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Research report

Koukopoulos' diagnostic criteria for mixed depression: A validation study

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ABSTRACT

Background: Mixed depression (MxD) is one subtype of depressive experiences within the depressive spectrum. MxD definition is debated among experts. Koukopoulos' proposed diagnostic criteria focused primarily on psychic agitation, marked irritability, and intense mood lability as markers of a mixed depressive episode. The present study validates Koukopoulos' criteria as diagnostic for MxD.
Methods: A sample of 435 patients from the International Mood Network (IMN), multi-center, international network of sites, and the Centro LucioBini of Rome was analyzed. Koukopoulos' criteria were assessed in all patients.
Results: The most prevalent MxD criteria were "absence of psychomotor retardation" (84%), "mood lability or marked reactivity" (78%), and "psychic agitation or inner tension" (75%). Multivariable predictors of a MxD (+) diagnosis were: higher current CGI (OR=1.23, 95% CI 1.23, 2.84), lower rates of previous bipolar type I diagnosis (OR=0.54, 95% CI −3.28, −0.13), mixed symptoms on the index episode (OR=10.02, 95% CI 2.32, 24.12), rapid cycling course (OR=2.6 95% CI 1.45, 3.56), past substance abuse (OR=3.02, 95% CI 2.01, 5.67) and lower education status (OR=0.44, 95% CI −3.23, −0.98). This model showed a sensitivity of 76.4%, specificity of 86.3%, negative predictive value of 75%, and positive predictive value of 86%.
Limitations: An external validation of these criteria in an independent sample is warranted.
Conclusion: A broad definition of mixed depression was internally validated with multiple diagnostic validators and was sensitively and specifically predicted. Contrary to DSM-5, Koukopoulos' broad criteria include agitation, irritability and mood lability as core features.

1. Introduction

Depression is defined as a state of dampened mood and energy, and reduction in motor and psychic activity. Yet some patients have many other depressive features, such as sad mood and diminished interest in activities, along with other features of psychomotor excitation. In the past, this presentation has been called agitated depression, and in the post DSM-III nosology, it has been seen as part of major depressive disorder (MDD). Agitated depression contrasts in phenomenology with what has traditionally been called melancholia—highly retarded psychomotor function and anhedonic depression in the absence of any irritability or mood lability. Yet both conditions are given the same post DSM-III diagnosis—MDD.

Psychomotor agitation is present in many cases, but not in all. In cases without psychomotor agitation, a depressed and anxious mood with inner, psychic agitation dominates the clinical picture. Koukopoulos first suggested that this depression combined with features of psychic excitation should be called "mixed depression" (MxD), and he postulated that it was different than other kinds of depressive syndromes (Koukopoulos et al., 1992).

Recently, some investigators have in part endorsed this position, suggesting that the term "mixed depression" be applied to

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the mixture of severe depression with some manic symptoms (Akiskal, 1992; Benazzi, 2000, 2003; Angst et al., 2011).

The DSM-5 definition of MxD is broader than the DSM-IV definition, and focuses on the presence of non-overlapping manic symptoms during a major depressive episode. However, this clinical picture seems to be rare (as ever present) and leaves a vast majority of patients undiagnosed and mistreated. Thus, our group has recently challenged this DSM-based view of MxD, highlighting its lack of clinical utility and scientific weakness (Koukopoulos and Sani, 2014; Koukopoulos et al., 2013).

Koukopoulos' perspective is broader, though, capturing not only DSM-based manic symptoms, but also psychic excitation in general (Koukopoulos and Koukopoulos, 1999; Koukopoulos et al., 2006). This proposal for the diagnosis of depressive mixed states focuses on psychic agitation, marked irritability, and marked mood lability, with or without the presence of other excitatory symptoms.

In this paper, we provide the first empirical examination of the potential nosological validity of this clinical definition of mixed depression based on criteria proposed by Koukopoulos et al. (2007) (see Table 1).

2. Methods

2.1. Participants

Subjects were enrolled in the study if they were diagnosed with a major depressive episode using DSM-IV-TR criteria (American Psychiatric Association, 2000) and confirmed through the Structured Clinical Interview (SCID-I) for DSM-IV-TR (First et al., 2002).

Any patient with at least three of the eight criteria (Table 1) during any major depressive episode over the course of his or her illness was considered "mixed depression positive" (MxD (+)). Patients were recruited through the International Mood Network (IMN) and the Centro Lucio Bini in Rome.

IMN is a multicenter, international network designed to answer research questions about mood disorders using long-term observational methods and large samples' sizes. Data from ten different countries were entered into the secure website database run through the Tufts Clinical and Translational Scientific Institute (CTSI; Boston, MA, USA). The IMN currently has collaborators in 40 sites (30 international, 10 US). Data were collected between November 2011 and December 2012 and analyzed in the Mood Disorders Program at Tufts Medical Center (Boston, MA, USA).

The Centro Lucio Bini is a psychiatric private center based in Rome renowned for the diagnosis and treatment of mood disorders. All patients were personally treated by two senior psychiatrists (GS, AK). All patients provided written informed consent for the collection of their data for research, participation in the study, and subsequent publication, as part of the International Mood Network project, approved by the Tufts Medical Center Institutional Review Board.

Table 1
Koukopoulos' diagnostic criteria for mixed depression.

Major depressive episode + at least 3 of 8 items
• Psychic agitation or inner tension
• Racing or crowded thoughts
• Irritability or unprovoked rage
• Absence of retardation
• Talkativeness
• Dramatic description of suffering or frequent spells of weeping
• Mood lability or marked reactivity
• Early insomnia

2.2. Statistical analysis

Descriptive analyses were conducted on an entire sample of patients in which Koukopoulos criteria were assessed. Continuous variables were reported as means with (±) standard deviations (SD). Categorical variables were reported as frequencies/percentages (%) of the total sample. Statistical significance was set at $p \leq 0.05$ overall, meaning $p \leq 0.025$ on simple comparison.

After univariate analysis, we performed a backward stepwise (using AIC criterion) variable selection procedure with all the statistically significant predictors to end up with a final set of six clinical predictors that were in turn introduced into a multivariable logistic regression for predicting Koukopoulos positive status.

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for the model. A receiver operating characteristic (ROC) curve was performed to

Table 2
Stratified descriptive analysis of diagnostic validators by mixed depression status.

Continuous variable	**MxD (+) N=221**	**MxD (−) N=214**	**Mean difference**	**95% CI**
Age	43.1	45.6	−2.5	−0.5, 5.5
Number of past hospitalizations	0.8	1.2	−0.36	**0.01, 0.75**
Number of past suicide attempts	0.53	0.54	−0.005	−0.26, 0.27
CGI IE	4.4	3.9	0.01	−0.2, 0.24
GAF IE	53.6	56.8	−3.66	**0.5, 6.7**
Number of current suicide attempts	0.54	0.52	0.02	−0.1, 0.3
Number of past depressive episodes	13.1	9.4	3.7	**−6.8, −0.5**
Categorical variable	**MxD(+)**	**MxD(−)**	**RR**	**95% CI**
Employed	123	112	1.30	0.8, 1.93
Female gender	125	141	0.89	0.6, 1.3
Substance abuse IE	25	16	1.6	0.7, 3.5
Past substance abuse	61	43	1.5	**1.3, 3.7**
Family history of mental illness	171	181	0.8	0.4, 1.5
DSM-IV-TR RC	42	18	2.5	**1.1, 3.1**
BD I diagnosis	56	83	0.72	**0.5, 0.9**
MxD IE	12	4	1.50	**1.1, 2.0**
High educational level	101	120	0.81	**0.6, 0.9**

Abbreviations: MxD=mixed depression criteria, CI=confidence interval, CGI=clinical global impression scale, GAF=global assessment of functioning, IE=index episode, RR= relative risk, CI=confidence interval, DSM=Diagnostic and Statistical Manual of Mental Disorders, RC=rapid cycling.

test the discriminative diagnostic utility of the developed model to diagnose MxD by assessing the c-statistic given by this curve. In other words, we assessed the probability of accurately diagnosing the MxD status by using the already selected clinical variables when picking two patients (one with the outcome and the other without it) totally at random from the sample. All analyses were performed using Stata 11 (LP, S., Stata 11, 2009).

3. Results

Of 435 patients (224 from the International Mood Network and 211 from the Centro Lucio Bini), 221 patients (50.8%) were mixed depression positive (MxD (+)) and 214 (49.2%) were mixed depression negative (MxD (−)).

No patients diagnosed with MxD met criteria for mania according to DSM-IV-TR; thus they were not diagnosable with a mixed episode according to DSM-IV-TR. Furthermore, no patients met criteria for depression with mixed features according to DSM-5.

Females comprised 61% of the subject population and the mean age was 44.1 years (SD=15.9). As shown in Table 2, in a stratified descriptive analysis, the MxD (+) group was younger, had lower current GAF, had almost equal past suicide attempts but fewer past hospitalizations, had less presence of pure depressive symptoms at index episode (43 (19%) vs. 144 (67%), 95% CI 39, 56) and was less likely to have bipolar disorder (BD) type I than the MxD (−) group. However, the MxD (+) group had an increased relative risk of past substance abuse and rapid cycling (Table 2).

The frequency of MxD criteria found among the MxD (+) group was as follows: “absence of retardation” (84%), “mood lability or marked reactivity” (78%), “psychic agitation or inner tension” (75%), “dramatic description of suffering or frequent spells of weeping” (73%), and “irritability or unprovoked rage” (64%) (see Table 3).

Finally, after a stepwise selection process was applied, multivariable regression predictive model was developed and the following predictors of Koukopoulos positive status were found: patients with past substance abuse behaviors were three times more likely to be MxD (+) (95% CI 2.01, 5.67), patients that presented mixed affective symptoms during the index episode were ten times more likely to be MxD (+) (95% CI 2.32, 24.12), patients that had a rapid cycling course were two times more likely to be MxD (+) (95% CI 1.45, 3.56); moreover, higher current CGI increased the likelihood of being MxD (+) by 23% (95% CI 1.23, 2.84), previous diagnosis of bipolar type I decreased the odds of being MxD (+) by 46% (95% CI −3.28, −0.13) and higher education level decreased the likelihood of being MxD (+) by 56% (95% CI −3.23, −0.98) (Table 4).

Model performance showed high specificity and sensitivity, as well as high PPV and NPV (sensitivity 76.4%; specificity 86.3%; PPV 86.0%; NPV 75.0%). The ROC curve showed a c-statistic of 0.88 (95% CI 0.76, 0.98), which may be considered a strong discriminative capacity (Fig. 1).

Table 3
Frequency of Koukopoulos mixed depression criteria (%).

Koukopoulos mixed depression criteria	MxD (+) 221 (%)	MxD (−) 214 (%)	Total 435 (%)
1. Psychic agitation or inner tension	166 (75)	15 (7)	181 (42)
2. Racing or crowded thoughts	101 (46)	9 (4)	110 (25)
3. Irritability or unprovoked rage	142 (64)	9 (4)	151 (35)
4. Absence of retardation	187 (84)	46 (21)	233 (53.5)
5. Talkativeness	106 (48)	3 (2)	109 (25)
6. Dramatic description of suffering or frequent spells of weeping	162 (73)	53 (25)	215 (49)
7. Mood lability or marked reactivity	172 (78)	3 (2)	175 (40)
8. Early insomnia	124 (56)	25 (12)	149 (34)

Table 4
A multivariable regression model of predictors of mixed depression.

	OR	SE	z	P>z	95% CI
MxD(+)					
CGI IE	1.23	0.12	2.1	0.032	**1.23, 2.84**
BD I diagnosis	0.54	0.20	−2.61	0.018	**−3.28, −0.13**
MxD IE	10.02	3.67	4.65	0.000	**2.32, 24.12**
RC course	2.6	0.65	2.78	0.017	**1.45, 3.56**
Past history SA	3.02	0.78	4.01	0.001	**2.01, 5.67**
High educational level	0.44	0.21	−2.13	0.033	**−3.23, −0.98**

Abbreviations: BD I=bipolar disorder type I; CGI=clinical global impression scale; CI=confidence interval; IE=index episode; KC=Koukopoulos criteria for mixed depression; MDD= major depressive disorder; MxD=mixed depression according to Koukopoulos criteria; OR=odds ratio; RC=rapid cycling course of illness; SA=substance abuse; SE= standard error.

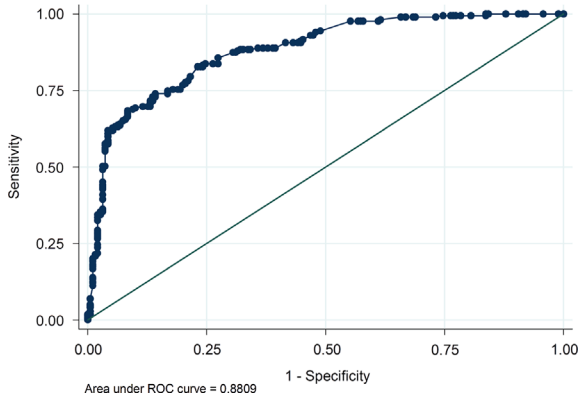

Fig. 1. Receiver-operating characteristic (ROC) analysis of predictive model for the diagnosis of mixed depression (sensitivity 76.4%, specificity 86.3%; AUC=0.8809).

4. Discussion

This study tested Koukopoulos' broad criteria for mixed depression (MxD). The definition of MxD was validated using diagnostic validators, many of which were usually associated with a broad MxD definition. The most common MxD criteria were psychic agitation, marked irritability and mood reactivity, with an absence of psychomotor retardation. MxD (+) patients were male, younger, less educated, more likely to have a history of substance abuse and likely to have received psychiatric treatment at an earlier age. Additionally, MxD (+) patients were clinically more severe, with higher current CGI, and more impaired, with lower GAF, than MxD (−) ones. Perhaps most notably, MxD (+) patients were prone to a rapid cycling course but had fewer hospitalizations. Moreover, MxD (+) patients were less likely to have bipolar disorder (BD) type I and had fewer pure (non-mixed) depressive episodes. MxD (+) patients experienced more mixed depressive episodes and more lifetime depressive episodes than MxD (−) patients. These data, in line with some (Pae et al., 2012; Koukopoulos et al., 2007) but not with all (Azorin et al., 2012) prior findings, suggest that MxD is real clinical subgroup of affective patients, not limited to patients with BD. This is in line with the DSM-5 “mixed feature specifier” that can be applied to patients not only with BD, but also with MDD.

This concept of mixed depression goes back to Kraepelin's nosology, before the current DSM-III based system, and suggests a different approach to diagnosing mood disorders than the current standard. Starting from Kraepelin's intuition (Kraepelin, 1921), Koukopoulos proposed that only an excitatory process, instead of a depressive one, could be the origin of psychic pain, suicidal ideas, anxiety, agitation and other symptoms (the core of mixed depression) (Koukopoulos and Koukopoulos, 1999). The key feature is marked psychic agitation, which also can have manifestations of motor agitation.

In Kraepelin's concept of manic-depressive insanity (MDI), mixed states, broadly conceived, were seen as the most common types of mood episodes. Kraepelin did not define MDI, in contrast to DSM-defined bipolar disorder (BD), based on polarity, but rather based on recurrence. Repeated mood episodes of any polarity were diagnosed as MDI; hence recurrent depression, without mania at all, was diagnosed as MDI in Kraepelin's system, but as "major depressive disorder" (MDD) in the post-DSM-III American nosology.

If mixed states are common, Kraepelin's non-polarity-based approach to nosology would be more supported than the DSM approach. In the DSM system, mixed episodes have been defined very narrowly, consistent with the need to define opposite poles for the MDD vs BD diagnosis. In DSM-IV, a full manic and depressive episode was required at the same time; on this definition, mixed episodes were very infrequent (Benazzi, 2000). With DSM-5, mixed states have been broadened and removed as diagnoses themselves, and made into modifiers instead. BD or MDD can be diagnosed with mixed features, and the mixed specifier definition requires "non-overlapping" symptoms. Thus for MDD with mixed features, depression is present but the allowed manic symptoms exclude irritability, agitation, and distractibility.

Other broader definitions of mixed states of depression have been proposed, such as DSM-defined depression along with three or more manic symptoms, without the exclusion of "overlapping" symptoms. With this definition, one study found that about half of all depressive episodes were mixed (Angst et al., 2011).

Accurately identifying mixed depression is essential for successful treatment; the first randomized clinical trial (RCT) of MxD showed a significant benefit with ziprasidone vs. placebo after six weeks of treatment (Patkar et al., 2012). These RCT findings confirmed the clinical impression of many renowned physicians that patients suffering from mixed depression need different treatments compared to those with non-mixed depressive states (Koukopoulos and Koukopoulos, 1999; Akiskal and Mallya, 1987; Prien et al., 1988; Koukopoulos et al., 1992; Akiskal and Pinto, 1999; Akiskal et al., 2005a, 2005b; Krüger et al., 2005; Goldberg et al., 2007).

Strengths of this study include a large sample size, careful clinical evaluation, generalizability to multiple clinical sites across different countries and cultures, and assessment of explicit diagnostic criteria for MxD. Limitations include reliance on retrospective recall of some clinical outcomes, absence of treatment data and the fact that this validation was performed with known datasets in order to obtain a predictive model that could be internally validated. A new independent dataset might be needed for an external validation for this very same set of clinical predictors of Koukopoulos' definition.

5. Conclusion

In sum, Koukopoulos' definition of mixed depression (MxD)—identifying mixed depressive features such as agitation, irritability and mood lability—was internally validated in this sample using multiple course validators. These data show that "overlapping" symptoms of excitement and depression are specific and may be valid symptoms of MxD. New MxD diagnostic criteria are internally validated in this sample. Further validation work in other samples will be needed to replicate and reevaluate these findings.

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Nothing declared.

Conflict of interest

In the past two years, Dr. Paolo Girardi has received research support from Lilly, Janssen, and Springer Healthcare, and has participated in Advisory Boards for Lilly, Otsuka, Pfizer, Schering, and Springer Healthcare and received honoraria from Lilly and Springer Healthcare. In the past 12 months, Dr. Nassir Ghaemi has received research grants from Pfizer and Takeda. Neither he nor his family holds equity positions in pharmaceutical corporations. All other authors declare that they have no conflict of interest.

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