313 patients with BD. Benazzi,<sup>6</sup> defining a mixed depressive state as a major depressive episode plus three or more hypomanic symptoms, including psychomotor agitation, irritability and distractibility, reported a prevalence of 43.9% among 144 patients with unipolar depression (UP) and 218 BD type II patients. In the study of Takeshima and Oka,<sup>7</sup> psychomotor agitation is the most frequently observed hypo/manic symptom in both patients with BD (59.8%) and those with MDD (48.8%).

Moreover, a growing number of contemporary psychiatrists have expressed dissatisfaction with the DSM-5 in considering psychomotor agitation as just a part of a subcriterion of major depression, proposing agitated depression as a mixed form of mood disorders.<sup>3,8–15</sup>

So, alternative diagnostic criteria of mixed depression have been proposed. They focused on the most common mixed symptoms, including psychomotor agitation, distractibility, irritability, racing/crowded thoughts, anger, increased talkativeness, indecisiveness, anxiety, emotional lability/tearfulness, inner tension, rumination, initial or middle insomnia, impulsivity and risky behaviors.<sup>16</sup>

One alternative set of mixed symptoms was proposed by Koukopoulos.<sup>2</sup> He recommended giving the name agitated depression to mixed depression with psychomotor agitation as defined by the research diagnostic criteria (RDC-A): the presence of at least two of the following manifestations of psychomotor agitation (not mere subjective anxiety) for several days during the current episode: pacing; hand wringing; unable to sit still; pulling or rubbing on hair, skin, clothing, or other objects; outburst of complaining or shouting; and over-talkativeness.<sup>5</sup>

He also proposed the name mixed depression (K-DMX) for mixed depression without psychomotor agitation when at least three of the following symptoms are present along with MDD: inner tension/agitation, racing or crowded thoughts, irritability or unprovoked feeling of rage, absence of signs of retardation, talkativeness, dramatic description of suffering or frequent spells of weeping, mood lability and marked emotional reactivity, and early insomnia. In his explanation, he believed that the origin of psychic pain, agitation and other mixed symptoms in depression is an underlying excitatory process.<sup>8</sup>

The specific diagnostic criteria for mixed depression without psychomotor agitation (K-DMX) have already been validated by a prior work by Sani et al.<sup>17</sup>

Although mixed depression with psychomotor agitation, i.e. agitated depression (RDC-A) has yet to be validated as a mixed depression subtype, it seems to have diagnostic utility.<sup>18</sup> Such a diagnostic utility could be related to its impact on treatment.<sup>19,20</sup>

Agitated depression (RDC-A) responds well to low-dose neuroleptics, lithium, anticonvulsants and electroconvulsive therapy, whereas it shows marked deterioration in the patient's condition in response to antidepressants,<sup>21–23</sup> in the form of increased agitation, insomnia, greater suffering and the emergence of psychotic symptoms and suicidal ideas and impulses.

Based on the validity of K-DMX<sup>17</sup> and the clinical utility of RDC-A as a mixed depression subtype,<sup>18–20</sup> the aim of this study is to evaluate the psychometric properties of the Shahin Mixed Depression Scale (SMDS) in measuring the non-DSM, Koukopoulos-defined mixed features in depression in a sample of patients with unipolar depression.

## Materials and Methods

### Study Settings

The study was conducted at the outpatient psychiatric clinic of Mansoura University Hospital, at the Shahin private mood clinic in Cairo, and the outpatient clinic of a private mental hospital in Alexandria.

The sample size was calculated through Epi-Info (Epidemiological information package) software version 6.1, according to the following collected data, taking into account that the frequency of the proposed non-DSM mixed depression is 33%–47% as reported by some studies,<sup>24,25</sup> with a confidence level 95% and a degree of precision 80%. The sample was 170, taken by systematic randomization.

### Participants

A total of 170 consecutive patients (off drugs for at least 2 weeks) with unipolar depressive disorder (UP) were randomly enrolled in the study from July 1, 2019 to September 30, 2019. Their proportional allocation was as follows: 74 from Mansoura clinic, 68 from Shahin mood clinic and 28 from Alexandria clinic.

### Inclusion Criteria

Patients with unipolar depression (UP), aged 19–65 years and diagnosed by clinical interview following DSM-5

criteria were included in the study. Montgomery–Asberg Depression Rating Scale (MADRS)<sup>26</sup> was used to assess depressive symptoms. A score of 20 or greater had to be met for a clinical depressive episode. Hypomania Interview Guide–Current assessment Version (HIGH-C)<sup>27</sup> was used to test for significant concurrent hypo/manic symptoms. A score less than 8 was required for patients with UP to be included in the study, following Benazzi’s dimensional definition of mixed depression.<sup>28</sup>

## Exclusion Criteria

To avoid confounding evaluation of the clinical picture, substance-related disorders, borderline personality disorder, psychotic symptoms, adult ADHD, dementia, mental retardation and intra-depressive hypo/manic symptoms mounting to DSM5-defined mixed depression diagnosis were excluded from the study (diagnosed by clinical interview following DSM-5 criteria). Illiterate patients and patients with unstable or severe general medical conditions were also excluded.

## Ethical Considerations

Official permission was obtained from Institutional Review Board (IRB) of Mansoura University. A verbal consent was obtained from the study group. It was informed verbal consent. The verbal consent process was approved by the IRB of Mansoura University. Our study complied with the Declaration of Helsinki.

## Shahin Mixed Depression Scale (SMDS)

The SMDS is a self-rated screening test comprising two parts. The first part (items 1–6) represents psychomotor agitation as defined by the research diagnostic criteria<sup>5</sup> with a cutoff score greater than or equal to 2. The other subscale (items 6–13) matched Koukopoulos mixed features K-DMX as validated by Koukopoulos and collaborators<sup>17</sup> with a cutoff score greater than or equal to 3. Of note, item no. 6 i.e. over-talkativeness, was shared by both subscales and could then be included in either context. Items no. 8 (racing or crowded thoughts), no. 9 (subjective or objective irritability), no. 10 (dramatic description of suffering or frequent spells of weeping), and no. 11 (early or middle insomnia) were further subdivided into two sub-items (a and b). Checking “Yes” to either (a or b) was considered a positive score. As there might be an overlap between depressive anxiety and inner tension,<sup>21</sup> we wanted to better clarify item no. 7, which represented inner tension. We further subdivided it into

three sub-items (a, b, and c) and for a positive score, a or b plus c had to be checked “Yes”. Item no. 13 (representing signs of retardation) was also subdivided into two sub-items (a and b). For a positive score, both sub-items (a and b) had to be checked “No”. For the remaining items, checking “Yes” to any of them was considered a positive score ([Appendix](#)).

The original English version was administered to a convenience group of English-speaking British patients with mood disorders to assess feasibility and face validity. The items were then revised on the basis of this experience and a final version was approved by the authors. The English version was translated into Arabic. Back translation was performed by a bilingual psychiatrist unaware of the original SMDS. A preliminary translated version was administered to 50 Arabic patients with mood disorders. The Arabic authors of the present study reviewed the results of this preliminary investigation, and a final version was approved by them. It was considered equivalent to the original English version.

## The Gold Standard

As it was the first scale of its kind and there was no gold standard with which to correlate, SMDS was validated against expert interviews as a gold reference standard. These interviews were carried out by senior psychiatrists with a minimum of 20 years of experience. They were blind to SMDS results. The experts used a semi-structured interview based on the SCID for DSM-5 (SCID-5) for symptoms such as over-talkativeness and racing thoughts.

For symptoms not found in the SCID-5, supplementary definitions were given: For psychomotor agitation, some questions were taken from Koukopoulos Mixed Depression Rating Scale KMDRS.<sup>29</sup> “Have you been so fidgety and restless that you couldn’t sit still? Do you have to keep pacing up and down?”, and we added others, following the RDC definition: “Have you kept wringing your hands, pulling or rubbing on your hair, skin or clothes? Have you had outbursts of complaining or shouting?”

For inner agitation (tension), patients had to score 3 on KMDRS item no. 9.<sup>29</sup>

For crowded thoughts, we followed Koukopoulos’ definition, i.e. the patient complains of the stream rather than the content: “Have you felt your head full of thoughts that you were unable to stop?”

Crowded thoughts should be differentiated from depressive ruminations which are few, and the patient suffers from the thought content rather than the stream.

For subjective feelings of unprovoked rage, the patient had to score 2 or 3 on KMDRS item no. 6.<sup>29</sup>

For objective expression of irritability, we followed KMDRS corresponding instruction no. 7: Rate overt expressions of irritability, annoyance and anger, including being argumentative, shouting, losing temper, as well as throwing things and being assaultive.

For dramatic description of suffering or frequent spells of weeping, patients had to score 2 or 3 on KMDRS.

For initial insomnia, the required score was at least 1 on the corresponding KMDRS item no. 11, and we followed the KMDRS instruction no. 11 in defining middle insomnia: Only waking up with agitation and/or difficulty falling back to sleep should be rated.

For mood lability, patients should score 3 on the corresponding KMDRS item no. 4.

For the definition of retardation, we followed the instructions of The Cornell Scale for Depression in Dementia CSDD.<sup>30</sup> Retardation is characterized by slow speech, delayed response to questions and decreased motor activity and/or reactions, and we made a small change to the question: "Have you been talking or moving more slowly than is normal for you?"

## Statistical Analysis

Data were collected by expert interviews, previous history and scales. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) software. Qualitative data were represented as number and percentage. Quantitative continuous data were represented by their means and standard deviations. The following are the tests used to assess significant differences:

1. Chi squared tests ( $\chi^2$ ) to assess difference and association of qualitative variables.
2. *t*-Tests to assess differences between quantitative continuous data. Agreement was tested by Kappa agreement. Significant probability was less than or equal to 0.05 ( $P \leq 0.05$ ). We established a factor analysis to determine the extent to which shared variance exists among SMDS variables within the pool of items.

## Results

### Socio-Demographic Data

We studied 170 patients with a mean age of 31.04±8.12, with minimum 19 and maximum 65; 44.1% were male and 55.9% were female. A positive family history of bipolar disorder was found in 22.9%, as shown in Table 1.

**Table 1** Demographic and Clinical Characteristics of the Sample

| Age                      | Mean±SD<br>Median (range) | 31.04±8.12<br>31.0 (19–65) |      |
|--------------------------|---------------------------|----------------------------|------|
|                          |                           |                            |      |
| Onset                    | Mean±SD<br>Median (range) | 13.28±8.4<br>17.0 (1–29)   |      |
|                          |                           |                            |      |
| Duration of index<br>MDE | Mean±SD<br>Median (range) | 13.62±10.8<br>4.0 (2–55)   |      |
|                          |                           |                            |      |
|                          |                           | N                          | %    |
| Sex                      | Male                      | 75                         | 44.1 |
|                          | Female                    | 95                         | 55.9 |
| Residence                | Urban                     | 83                         | 48.8 |
|                          | Rural                     | 87                         | 51.2 |
| Occupation               | Unemployed                | 60                         | 35.3 |
|                          | Employed                  | 110                        | 64.7 |
| Marital status           | Single                    | 43                         | 25.3 |
|                          | Married                   | 38                         | 22.4 |
|                          | Divorced                  | 78                         | 45.9 |
|                          | Widow                     | 11                         | 6.5  |
| Education                | Primary                   | 70                         | 41.2 |
|                          | Preparatory and secondary | 88                         | 51.7 |
|                          | High                      | 12                         | 7.1  |
| Family history           | –VE                       | 131                        | 77.1 |
|                          | +VE                       | 39                         | 22.9 |

**Abbreviations:** MDE, major depressive episode; SD, standard deviation; +VE, positive; –VE, negative.

## Frequencies and Symptom Endorsements

Regarding RDC-A, the highest symptom endorsement was RDC2 (Inability to sit still), the lowest symptom endorsement was RDC6 (Over-talkativeness) and overall RDC-A was present in 18.2%, as shown in Figure 1. Regarding K-DMX, the highest symptom endorsement was DMX1 (Absence of signs of retardation), the lowest symptom endorsement was DMX2 (Over-talkativeness) and overall K-DMX was present in 22.9%, as shown in Figure 2. Regarding SMDS items, the highest item endorsement was item no. 12 (Mood lability) and the lowest was item no. 3 (Hand wringing). Pure depression according to SMDS was 61.2% and mixed depression was 38.8%, as shown in Table 2.

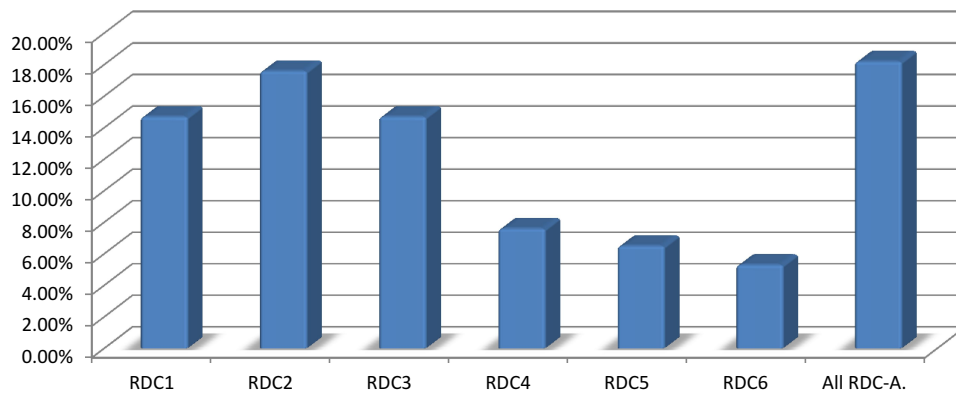
## Internal Consistency

SMDS demonstrated high reliability, and internal consistency was good (Cronbach's Alpha=0.87).

## Factor Analysis

A confirmatory factor analysis identified two components: a factor for mixity without psychomotor agitation and

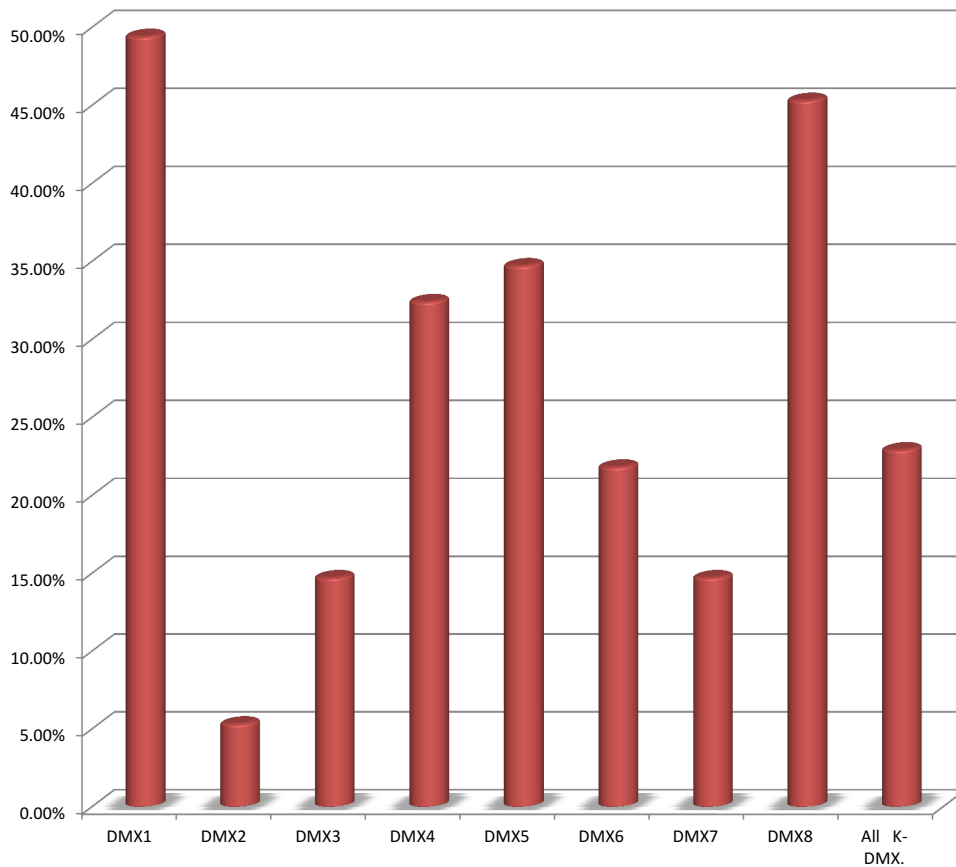
## RDC-A



**Figure 1** RDC-A distribution among studied group.

**Notes:** RDC1: pacing. RDC2: inability to sit still. RDC3: hand wringing. RDC4: pulling or rubbing on hair, skin or clothing. RDC5: outbursts of complaining or shouting. RDC6: over talkativeness.

## K-DMX



**Figure 2** K-DMX distribution among studied group.

**Notes:** DMX1: absence of retardation. DMX2: over talkativeness. DMX3: psychic agitation or inner tension. DMX4: dramatic description of suffering or frequent spells of weeping. DMX5: racing/crowded thoughts. DMX6: irritability or unprovoked rage. DMX7: mood lability and marked reactivity. DMX8: early or middle insomnia.

a factor for psychomotor agitation. From item 7 to item 13, each item accounted for smaller and smaller amounts of the total variance, and items nos. 1, 2, 3, 4, 5, 6 and 13 were

related to both factors but more to agitation. Items nos. 8 and 12 were related only to mixity, and items nos. 7, 9, 10 and 11 were related to both factors but more to mixity.

**Table 2** SMDS Item Distribution and Related Diagnosis

|                     |  |           | N     | %    |
|---------------------|--|-----------|-------|------|
| Agitated depression | Item no. 1, Inability to sit still   | Negative  | 112   | 65.9 |
|                     |  | Positive  | 58    | 34.1 |
| Mixed depression    | Item no. 2, Pacing   | Negative  | 133   | 78.2 |
|                     |  | Positive  | 37    | 21.8 |
|                     | Item no. 3, Hand wringing  | Negative  | 155   | 91.2 |
|                     |  | Positive  | 15    | 8.8  |
|                     | Item no. 4, Pulling or rubbing on hair, skin or clothing                     | Negative  | 146   | 85.9 |
|                     |  | Positive  | 24    | 14.1 |
|                     | Item no. 5, Outbursts of complaining or shouting                             | Negative  | 146   | 85.9 |
|                     |  | Positive  | 24    | 14.1 |
|                     | Item no. 6, Over-talkativeness   | Negative  | 151   | 88.8 |
|                     |  | Positive  | 19    | 11.2 |
|                     | Item no. 7, Psychic agitation  | Negative  | 133   | 78.2 |
|                     |  | Positive  | 37    | 21.8 |
|                     | Item no. 8, Racing/crowded thoughts  | Negative  | 114   | 67.1 |
|                     |  | Positive  | 56    | 32.9 |
|                     | Item no. 9, Irritability or unprovoked rage                                  | Negative  | 126   | 74.1 |
|                     |  | Positive  | 44    | 25.9 |
|                     | Item no. 10, Dramatic description of suffering or frequent spells of weeping | Negative  | 129   | 75.9 |
|                     |  | Positive  | 41    | 24.1 |
|                     | Item no. 11, Early or middle insomnia  | Negative  | 104   | 61.2 |
|                     |  | Positive  | 66    | 38.8 |
|                     | Item no. 12, Mood lability   | Negative  | 92    | 54.1 |
|                     |  | Positive  | 78    | 45.9 |
|                     | Item no. 13, Absence of retardation  | Negative  | 122   | 71.8 |
|                     |  | Positive  | 48    | 28.2 |
| Diagnosis           | Pure depression  |           | 104   | 61.2 |
|                     | Mixity   |           | 35    | 20.6 |
|                     | Agitation  |           | 31    | 18.2 |
|                     | Overall  | Not mixed | 104   | 61.2 |
| Mixed               |  | 66        | 38.8  |      |
| Total               |  | 170       | 100.0 |      |

## Association Between Mixity and Demographic Characteristics

There were significantly more mixed cases in later age: mixed group 35.66±10.25 and pure depression group 28.11±4.42. The mixed group was further significantly associated with being single and with primary and high education levels. It was also significantly associated with a positive family history of bipolar disorder and moderate CGI. However, there was no significant association with sex, residence or occupation, as shown in Table 3.

## Validity of SMDS

We found significant association and agreement between mixity according to SMDS and the gold standard (K-DMX according to expert interview) with sensitivity 87.1%, specificity 99.2%, +VE predictive 97.1%, -VE predictive 96.2% and accuracy 96.4%. Also, we found significant association and agreement between agitation according to SMDS and the gold standard (RDC-A according to expert interview) with sensitivity 96.8%, specificity 99.3%, +VE predictive 96.7%, -VE predictive 99.2% and accuracy 98.8%. Regarding overall mixity, we found significant association and agreement between overall mixity according to SMDS and the gold standard with sensitivity 91.4%, specificity 98.0%, +VE predictive 96.9%, -VE predictive 94.2% and accuracy 95.2% as shown in Table 4.

## Discussion

This is the second study assessing, in an outpatient sample, the validity of SMDS, a self-rated screening instrument designed to measure the non-DSM mixed features in depression, as proposed by Koukopoulos. Against an expert interview diagnosis of the clinically valid Koukopoulos criteria K-DMX, and of the clinically utilized research diagnostic criteria of agitated depression RDC-A, which is used as the “gold standard”, the sensitivity against RDC-A was 96.8% and the specificity was 99.3%; the sensitivity against K-DMX was 87.1% and the specificity was 99.2%. Factor analysis identified two components that capture the proposed mixed features: a factor for psychomotor agitation and a factor for mixity without psychomotor agitation. In our study, we found that SMDS had good reliability and internal consistency (Cronbach's Alpha=0.87). We also found that mixed states were significantly more frequent in later age. This finding is in line with some studies<sup>31</sup> but contradicts others.<sup>4,32–35</sup>

Our aim in this, as in our earlier investigation<sup>36</sup> was to include only patients with unipolar depression. This may account for the higher age finding. It is essential to note that in patients with non-DSM mixed features, bipolar latency is not the only important consideration. The more practical and clinically relevant negative impact of antidepressant treatment, irrespective of any actual switch to frank hypo/mania, must also be borne in mind. Of note, as reported,<sup>32,34,35,37–39</sup> there was more positive family history of bipolar disorder in cases with mixed depression.

This is the first self-rated scale of its kind that addresses the most common non-DSM mixed features as proposed by

**Table 3** Basic Demographic and Clinical Data Distribution Among Pure Depression and Mixed Groups

|                                    |                           |        | Group           |             | $\chi^2$    | P       |        |
|------------------------------------|---------------------------|--------|-----------------|-------------|-------------|---------|--------|
|                                    |                           |        | Pure Depression | Mixed       |             |         |        |
| Age                                | Mean±SD                   |        | 28.11±4.42      |             | 35.66±10.25 | -6.612  | 0.00** |
| Sex                                | Male                      | N<br>% | 52<br>50.0      | 23<br>34.8  | 3.76        | 0.053   |        |
|                                    | Female                    | N<br>% | 52<br>50.0      | 43<br>65.2  |             |         |        |
| Residence                          | Rural                     | N<br>% | 46<br>44.2      | 37<br>56.1  | 2.26        | 0.13    |        |
|                                    | Urban                     | N<br>% | 58<br>55.8      | 29<br>43.9  |             |         |        |
| Occupation                         | Employed                  | N<br>% | 41<br>39.4      | 19<br>28.8  | 2.69        | 0.18    |        |
|                                    | Unemployed                | N<br>% | 63<br>60.6      | 47<br>71.2  |             |         |        |
| Marital status                     | Single                    | N<br>% | 20<br>19.2      | 23<br>34.8  | 15.55       | 0.001** |        |
|                                    | Married                   | N<br>% | 32<br>30.8      | 6<br>9.1    |             |         |        |
|                                    | Divorced                  | N<br>% | 43<br>41.3      | 35<br>53.0  |             |         |        |
|                                    | Widow                     | N<br>% | 9<br>8.7        | 2<br>3.0    |             |         |        |
| Education                          | Primary                   | N<br>% | 20<br>19.2      | 50<br>75.8  | 88.41       | 0.00**  |        |
|                                    | Preparatory and secondary | N<br>% | 84<br>80.8      | 4<br>6.1    |             |         |        |
|                                    | High                      | N<br>% | 0<br>0.0        | 12<br>18.2  |             |         |        |
| Family history of bipolar disorder | No                        | N<br>% | 94<br>90.4      | 37<br>56.1  | 26.9        | 0.00**  |        |
|                                    | Yes                       | N<br>% | 10<br>9.6       | 29<br>43.9  |             |         |        |
| CGI                                | Mild                      | N<br>% | 54<br>51.9      | 15<br>22.7  | 14.27       | 0.00**  |        |
|                                    | Moderate                  | N<br>% | 50<br>48.1      | 51<br>77.3  |             |         |        |
| Total                              |                           | N<br>% | 104<br>100.0    | 66<br>100.0 |             |         |        |

Note: \*\*Highly significant.

Koukopoulos. The Koukopoulos Mixed Depression Rating Scale (KMDRS)<sup>29</sup> is a clinician-rated scale that captures the same construct. However, for a busy clinician, it might be

time consuming to use it on a regular basis. Another clinician-rated bivariate scale for both manic and depressive mixed features has been developed by Cavanagh et al.<sup>40</sup>

**Table 4** Association, Agreement and Validity of SMDS

|                             |     |   | K-DMX According to Expert Interview          |             | $\chi^2$       | P              | Kappa Agreement |
|-----------------------------|-----|---|--|-------------|----------------|----------------|-----------------|
|                             |     |   | -VE  | +VE         |                |                |                 |
| Mixity according to SMDS    | -VE | N | 130  | 5           | 124.5          | 0.00**         | 0.82            |
|                             |     | % | 99.2   | 12.9        |                |                |                 |
|                             | +VE | N | 1  | 34          |                |                |                 |
|                             |     | % | 0.8  | 87.1        |                |                |                 |
| Total                       |     | N | 131  | 39          |                |                |                 |
| Validity                    |     |   | Sensitivity                                  | Specificity | +VE Predictive | -VE Predictive | Accuracy        |
|                             |     |   | 87.1%  | 99.2%       | 97.1%          | 96.2%          | 96.4%           |
|                             |     |   | RDC-A According to Expert Interview          |             | $\chi^2$       | P              | Kappa Agreement |
|                             |     |   | -VE  | +VE         |                |                |                 |
| Agitation according to SMDS | -VE | N | 138  | 1           | 156.85         | 0.00**         | 0.95            |
|                             |     | % | 99.3   | 3.2         |                |                |                 |
|                             | +VE | N | 1  | 30          |                |                |                 |
|                             |     | % | 0.7  | 96.8        |                |                |                 |
| Total                       |     | N | 139  | 31          |                |                |                 |
| Validity                    |     |   | Sensitivity                                  | Specificity | +VE Predictive | -VE Predictive | Accuracy        |
|                             |     |   | 96.8%  | 99.3%       | 96.7%          | 99.2%          | 98.9%           |
|                             |     |   | Overall Mixity According to Expert Interview |             | $\chi^2$       | P              | Kappa Agreement |
|                             |     |   | -VE  | +VE         |                |                |                 |
| Overall mixity by SMDS      | -VE | N | 98   | 6           | 146.1          | 0.00**         | 0.91            |
|                             |     | % | 98.0   | 8.6         |                |                |                 |
|                             | +VE | N | 2  | 64          |                |                |                 |
|                             |     | % | 2.0  | 91.4        |                |                |                 |
| Total                       |     | N | 100  | 70          |                |                |                 |
| Validity                    |     |   | Sensitivity                                  | Specificity | +VE Predictive | -VE Predictive | Accuracy        |
|                             |     |   | 91.4%  | 98.0%       | 96.9%          | 94.2%          | 95.2%           |

**Note:** \*\*Highly significant.

However, it limits itself to the DSM-defined manic symptoms and neglects the most common excitatory symptoms. One other self-rated scale has been developed for mixed depression, the CUDOS-M.<sup>41</sup> It differs from our scale in that it assesses only the DSM-5 mixed specifier. Again, it neglects the most common agitation and other excitatory

symptoms. Defining the basic nature of “psychic depressive states”, Griesinger<sup>42</sup> stated that the basic nature that underlies the psychic depressive states is not inactivity and suppression of the psychic processes. He assumed that the cause of such states is mostly an intense state of irritation of the brain and excitation of the psychic processes. Following



Griesinger's use of the phrase "excitation of the psychic processes", and given what is really encountered in clinical practice, we suggest, just like others,<sup>24</sup> that mixed symptoms of depression might be better called excitatory rather than hypo/manic symptoms. Patients with excitatory (mixed) depression lack expansiveness and easy performance of activities. They are tormented by their psychic pain and unable to perform activities.<sup>24</sup> However, we are not inclined to abandon the DSM-5-defined mixed specifier or assume it is nothing but a kind of mixed hypomania as proposed elsewhere.<sup>24</sup> Also, one cannot claim, as it is the case in expansive mixity, that excitatory mixity could be a marker of bipolarity. Instead, the negative impact of antidepressants on such symptoms, be they excitatory or expansive, is what we insist on and develop the scale to guard against. The same might be argued for psychomotor agitation which is represented in the first subscale. The utility of the concept of psychomotor agitation as a mixed feature is supported by the negative impact of antidepressants on it and by being a precursor to suicidality related or unrelated to antidepressants.<sup>35,43–46</sup> Based on the notion that a definition of mixed depression which will better show the impact of treatment is the definition of choice in clinical practice,<sup>44</sup> K-DMX and RDC-A should be considered important and clinically relevant mixed features in depression and the development of a scale as an aid to capture them is worthwhile.

## Limitations

1. The assessment was cross-sectional; thus, we did not examine the long-term stability of the scale.
2. As the study was conducted in a sample of outpatients, replication in other samples with different clinical characteristics might be warranted.
3. Taking in consideration the patients' extreme suffering as well as the reported dramatic, unique and fast improvement on Olanzapine alone in such mixed cases,<sup>22,36,47</sup> we did not delay the use of Olanzapine at the expense of assessing test-retest reliability.

## Conclusion

The SMDS showed good psychometric properties with good internal consistency, high sensitivity, specificity, positive predictive value and negative predictive value. It demonstrated a two-factor structure; one for mixity without psychomotor agitation and another for psychomotor agitation.

Overall, SMDS can be considered a useful instrument for measuring the non-DSM mixed features in UP as proposed by Koukopoulos. We recommend the routine use of our scale in all apparently depressed patients in order to screen for a possible clinically relevant mixity. In addition, we recommend conducting further studies on what Koukopoulos named excitatory symptoms. We hypothesize that such excitatory symptoms could constitute a third polarity or, at the very least, fall on a continuum between inhibited/retarded depression and expansive hypo/mania.

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