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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 depression.

Table 1
Koukopoulos criteria for mixed depression.

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

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. Crombach'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