



Research paper

The Koukopoulos Mixed Depression Rating Scale (KMDRS): An International Mood Network (IMN) validation study of a new mixed mood rating scale

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ABSTRACT

Background: It has been proposed that the broad major depressive disorder (MDD) construct is heterogenous. Koukopoulos has provided diagnostic criteria for an important subtype within that construct, "mixed depression" (MxD), which encompasses clinical pictures characterized by marked psychomotor or inner excitation and rage/anger, along with severe depression. This study provides psychometric validation for the first rating scale specifically designed to assess MxD symptoms cross-sectionally, the Koukopoulos Mixed Depression Rating Scale (KMDRS).

Methods: 350 patients from the international mood network (IMN) completed three rating scales: the KMDRS, Montgomery-Asberg Depression Rating Scale (MADRS) and Young Mania Rating Scale (YMRS). KMDRS' psychometric properties assessed included Cronbach's alpha, inter-rater reliability, factor analysis, predictive validity, and Receiver Operator Curve analysis.

Results: Internal consistency (Cronbach's alpha = 0.76; 95% CI 0.57, 0.94) and interrater reliability (kappa = 0.73) were adequate. Confirmatory factor analysis identified 2 components: anger and psychomotor excitation (80% of total variance). Good predictive validity was seen (C-statistic = 0.82 95% CI 0.68, 0.93). Severity cut-off scores identified were as follows: none (0–4), possible (5–9), mild (10–15), moderate (16–20) and severe (> 21) MxD.

Limitations: Non DSM-based diagnosis of MxD may pose some difficulties in the initial use and interpretation of the scoring of the scale. Moreover, the cross-sectional nature of the evaluation does not verify the long-term stability of the scale.

Conclusions: KMDRS was a reliable and valid instrument to assess MxD symptoms.

1. Introduction

It has been proposed that the construct of depression – even the relatively well-defined major depressive episode – is heterogenous, and therefore invalid as a single diagnosis (Ghaemi et al., 2012). An important subtype within that construct has been called "mixed depression" (MxD), by which is meant marked psychomotor or inner excitation along with severe depression (Kraepelin, 1899). This psychomotor

excitation can be reflected in physical agitation, but also in marked mood lability and rage or inner tension. This marked anger and lability/reactivity differentiates these depressed patients notably from classic melancholic states, where usually psychomotor retardation, anhedonia and anergia are the key components of the clinical picture (Parker et al., 2013). Such mixed depressive states may reflect the nature of depression, which cannot be separated into purely unipolar or purely bipolar types (Akiskal et al., 2005), and are associated with

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severe course of illness, psychotic symptoms (Perugi et al., 2013), many hospitalizations (Pacchiarotti et al., 2011) high risk of suicide (Sani et al., 2011), and non-response to, or worsening with, antidepressants (Sani et al., 2014a).

Mixed depression has not been accepted as central to mood conditions in the DSM system (Koukopoulos et al., 2013; Koukopoulos and Sani, 2014). In DSM-5, a construct for MDD with mixed features was included, in which depression was associated only with classic manic symptoms, such as high libido or overactivity or flight of ideas, excluding all symptoms, such as irritability, that can be present both in mania and in depression. This construct has been criticized as being rare in the clinical practice and not necessary to diagnose MxD, as defined by Koukopoulos and others (Koukopoulos et al., 2007). The traditional concept of mania in psychopathology, as used by Kraepelin and others for centuries, is not the same as the DSM-defined manic criteria. “Mania” traditionally meant being sped up in thought, affect, and behavior. Depression, which was called “melancholia,” meant being slowed down in thought, affective, and behavior. If one has some thought, affect, and behavior that is sped up, and some that is slowed down, that is what Kraepelin and others meant by “mixed states.” The DSM definition of melancholia is not the same, since it includes agitation, which has to be excluded in the pre-DSM usage of melancholia. The DSM definition of mania is not the same, since it is more narrow and requires specific types of sped-up experiences, such as flight of ideas, and increased goal-directed activities. Mood states, whether euphoric or irritable or sad, are epiphenomenal or optional in the classic 19th century and later definitions of mania and melancholia (one can have depression without sadness, or mania without happiness), but they are central to DSM-defined mania or depression. The traditional pre-DSM psychopathological construct of mania as reflecting a core of psychomotor excitation has been confirmed by post-DSM psychopathology research as well (Scott et al., 2017), even though the DSM definitions have remained largely unchanged despite this research. Based on decades of psychopathology research, it can be asserted that DSM criteria are too narrow for mania and too broad for depression. Such DSM criteria fail to capture the essence of mixed states because the DSM approach seeks to split mood states into two parts, depression and mania, in a way that may be invalid empirically. The DSM approach does not take psychomotor excitation as central to mania, nor psychomotor slowing as central to depression, with mixed states reflecting a combination. If these clinical constructs are correct, then the DSM approach is unable to capture mixed states defined in this manner. Prior work has validated Koukopoulos specific diagnostic criteria for MxD (Sani et al., 2014b) (Table 1). In these patients, depressed/anxious mood, inner unrest and inner/psychic agitation dominate the clinical picture.

Based on these clinically validated diagnostic criteria, Koukopoulos and collaborators developed a rating scale specifically designed to enable clinicians and research investigators to assess the presence and severity of MxD. The “Koukopoulos Mixed Depression Rating Scale” (KMDRS), published here for the first time (see Appendix), was developed for Koukopoulos’ construct of MxD. This report validates the KMDRS in a large international sample of patients with clinical

Table 1
Koukopoulos criteria for mixed depression.

<i>Positive if: Major depressive episode + at least 3 of 8 items</i>
Absence of retardation
Talkativeness
Psychic agitation or inner tension
Description of suffering or spells of weeping
Racing or crowded thoughts
Irritability or unprovoked rage
Mood lability or marked reactivity
Early insomnia

depression.

2. Methods

This study utilized a database of 350 outpatients, 192 with a diagnosis of Major Depressive Disorder (MDD) and 158 with a diagnosis of Bipolar Disorder (BD) according to DSM-IV criteria, presenting a DSM-IV major depressive episode enrolled at the IMN network. Ninety five subjects (83 MDD, 12 BD, 57 Caucasian, 12 Hispanic, 26 African-American patients) from Boston (USA), 153 (23 MDD, 130 BD, all Caucasian) from Rome (Italy), and 102 (92 MDD, 10 BD, 20 Caucasian, 82 Hispanic) from Santiago (Chile) were included. All sites obtained IRB approval from their local academic institutions and patients signed an informed consent before enrollment. Patients were recruited between 2012 and 2016.

Mixed depression was defined according to the definition proposed by Koukopoulos (2007). Clinical features of the sample were described as percentages for categorical/binary variables, and means with SD for continuous ones. Initially, as a face validity process three experts in mood disorders research (SNG, GS, PV), examined each item's content for the KMDRS, MADRS and YMRS. Then, as a criterion validity process using subject matter knowledge, these experts decided which KMDRS items were correlated with MADRS or YMRS items and therefore pairwise spearman correlations were obtained from those paired items of MADRS and YMRS with KMDRS. Additionally, to obtain an accurate content validity, a confirmatory factorial analysis was done, using a scree plot to confirm the number of factors proposed a priori. Cronbach's alpha was calculated for internal reliability. Interrater reliability between IMN clinicians was performed on-line and was assessed by kappa values. Predictive validity was assessed by logistic regression models using the scores of the KMDRS. ROC curve was obtained to assess its predictive capacity (C-statistic). In order to assess how the scale differentiated clinical diagnosis (mixed vs non-mixed) in depressed patients, the aim was to capture with the KMDRS the “mixed depression” concept, as originally propounded by Koukopoulos and recently validated (Sani et al., 2014b). This concept entails a full clinical depressive episode, along with manic-like symptoms of psychomotor excitation. In accordance with the diagnostic criteria, a concomitant full manic episode is not required and the manic symptoms do not meet full DSM manic episode criteria in most cases. To operationalize this concept, the sample was defined as meeting usual MADRS cutoff scores of 20 or greater for a clinical depressive episode, and as being below usual YMRS scores of 20 or greater for a manic episode. Further, since some manic symptoms were expected to be present, YMRS scores would be above the usual cut-off for full remission of 4 points. Hence, the operationalized assessment of mixed depression was MADRS score of > 20 and YMRS scores of 4–19. To obtain clinically meaningful cut-off points for the KMDRS, we compared the sample distribution for the total scores of MADRS with the sample distribution for the total scores of KMDRS. Testing for normality in both distribution was done before comparing then, using histograms, Q-Q plots and Shapiro-Wilkins test. Cut-off points were considered as follows: Below 50th percentiles scores were considered no depression, between 50th and 63th percentiles scores mild depression, between 63th percentiles and 75th percentiles moderate, and scores above the 75th percentiles were deemed severe depression cases. Parameters were reported as effects sizes when possible, along their 95% confidence intervals. All statistics were done using STATA 12. All plots are available upon request.

3. Results

Clinical and demographic characteristics of the sample are provided on Table 2. Some similarities and differences can be noted between the bipolar and MDD subgroups in the IMN sample. The MDD group, as expected, had more overall depressive symptomatology (higher MADRS

Table 2
Clinical and demographic characteristic of the sample (n = 350).

Variables	Total sample N = 350 %	K-MxD N = 169 %	Non-MxD N = 181 %	RR ^a	95% CI
Diagnosis					
MDD	55	50	60	0.83	0.67 – 1.03
Bipolar	45	50	40	1.20	0.93 – 1.50
Sex					
Male	50	51	48	1.07	0.86 – 1.33
Female	50	49	52	0.96	0.76 – 1.19
Ethnicity					
Caucasian	66	61	70	0.81	0.65 – 1.01
Hispanic	27	28	25	1.55	1.17 – 2.05
African-Americans	7	11	5	1.28	0.82 – 2
Employed					
Yes	60	60	59	1.31	1.04 – 1.66
No	40	40	41	0.97	0.77 – 1.21
Civil Status					
Single	22	25	20	1.13	0.88 – 1.44
Married/Cohabitation	36	50	55	0.89	0.71 – 1.1
Divorced	13	18	15	1.15	0.88 – 1.51
Widow	12	7	10	0.82	0.53 – 1.27
Current Substance Abuse					
Yes	12	14	10	1.15	0.85 – 1.55
No	88	86	90	0.86	0.64 – 1.16
Past Substance Abuse					
Yes	11	13	10	1.15	0.85 – 1.57
No	89	87	90	0.86	0.63 – 1.16
Past/current suicidality					
Yes	42	46	38	1.16	0.94 – 1.45
No	58	54	62	0.85	0.68 – 1.06
Koukopoulos criteria for MxD					
1. Absence of retardation	60	87	36	2.38	1.95 – 2.91
2. Talkativeness	23	45	3	13.6	6.06 – 30.32
3. Psychic agitation or inner tension	47	74	21	3.46	2.58 – 4.63
4. Description of suffering or spells of weeping	44	66	23	2.85	2.14 – 3.8
5. Racing or crowded thoughts	11	20	2	7.06	2.82 – 17.68
6. Irritability or unprovoked rage	28	47	11	4.23	2.71 – 6.59
7. Mood lability or marked reactivity	35	64	15 (8)	7.71	4.68 – 12.68
8. Early insomnia	37	60	16	3.60	2.54 – 5.11
Age (years)	Mean (SD) 41.7 (20.6)	Mean (SD) 41.6 (9.5)	Mean (SD) 41.7 (21.6)	MD 0.1	95% CI –3.45 – 3.65
Scores on clinical measures at assessment					
CGI-lifetime severity	4.4 (1)	4.5 (0.9)	4.3 (1.1)	–0.2	–0.41 – 0.01
CGI-current symptoms	4 (1)	4.3 (1)	3.8 (0.9)	–0.5	–0.69 to –0.3
GAF	55.9 (12)	52.2 (12.2)	59.3 (10.8)	7.1	– 9.51

CGI = clinical global impression; GAF = global assessment functioning; MDD = major depressive disorder; RR = Relative Risk; CI = confidence interval.

^a RR compares MxD and non-MxD groups.

scores), but both groups had similar mixed depressive symptomatology (similar KMDRS scores). Past suicidality was more common in the bipolar subgroup.

As shown in Table 3, confirmatory factor analysis identified two underlying components that explain 80% of the variance. Additionally, Table 4 shows that an “Anger/tension/impulsivity” factor comprised KMDRS items number 6, 7, 8, 9, 10, 11 and 12, and a “Psychomotor excitation” factor, comprised items number 1, 2, 3, 4, 5, 13 and 14.

Initial content analysis identified those items which overlapped

Table 3
Confirmatory factorial analysis of KMDRS.

KMDRS	Eigenvalue	Difference	Proportion	Cumulative
Factor 1 Anger/tension/ impulsivity	2.42726	1.04855	0.5061	2.42726
Factor 2 Psychomotor excitation	1.37871	0.42610	0.2975	0.8036

between the three scales based on the symptoms or signs described. It will be noted that the KMDRS seemed to overlap slightly more with the YMRS (8/11 items) than with the MADRS (6/10 items). One item in the KMDRS (muscular tension) was not captured in either of the two other scales in terms of content description.

Pairwise correlation of the above items found effect sizes and statistical significance. Of the original 20 similar items identified by content analysis, 4 items did not have statistically significant correlations in pairwise analysis, leaving 16 items as correlated. Selection of the largest correlation per item that was statistically significant led to a model of overlap between the three scales as shown on Table 5. Overall, significant correlations in the final model were shown with 4 MADRS items (1,2,3,10) and 7 YMRS items (2–9)

MADRS item 3, “inner tension”, best correlated twice with two different KMDRS items (4 and 9). In the final model, we reserved that MADRS item 3 for KMDRS item 9, which has the same title and content of “inner tension.” The other KMDRS item 4 (emotional lability) was fit with the next best MADRS item correlation (item 2, reported sadness). Two KMDRS items (2, vivacious facial expression, and 10, muscular

Table 4
Content analysis and pairwise correlations of the three rating scales.

KMDRS item	KMDRS description	Similar MADRS item	MADRS description	Similar YMRS item	YMRS description	Pairwise correlation (r)
1	Expression of suffering	1,2,3, 8	Apparent sadness Reported sadness Inner tension, Inability to feel	None	NA	MADRS-1 (0.40)* MADRS-2 (0.42)* MADRS-3 (0.27)* MADRS-8 (0.30)*
2	Vivacious facial expression	none	NA	2	Increased motor activity/energy	YMRS-2 (0.06)
3	Speech	none	NA	6	Speech	YMRS-6 (0.57)*
4	Emotional lability	1, 2, 3	Apparent sadness Reported sadness Inner tension	1, 9	Elated mood, Disruptive/aggressive behavior	MADRS-1 (0.32), * MADRS-2 (0.30), * MADRS-3 (0.46), * YMRS-1 (-0.006) YMRS-9 (0.20)*
5	Psychomotor activity	3, 7	Inner tension Lassitude	2, 9	Increased motor activity/energy Disruptive/aggressive behavior	MADRS-3 (0.17)*, MADRS7 (-0.008) YMRS 2 (0.28)* YMRS-9 (0.09)
6	Subjective irritability	None	NA	5	Irritability	YMRS-5 (0.12)*
7	Overt anger	None	NA	9	Disruptive/aggressive behavior	YMRS-9 (0.14)*
8	Accelerated thinking	None	NA	7	Language/thought disorder	YMRS-7 (0.17)*
9	Inner tension	3	Inner tension	None	NA	MADRS-3 (0.22)*
10	Muscular tension	None	NA	None	NA	NA
11	Insomnia	4	Reduced sleep	4	Sleep	MADRS-4 (0.30)* YMRS-4 (0.30)*
12	Suicidal impulsivity	10	Suicidal thoughts	None	NA	MADRS -10 (0.18)*
13	Sexuality	None	NA	3	Sexual interest	YMRS-3 (0.4)*
14	Psychotic symptoms	None	NA	8	Thought content	YMRS-8 (0.62)*

tension) did not have any similar or correlating MADRS/YMRS items. In the final model, those two item scores from the KMDRS scale were imputed into the model of corresponding MADRS/YMRS items.

To show that the selected MADRS/YMRS items capture the corresponding KMDRS items, Spearman correlation was performed on the total score of the combined selected MADRS/YMRS items versus the total KMDRS score (Table 6). The model shown had a strong correlation of 0.575 (P < 0.0001).

Predictive validity testing drawn that 43.7% of the sample had YMRS scores of 4–19 (manic symptoms below the threshold of usual full manic episodes). 58.0% had MADRS score of > 20. Combining both groups, 21.1% (n = 74) of subjects were operationalized as above to approximate Koukopoulos' concept of mixed depression.

As shown in Table 7, logistic regression modeling of the above operationalized sample of mixed depression (n = 74) with the KMDRS as the primary predictor was highly significant (OR = 1.10 ± 0.03 (SE), [95% confidence intervals 1.04,1.16], p < 0.00001). The ROC curve drawn for this model obtained a C-statistic of 0.82 (95% CI 0.68, 0.93).

To test reliability, internal consistency was measured, calculating Cronbach's alpha testing, which was good (alpha = 0.76, 95% CI 0.57, 0.94).

Discriminant validation was assessed by examining KMDRS scores

Table 5
Final model correlating KMDRS to corresponding MADRS/YMRS item.

KMDRS item	KMDRS description	Best correlated MADRS or YMRS item	MADRS or YMRS description	Pairwise correlation
1	Expression of suffering	MADRS-2	Reported sadness	0.42*
2	Vivacious facial expression	None	NA	0.06
3	Speech	YMRS-6	Speech	0.57*
4	Emotional lability	MADRS-1	Apparent sadness	0.32*
5	Psychomotor activity	YMRS-2	Increased motor activity/energy	0.28*
6	Subjective irritability	YMRS-5	Irritability	0.12*
7	Overt anger	YMRS-9	Disruptive/aggressive behavior	0.14*
8	Accelerated thinking	YMRS-7	Language/thought disorder	0.17*
9	Inner tension	MADRS-3	Inner tension	0.22*
10	Muscular tension	None	NA	NA
11	Insomnia	YMRS-4	Reduced sleep	.30*
12	Suicidal impulsivity	MADRS-10	Suicidal thoughts	0.18*
13	Sexuality	YMRS-3	Sexual interest	0.40*
14	Psychotic symptoms	YMRS-8	Thought content	0.62*

Table 6
Discriminant validation of KMDRS in Koukopoulos' criteria mixed depression.

	Koukopoulos' criteria Mixed depression (n = 169)	Non-mixed depression (n = 181)	Total (n = 350)
KMDRS	15.0 ± 5.4*	7.9 ± 4.1	11.5 ± 6.0
MADRS	23.0 ± 8.7	22.0 ± 10.1	22.5 ± 9.4
YMRS	4.9 ± 4.5**	3.3 ± 3.3	4.1 ± 4.0
Modified MADRS/ YMRS model	15.9 ± 4.7***	12.1 ± 4.9	13.9 ± 5.2
Factor 1 Anger/tension/ impulsivity	7.86 ± 4.1	3.22 ± 2.22	5.71 ± 4.08
Factor 2 Psychomotor excitement	8.6 ± 4.81	5.49 ± 3.50	7.15 ± 4.52

MADRS score differences were not statistically significant ((t=0.99, p = 0.30).

* Pairwise comparison, t = 13.7, p < 0.0001, mixed versus non-mixed sample.

** Pairwise comparison, t = 3.8, p < 0.002, mixed versus non-mixed sample.

*** Pairwise comparison, t = 7.4, p < 0.0001, mixed versus non-mixed sample.

Table 7
Logistic regression model for Predictive validity of KMDRS.

Variable	OR	CI95%	p-value
KMDRS total score	1.097928	1.041943 – 1.156921	0.000

versus the other scales in patients in the sample who met the definition of mixed depression as proposed by Koukopoulos' criteria (see methods). 48.2% of the sample (n = 169) met that mixed depression definition.

Interrater reliability was measured at the two main sites of the IMN sample (Boston and Santiago) was determined to be adequate (κ = 0.73 95% CI 0.64, 0.85).

As described in the methods section, based on the similarity of the normal distributions of the MADRS and KMDRS scales, the following cut-off scores were obtained for no, possible, mild, moderate and severe mixed depression, respectively: 0–4, 5–9, 10–15, 16–20 and above 21.

4. Discussion

This analysis is the first study of a new rating scale for mixed depression, the Koukopoulos Mixed Depression Rating Scale (KMDRS). It found that the KMDRS was a reliable and valid rating scale for the assessment of the mixed depression (MxD) construct. Factor analysis identified two components that capture the main symptoms of MxD: a factor for anger/tension/impulsivity and a factor for psychomotor excitation. Good predictive validity was shown for discrimination of patients meeting MxD diagnostic criteria. Cut-off scores were identified for mild, moderate and marked severity of MxD symptoms.

There are no prior studies of this scale, since it is newly developed and published in this paper. No other rating scales exist specifically for the MxD concept, as defined by Koukopoulos. Only one other rating scale has been developed specifically to assess mixed states of manic and depressive symptoms (Cavanagh et al., 2009). That scale limited itself to DSM-defined manic criteria, and identified two components of mixed states in factor analysis: one factor for psychomotor excitation, and another for neurovegetative symptoms and pain. The KMDRS differs from this prior scale by not limiting itself to DSM-defined manic criteria. As discussed in the introduction, the excitatory process underlying MxD is not the same as DSM-defined manic symptoms, but reflects the traditional core of mania defined as psychomotor excitation, as supported by recent psychopathology research as well (Scott et al., 2017). For this reason, we suggest the term *excitatory symptoms* instead of manic symptoms to describe the manic aspect of MxD. In our view, this term is closer to the neurophysiological mechanism underlying MxD and has strong clinical and psychopathological validity. Further, unlike the other scale, the KMDRS captures the psychopathology of marked irritability/rage, which is central to Koukopoulos' construct of MxD.

The only other relevant study used the Hypomania Checklist to assess manic symptoms during an acute clinical depressive episode (Angst et al., 2005). The current study differs from this prior report in that the KMDRS was developed specifically to assess MxD, unlike the HCL which was developed to assess hypomanic episodes. Further, the HCL is a screening tool, not a rating scale of symptom severity. Also, the HCL is self-rated, not clinician-rated, which introduces some risk of reporting bias. Again, the HCL is limited to DSM-defined manic symptoms, and does not capture marked anger/rage and psychomotor excitation more broadly, unlike the KMDRS.

The clinical relevance of the development of the KMDRS is that it may help in the conduct of clinical trials of MxD and further in assessing such symptomatology in clinical practice. The identification of MxD patients may help improve clinical care of this subgroup of depressed subjects. As noted in the introduction, it has been found that antidepressants appear to worsen MxD, being associated with 2.5 times

more suicide attempts in such subjects. Instead, benefit has been shown with dopamine blocking agents (Centorrino et al., 2005), including the first randomized trial of any agent for mixed depression (Patkar et al., 2012), or electroconvulsive therapy (Perugi et al., 2017). Other studies have identified as well the importance of paying attention to the concept of mixed depressive states. Koukopoulos' definition of MxD was validated in a prior study, with association of MxD with more severe course of illness, antidepressant nonresponse, and suicidality (Sani et al., 2011; Sani et al., 2014a). The largest study of mixed depression was the BRIDGE study (Angst et al., 2011), with over 5000 patients with clinical depression; in that study, mixed depression, defined as depression plus three or more excitatory symptoms, was present in almost half of the sample. Diagnostic validation of the mixed depressive sample was suggested by elevated family history rates of bipolar illness as well increased risk of antidepressant-induced mania. A similar set of criteria together with one external validator such as family history and specific illness course identified about 30% of depressive patients as having mixed states (Perugi et al., 1997). MxD appears to occur commonly in persons with affective temperaments of cyclothymia or hyperthymia (Akiskal, 1992; Akiskal et al., 1998; Koukopoulos et al., 2005; Röttig et al., 2007; Pacchiarotti et al., 2013) Thus, it is crucial to detect, correctly diagnose and adequately treat these patients.

4.1. Limitations

Before presenting our conclusion, we must acknowledge some issues that may limit our findings. Firstly, the non DSM-based diagnosis of MxD may pose some difficulties in the initial use and interpretation of the scoring of the scale. However, as noted before, DSM-5 diagnostic criteria for depression with mixed features have, in our view, limited clinical utility, therefore, new tools based on the same criteria would incur in those same limitations. Furthermore, the cross-sectional assessment does not allow the evaluation of the long-term stability of the scale. A longitudinal study that includes the use of the KMDRS during different phases of the mood disorder is needed to confirm the present observation.

5. Conclusion

This study provides the first psychometric validation of a new scale developed for Koukopoulos' mixed depression construct. The KMDRS was found to be a reliable and valid instrument to assess MxD symptoms. Two main factors identified were anger/tension/impulsivity and psychomotor excitation. Severity cut-off points were obtained. The KMDRS can be used in future clinical trials of mixed depression.

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Appendix. The Koukopoulos Mixed Depression Rating Scale

Koukopoulos Mixed Depression Rating Scale ©

by

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INSTRUCTIONS

This scale was developed in order to enable clinicians and research investigators to collect data assessing the presence and severity of symptoms of excitatory or mixed nature in individuals diagnosed as suffering from a Major Depressive Episode (MDE) according to the DSM-IV criteria. Case records and previous assessments supporting the diagnosis of MDE should be reviewed before interviewing the patient. For Agitated Depression with clear motor agitation the RDC 1978 criteria are considered sufficient by the authors, but an item on motor agitation is included in this scale.

As the more typical depressive and anxiety symptoms present during an episode of depression are not covered by the scale, this instrument is best used together with other scales assessing these symptoms like the Hamilton Rating Scale for Depression, the Hamilton Anxiety Scale and the Montgomery-Asberg Depression Rating Scale. The evaluation of manic symptoms could be investigated by the Young Mania Rating Scale.

Unless otherwise specified, the time period under study for each item is the week prior to the interview.

Typically, ratings will be made on the basis of observations made during interviews, of self-reports and/or information reported by reliable informants. The first five items are to be rated primarily on the basis of observations made during the diagnostic interviews.

(NB: Patients tend to hide aggressive and hypersexual behavior, in their presence the relatives also do not mention them. It is therefore useful to have a talk with the relatives separately).

1) EXPRESSION OF SUFFERING

Rate both the extent of internal feelings and their expression, i.e. experience and display. Also determine signs of suffering from behavior during interview, particularly dramatic speech and gesturing. This item need not be rated on behavioral observation alone, reports are also considered.

2) VIVACIOUS FACIAL EXPRESSION

Rate on the basis of behavior during interview.

3) AMOUNT OF SPEECH

Rate on the basis of the quantity of verbal productions, regardless of content. This item need not to be rated on behavioral observation alone, reports are also considered.

4) EMOTIONAL LABILITY

This item concerns the changing from anxiety to sadness, to despair, to anger, to normal mood, to elation. The item should be rated on observations during the interview. Reliable and careful reports may also be considered.

5) MOTOR ACTIVITY/RESTLESSNESS

Rate on the basis of observed motor movements. If reports are considered, as they should, make certain that the motor hyperactivity actually occurred and was not merely a subjective feeling.

6) SUBJECTIVE FEELINGS OF IRRITABILITY AND UNPROVOKED ANGER

This symptom is of cardinal importance. This item should rate only feelings of irritation or anger which may be recognized by patients as being unprovoked. Overt expressions of these feelings are rated in the next item.

7) OVERT EXPRESSION OF IRRITABILITY AND ANGER

Rate overt expressions of irritability, annoyance and anger, including being argumentative, shouting, losing temper, as well as throwing things and being assaultive. Do not include mere subjective feelings no matter how intense. Patients rarely report aggressive behavior. Reports from family members should be considered.

8) RACING OR CROWDED THOUGHTS

This symptom is of cardinal importance. Note spontaneous reports before direct questioning. Rate on the basis of subjective experience that thoughts/memories are more than usual, and/or thinking is accelerated. Depressive ruminations are different: they are made

up by few (often only one) depressive preoccupation.

9) INNER TENSION

Consider spontaneous reports before direct questioning. This symptom is of cardinal importance. When present even to a moderate degree, tension is reported spontaneously as being very distressing. When severe, tension may be described as a painful and tormenting feeling. Patients may complain of blockade of thoughts, sensations and emotions. There is no need for autonomic or motor accompaniments for this symptom to be rated present. If motor agitation actually occurred, rate it separately.

10) MUSCULAR TENSION

It is an unpleasant sensation of muscular tension without the ability of relaxing and the tension is unrelated to any specific voluntary muscular effort. The patient may complain of muscular soreness.

11) INITIAL AND MIDDLE INSOMNIA

The patients have difficulties in falling asleep. It is often associated with racing or crowded thoughts. As far as middle insomnia is concerned, waking up for a few minutes and falling back to sleep should not be taken into account. Only waking up with agitation and/or difficulty falling back to sleep should be rated.

12) SUICIDAL IMPULSIVENESS

This item will consider mainly the impulsive onset of suicidal ideation and/or the impulsive characteristics of suicidal attempts. Suicidal thoughts not impulsive must be rated zero.

13) SEXUALITY

This item will consider the activity level of sex drive, whether or not consummated. The patient rarely reports on sexual activity while depressed. Thus the most useful source of information will be the interview with the patient's partner.

14) PSYCHOTIC SYMPTOMS

This item will consider the presence of thought or perception alterations. Whenever present, congruous or incongruous delusions are scored equally.

KOUKOPOULOS MIXED DEPRESSION RATING SCALE©

Date (dd/mm/yyyy): _ / _ / _ _ _ _

Patient's Name: _____

Date of Birth (dd/mm/yyyy): _ / _ / _ _ _ _

Gender: M F

Rater: _____

The time period under study for each item is the week preceding the interview. The first five items should be rated primarily, but not only, on the basis of observations made during the diagnostic interviews.

1) EXPRESSION OF SUFFERING

- 0 = laconic expressions of depressive suffering
- 1 = animated and prolonged descriptions of suffering
- 2 = dramatic utterances of suffering and despair
- 3 = outbursts of complaining and spells of crying

2) VIVACIOUS FACIAL EXPRESSION

- 0 = reduced facial expression
- 1 = facial expression clearly manifesting emotions
- 2 = vivacious expression of emotions
- 3 = dramatic expression of emotions

3) AMOUNT OF SPEECH

- 0 = retarded speech
- 1 = normal speech
- 2 = talkative, conversation not compromised
- 3 = clearly logorrhoeic; the conversation is compromised

4) EMOTIONAL LABILITY

- 0 = absent
- 1 = shifts of mood limited to a depressive-dysphoric range, i.e. changes from sadness to anger
- 2 = shifts are still within the depressive-dysphoric range, but emotions are more intense, i.e. despair, rage
- 3 = shifts from depressed mood to elation

5) PSYCHOMOTOR ACTIVITY

Make certain that motor hyperactivity/restlessness is visible (or actually occurred) and is not merely a subjective feeling. (Have you been so fidgety and restless that you couldn't sit still? Do you have to keep pacing up and down?)

- 0 = psychomotor retardation
- 2 = normal rate of psychomotricity
- 4 = evident restlessness but able to remain seated
- 6 = unable to sit still or paces about a great deal

6) SUBJECTIVE FEELINGS OF IRRITABILITY AND UNPROVOKED ANGER

How annoyed, angry, or resentful have you felt - whether you showed it or not?

(How strongly did you feel this way? How much of the time did you feel this way?)

- 0 = absent
- 1 = complaints of irritability for minor reasons
- 2 = feels quite angry without any reason
- 3 = feels like breaking things (or feels acting against oneself or others)

7) OVERT EXPRESSION OF IRRITABILITY AND ANGER

How did you show your (anger, annoyance, irritability)? (Did you get into arguments?) (Did you lose your temper, throw or break things?)

(What about hitting anybody?)

- 0 = absent
- 2 = quick to express annoyance, impatience, occasional verbal aggression
- 4 = occasional violence against things
- 6 = occasional violence against oneself or others

8) CROWDED AND/OR ACCELERATED THINKING

Note spontaneous reports before direct questioning.

Have you had more thoughts than usual or more than you can handle? (Did it interfere with your falling asleep?) (Have your thoughts raced through your mind?)

- 0 = absent
- 1 = depressive or painful ruminations
- 2 = crowded thoughts or memories, some of which may not be painful.
- 3 = persistent racing thoughts or musical tunes in the head.

9) INNER TENSION

Note spontaneous report before questioning. This is a particular and distressing sensation of nervous tension. This sensation may be accompanied by a feeling of being blocked in your mental activities. (Do you feel on edge, or keyed-up or stressed?) (Does this tension prevent you from doing things, from thinking?)

- 0 = absent
- 1 = this sensation is reported only on questioning
- 2 = this sensation is spontaneously reported as a distressing part of the condition
- 3 = the patient reports being tormented by a sensation of tension and inner agitation. Diastolic blood pressure may be > 90 mmHg.

10) MUSCULAR TENSION

Have you had difficulty relaxing your muscles since you have been depressed? (Do your muscles feel tense?) (Where did you feel the tension?) (Were you able to relax?)

- 0 = absent
- 1 = muscular tension is reported only on questioning
- 2 = slight recurrent muscular tension with some ability to relax
- 3 = definite experience of muscular tension without the ability to relax, or visible tension (possibly tremors). The patient may complain of muscle soreness, especially in the neck and back.

11) INITIAL AND MIDDLE INSOMNIA

Have you had difficulty falling asleep? (How long does it take to fall asleep once you go to bed? Do you wake up in the middle of the night? Do you fall asleep again once you wake up?

0 = absent

- 1 = complaints of difficulty falling asleep of no more than 1/2 h
- 2 = complaints of difficulty falling asleep of more than one hour and/or two or more awakenings during the night
- 3 = practically sleepless because of difficulty falling asleep and of several awakenings during the night

12) SUICIDAL IMPULSIVENESS -

Have you had thoughts about killing or hurting yourself? (Were these thoughts impulsive, coming suddenly? Often in moments of anger?) (Have you actually done anything?)

- 0 = absent
- 2 = suicidal thoughts possibly impulsive
- 4 = impulsive suicidal thoughts definitely present
- 6 = impulsive suicidal attempt(s) (like trying to jump out of a car)

13) SEXUALITY

When a person gets depressed, (s)he has less sexual desire than usual. Have you noticed occasionally an increased sexual desire and/or activity?

- 0 = reduced sexual activity and/or desire
- 1 = sexual activity normal
- 2 = occasional hypersexuality
- 3 = frequent hypersexuality

14) PSYCHOTIC SYMPTOMS

Have you ever thought that others were doing something against you? Have you ever thought to be in the middle of others' interest? Have you ever heard noises or voices?

- 0 = absent
- 1 = suspiciousness
- 2 = ideas of reference
- 3 = delusions and/or hallucinations

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References

- Akiskal, H.S., 1992. The distinctive mixed states of bipolar I, II, and III. *Clin. Neuropharmacol.* 15 (Suppl. 1), 632A–633A.
- Akiskal, H.S., Hantouche, E.G., Bourgeois, M.L., Azorin, J.M., Sechter, D., Allilaire, J.F., Lancrenon, S., Fraud, J.P., Châtenet-Duchêne, L., 1998. Gender, temperament, and the clinical picture in dysphoric mixed mania: findings from a French national study (EPIMAN). *J. Affect. Disord.* 50, 175–186.
- Akiskal, H.S., Benazzi, F., Perugi, G., Rihmer, Z., 2005. Agitated "unipolar" depression re-conceptualized as a depressive mixed state: implications for the antidepressant-suicide controversy. *J. Affect. Disord.* 85, 245–258.
- Angst, J., Adolfsson, R., Benazzi, F., Gamma, A., Hantouche, E., Meyer, T.D., Skeppar, P., Vieta, E., Scott, J., 2005. The HCL-32: towards a self-assessment tool for hypomanic symptoms in outpatients. *J. Affect. Disord.* 88, 217–233.
- Angst, J., Azorin, J.M., Bowden, C.L., Perugi, G., Vieta, E., Gamma, A., Young, A.H., BRIDGE Study Group, 2011. Prevalence and characteristics of undiagnosed bipolar disorders in patients with a major depressive episode: the BRIDGE study. *Arch. Gen. Psychiatry* 68, 791–798.
- Cavanagh, J., Schwannauer, M., Power, M., Goodwin, G.M., 2009. A novel scale for measuring mixed states in bipolar disorder. *Clin. Psychol. Psychother.* 16, 497–509.
- Centorrino, F., Fogarty, K.V., Cimbolli, P., Salvatore, P., Thompson, T.A., Sani, G., Cincotta, S.L., Baldessarini, R.J., 2005. Aripiprazole: initial clinical experience with 142 hospitalized psychiatric patients. *J. Psychiatr. Pract.* 11, 241–247.
- Ghaemi, S.N., Vöhringer, P.A., Vergne, D.E., 2012. The varieties of depressive experience: diagnosing mood disorders. *Psychiatr. Clin. N. Am.* 35, 73–86.
- Koukopoulos, A., Albert, M.J., Sani, G., Koukopoulos, A.E., Girardi, P., 2005. Mixed depressive states: nosologic and therapeutic issues. *Int. Rev. Psychiatry* 17, 21–37.
- Koukopoulos, A., Sani, G., Koukopoulos, A.E., Manfredi, G., Pacchiarotti, I., Girardi, P., 2007. Melancholia agitata and mixed depression. *Acta Psychiatr. Scand.* 115 (Suppl. 433), 50–57.
- Koukopoulos, A., Sani, G., Ghaemi, S.N., 2013. Mixed features of depression: why DSM-5 is wrong (and so was DSM-IV). *Br. J. Psychiatry* 203, 3–5.
- Koukopoulos, A., Sani, G., 2014. DSM-5 criteria for depression with mixed features: a farewell to mixed depression. *Acta Psychiatr. Scand.* 129, 4–16.
- Kraepelin, E., 1899. *Psychiatrie*, sixth ed. J.A. Barth, Leipzig.
- Pacchiarotti, I., Mazarini, L., Kotzalidis, G.D., Valentí, M., Nivoli, A.M., Sani, G., Torrent, C., Murru, A., Sanchez-Moreno, J., Patrizi, B., Girardi, P., Vieta, E., Colom, F., 2011. Mania and depression. Mixed, not stirred. *J. Affect. Disord.* 133, 105–113.
- Pacchiarotti, I., Nivoli, A.M., Mazarini, L., Kotzalidis, G.D., Sani, G., Koukopoulos, A., Scott, J., Strejilevich, S., Sánchez-Moreno, J., Murru, A., Valentí, M., Girardi, P., Vieta, E., Colom, F., 2013. The symptom structure of bipolar acute episodes: in search for the mixing link. *J. Affect. Disord.* 149, 56–66.
- Parker, G., McCraw, S., Blanch, B., Hadzi-Pavlovic, D., Synnott, H., Rees, A.M., 2013.

- Discriminating melancholic and non-melancholic depression by prototypic clinical features. *J. Affect. Disord.* 144, 199–207.
- Patkar, A., Gilmer, W., Pae, C.U., Vöhringer, P.A., Ziffra, M., Pirok, E., Mulligan, M., Filkowski, M.M., Whitham, E.A., Holtzman, N.S., Thommi, S.B., Logvinenko, T., Loebel, A., Masand, P., Ghaemi, S.N., 2012. A 6 week randomized double-blind placebo-controlled trial of ziprasidone for the acute depressive mixed state. *PLoS One* 7, e34757.
- Perugi, G., Akiskal, H.S., Micheli, C., Musetti, L., Paiano, A., Quilici, C., Rossi, L., Cassano, G.B., 1997. Clinical subtypes of bipolar mixed states: validating a broader European definition in 143 cases. *J. Affect. Disord.* 43, 169–180.
- Perugi, G., Medda, P., Reis, J., Rizzato, S., Giorgi Mariani, M., Mauri, M., 2013. Clinical subtypes of severe bipolar mixed states. *J. Affect. Disord.* 151, 1076–1082.
- Perugi, G., Medda, P., Toni, C., Mariani, M.G., Socci, C., Mauri, M., 2017. The role of electroconvulsive therapy (ECT) in bipolar disorder: effectiveness in 522 patients with bipolar depression, mixed-state, mania and catatonic features. *Curr. Neuropharmacol.* 15, 359–371.
- Röttig, D., Röttig, S., Brieger, P., Marneros, A., 2007. Temperament and personality in bipolar I patients with and without mixed episodes. *J. Affect. Disord.* 104, 97–102.
- Sani, G., Tondo, L., Koukopoulos, A., Reginaldi, D., Kotzalidis, G.D., Koukopoulos, A.E., Manfredi, G., Mazzarini, L., Pacchiarotti, I., Simonetti, A., Ambrosi, E., Angeletti, G., Girardi, P., Tatarelli, R., 2011. Suicide in a large population of former psychiatric inpatients. *Psychiatry Clin. Neurosci.* 65, 286–295.
- Sani, G., Napoletano, F., Vöhringer, P.A., Sullivan, M., Simonetti, A., Koukopoulos, A., Danese, E., Girardi, P., Ghaemi, N., 2014a. Mixed depression: clinical features and predictors of its onset associated with antidepressant use. *Psychother. Psychosom.* 83, 213–221.
- Sani, G., Vöhringer, P.A., Napoletano, F., Holtzman, N.S., Dalley, S., Girardi, P., Ghaemi, S.N., Koukopoulos, A., 2014b. Koukopoulos' diagnostic criteria for mixed depression: a validation study. *J. Affect. Disord.* 164, 14–18.
- Scott, J., Murray, G., Henry, C., Morken, G., Scott, E., Angst, J., Merikangas, K.R., Hickie, I.B., 2017. Activation in bipolar disorders: a systematic review. *JAMA Psychiatry* 74, 189–196.