Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

The Koukopoulos mixed depression rating scale (KMDRS) and the assessment of mixed symptoms during the perinatal period

Alexia E. Koukopoulos[a,b,*], Lavinia De Chiara[b,c,d], Alessio Simonetti[b,c,e,f], Georgios D. Kotzalidis[b,c,d], Delfina Janiri[b,e], Giovanni Manfredi[b,d,g], Gloria Angeletti[b,c,d], Gabriele Sani[h,i]

[a] Azienda Ospedaliera Universitaria Policlinico Umberto I, Viale dell'Università 30, Rome 00185, Italy
[b] Centro Lucio Bini, Via Crescenzio 42, Rome 00193, Italy
[c] Department of Neurosciences, Mental Health, and Sensory Organs (NESMOS), Sapienza University, Via di Grottarossa 1035-1039, Rome 00189, Italy
[d] Center for Prevention and Treatment of Women's Mental Health at Sant'Andrea Hospital of Rome, Sapienza University, Via di Grottarossa 1035-1039, Rome 00189, Italy
[e] Department of Human Neurosciences, Sapienza University, Viale dell'Università 30, Rome 00185, Italy
[f] Menninger Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, TX, United States
[g] UOC Psichiatria, Day Hospital, Azienda Ospedaliera-Universitaria Sant'Andrea, Via di Grottarossa 1035-1039, Rome 00189, Italy
[h] Departmentof Neuroscience, Section of Psychiatry, Università Cattolica del Sacro Cuore, Largo F. Vito 1, Rome 00168, Italy
[i] Fondazione Policlinico Universitario "Agostino Gemelli" IRCCS, Rome, Italy

ARTICLE INFO

Keywords:
Postpartum depression
Mixed depression
Psychometric scales
Temperament
Pregnancy
Perinatal period

ABSTRACT

Background: Mixed symptoms in depression may underlie bipolar diathesis rather than unipolarity. Uncovering mixed depression (MxD) is crucial for appropriate management, especially in the perinatal period, as it may affect treatment planning and impact future child development. We used a scale specific for identifying MxD and tested its validity in pregnant and postpartum women with depression.

Methods: Women developing a major depressive episode (MDE) during their perinatal period extending from pregnancy to one year postpartum from November-2012 through June-2019 were assessed with BPRS-18, EPDS, CGI-S, GAF, HAM-A, HAM-D, Koukopoulos' Mixed Depression Rating Scale (KMDRS), TEMPS, and YMRS. They were classified, based on KMDRS criteria, as with mixed (MxD) or without (nonMxD) mixed symptoms. We conducted ROC analysis and performed factor analysis of the KMDRS.

Results: Of 45 included, MxD ($N = 19$) were biased towards diagnosis of bipolar disorder and nonMxD ($N = 26$) towards major depressive disorder. Other sociodemographic variables did not differ significantly between MxD and nonMxD. MxD scored higher on total YMRS, BPRS, and KMDRS, and on KMDRS-6 Subjective Feelings of Irritability and KMDRS-12 Suicidal Impulsiveness items. The KMDRS correlated in the entire sample, in MxD and nonMxD, with the YMRS and the BPRS, while correlating with the HAM-D in nonMxD only. The KMDRS showed acceptable AUC distribution, with a 68% sensitivity and 58% specificity. Best-fit was three-factor-structure, explaining 54.66% of cumulative variance.

Limitations: Small sample and cross-sectional design.

Conclusions: The KMDRS is fit for investigating MxD along with the YMRS and the BPRS in perinatal women with a MDE.

1. Introduction

Perinatal psychiatric episodes are commonly viewed as consisting exclusively of either depressive episodes or postpartum psychosis. Literature on both topics abounds, especially in the last decade. It is common clinical experience that depressive episodes differ in clinical presentation, response to treatment, and prognosis. Research nonetheless strongly focuses on typical depression and the excitatory symptoms, which often accompany depressive states, receive little attention (Çelik et al., 2016). The least studied and most misdiagnosed affective mood states during the perinatal period are mixed depression and hypomania. Symptoms like irritable mood, mood lability, inner tension, distractibility, psychomotor agitation, impulsiveness, aggressiveness, racing or crowded thoughts, talkativeness, early insomnia,

* Corresponding author.
E-mail address: alexiakoukopoulos@gmail.com (A.E. Koukopoulos).

https://doi.org/10.1016/j.jad.2020.08.080
Received 9 April 2020; Received in revised form 5 July 2020; Accepted 24 August 2020

dramatic episodes of sufferance or weeping spells are frequently observed among patients diagnosed with a major depressive episode (MDE) (Maj et al., 2003, 2006; Sharma et al., 2014). In our view, these are symptoms of nervous excitability and constitute the essence of a mixed affective episode (Akiskal and Benazzi, 2003; Sato et al., 2003; A. Koukopoulos et al., 2005; A. Koukopoulos et al., 2007; Sani et al., 2014a; A.E. Koukopoulos et al., 2020).

Mixed states were found to occur around 2% of all pregnancies both prepartum and peripartum, in about 8% of bipolar disorder type 1 (BD-I) prepartum and 6.5% postpartum, and in about 3.5% of bipolar disorder type 2 (BD-II) cases prepartum and 2.5% postpartum (Viguera et al., 2011; Maina et al., 2014). Obviously, these figures, which are mainly based on the DSM-IV criteria for mixed states, are likely to change with the advent of the DSM-5. Compared with nonmixed depression, mixed depression (MxD) is held to be more severe and more common in bipolar disorders (BDs). In women, it is associated with BD-II and hyperthymic temperament (Sani et al., 2014a). MxD is also associated with younger age at onset, more family history of BD, comorbidities, longer duration of illness, worse outcome, more suicide attempts, poorer response to treatments (Maj et al., 2003; A. Koukopoulos et al., 2005; Akiskal and Benazzi, 2003; Maj et al., 2006; Altinbas et al., 2014), and higher switch rates with antidepressant treatment (Sato et al., 2003; Bottlender et al., 2004; Akiskal et al., 2005a; Akiskal and Benazzi, 2005; Vieta et al., 2014; Perugi et al., 2015).

Mixed states were first described by Emil Kraepelin (1899) and his pupil Wilhelm Weygandt (1899). However, the classical dichotomization of psychiatric disorders into neurotic and psychotic disorders relegated mood disorders to the former, and contributed to the neglect where MxD was cast, until the last version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (Prieto et al., 2015; Shansis et al., 2016), where MxD was defined as consisting of a MDE with at least three concurrent (hypo)manic symptoms (American Psychiatric Association, 2013). However, controversy over the mixed state concept is still ongoing (Perugi et al., 2015; Maj, 2015; Goldberg, 2015). The mixed specifier can be used for depressive episodes in major depressive disorder (MDD), and BD-I and -II (Altinbas et al., 2014; Prieto et al., 2015).

Since rates of mixed affective states in women (Cassidy and Carroll, 2001; Kessing, 2004; Grant et al., 2005; Suppes et al., 2005; Kessing, 2008) and mood recurrences during the perinatal period (Viguera et al., 2007; Sharma et al., 2008) are high, the perinatal period is considered to be critical for the onset of MxD. Prompt MxD diagnosis during this period favorably impacts treatment and prevents possible negative consequences on the offspring's future development (Rusner et al., 2016). Hence, a specific diagnostic tool could prove helpful in clinical practice (Çelik et al., 2016; A.E. Koukopoulos et al., 2020).

A mixed state is more than the addition of its manic and depressive parts (Cavanagh et al., 2009). For this reason, it needs to be assessed of its own. An 18-item self-rating scale has been developed for this purpose and showed good psychometric properties in a bipolar sample, but this scale did not guide clinicians in assigning patients to mixed or nonmixed groups (Cavanagh et al., 2009). To measure MxD we developed a new scale, the Koukopoulos Mixed Depression Rating Scale (KMDRS) (Sani et al., 2014b) and validated it in a patient sample with mood disorders (Sani et al., 2018).

The primary aim of this study was to identify sociodemographic and psychometric variables in a sample of women with a MDE occurring any time during the entire perinatal period (pregnancy and postpartum) that could distinguish between MxD and nonMxD groups.

Secondary aims were to detect differences in affective temperaments, as assessed through the Temperament Evaluation of Memphis, Pisa, Paris and San Diego-Autoquestionnaire (TEMPS-A), and evaluate the performance of the KMDRS in distinguishing between MxD and nonMxD in a sample of women during their peripartum period.

We hypothesized that women with MxD and nonMxD would differ on several parameters, i.e., YMRS, BPRS, CGI-S, TEMPS individual temperaments, and mostly on the KMDRS.

2. Materials and methods

Women were evaluated and treated as outpatients at the Center for Prevention and Treatment of Women's Mental Health at Sant'Andrea Hospital, Rome, Italy. They were treated with pharmacotherapy and/or psychotherapy by our team according to their needs and clinical decision-making. Recruitment initiated on November 1, 2012 and ended on June 30, 2019. For this study, we included consecutive patients with a DSM-IV-TR/−5 MDE.

Patients provided written, informed consent at intake for potential research analysis and anonymous reporting of findings in aggregated form, in accordance with Italian legal and ethical requirements for clinical data.

The study design was cross-sectional. Any first MDE occurrence at any point between pregnancy and 12 months postpartum was termed baseline (BL) and was entered in intergroup comparisons. By first occurrence we intend MDEs occurring during the index pregnancy, not lifetime.

Medical and psychiatric history was collected from patients and their available relatives, most often from the father of the baby. Data were systematically and consistently collected using interviews and semistructured clinical assessments. Psychopathology was assessed using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version (SCID-IV-TR) (First et al., 2002) or the Structured Clinical Interview for DSM-5®-Clinician Version (SCID-5-CV) (First et al., 2016), according to the period of patient recruitment. Certified psychiatrists (all authors) conducted interviews. Patients were assessed with the Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960), Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1959), Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987; Murray and Cox, 1990), Young Mania Rating Scale (YMRS) (Young et al., 1978; Tohen et al., 2000), Brief Psychiatric Rating Scale (BPRS) , the severity item of the Clinical Global Impressions (CGI-S) (Guy, 1976)-Bipolar version (CGI-BP) (Spearing et al., 1997), Global Assessment of Functioning (GAF) (Endicott et al., 1976; American Psychiatric Association, 2000), Temperament Evaluation of the Memphis, Pisa, Paris and San Diego-Autoquestionnaire (TEMPS) (Akiskal et al., 2005b; Pompili et al., 2008) Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962; Overall, 1974; Ventura et al., 1993), and Koukopoulos' Mixed Depression Rating Scale (KMDRS) (Sani et al., 2014b; 2018). Assignment to MxD and nonMxD groups was based on A. Koukopoulos' et al. (2007) criteria, i.e., presence of MDE and at least three out of the following eight items: 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, and early insomnia. Details are provided in the Supplement. The KMDRS is detailed in the Appendix of the Supplement.

2.1. Statistical analysis

Means and standard deviations were provided for all continuous and nominal variables; normality of distribution was tested through the Shapiro and Wilk (1965) test and found to be acceptable at the $p = 0.01$ cutoff ($W = 0.938$). We therefore proceeded with performing parametric tests. We assessed BL differences in continuous variables through the Welch's (1947) Two-Sample t-test for continuous variables with Unequal Variances assumption. For nominal and ordinal variables we used the chi-squared (χ^2) test with Yates' correction. Correlations between scale scores were sought through Pearson's r coefficient to look for convergence with the KMDRS. MxD–nonMxD comparisons on rating scales were analyzed through 1-way analysis of variance

(ANOVA1way). To test the predictive validity of the KMDRS, we carried-out a logistic regression analysis and calculated odds ratios (ORs); we performed receiver operating characteristics (ROC) analysis to test KMDRS' sensitivity (true-positive rate) and specificity (100-false-positive rate) by plotting sensitivity against specificity to determine the ROC curve and area under the curve (AUC), testing for the optimal cutoff point. The AUC thus obtained describes the extent to which a measure distinguishes between MxD and nonMxD. To establish a diagnostic threshold and the corresponding sensitivity and specificity of the KMDRS, we established the cutoff as the value where the highest true-positive and true-negative proportions were correctly classified.

We performed a factor analysis on KMDRS scores using as extraction method the Principal Component Analysis (PCA). The rotation method was Oblimin with Kaiser normalization. To enter in a factor, a cutoff of 0.35 was required. If an item entered in more than one factor, the one with the higher correlation was retained.

For all analyses, significance was set at $p < 0.05$, corrected to their respective Bonferroni cutoff to avoid type I error due to multiple comparisons. All data were analyzed using IBM SPSS Statistics for Windows, Version 25.0. Armonk, New York: IBM Corporation, 2017.

3. Results

3.1. Sociodemographic and clinical-psychometric data

Clinical and demographic characteristics of the sample are provided in Table 1. Of 60 women screened (mean age = 36.3), 45 met criteria for inclusion (age, mean = 36.84 years, standard deviation [SD] ± 4.743). Of these, 19 were assigned to the MxD group (age, mean = 36.21 years, SD = 5.493) and 26 to the nonMxD (age, mean = 37.31 years, SD = 4.164). The two groups did not differ significantly in age.

Most participants were Italian (N = 38; 84.44%), had a stable partner (N = 41; 91.11%), employment (N = 39; 86.67%), and a high educational level (N = 25; 55.56%). Two thirds (N = 30; 66.67%) were positive for a family psychiatric history, while more than half (N = 25; 55.56%) were positive for personal psychiatric history. In our sample, more than half of the women had a non-perinatal onset of their disorder (N = 25; 55.56%), while the current episode had its onset more often in the postpartum period (N = 29; 64.44%) than during pregnancy (N = 16; 35.56%). However, in none of these measures did MxD and nonMxD groups differ. Current mood disorder diagnoses were almost equally distributed between MDD (N = 22; 48.89%) and BD spectrum (N = 23; 51.11%), but their distribution differed between the MxD and nonMxD groups, with significantly more MDD cases in the nonMxD group and significantly more BD spectrum cases in the MxD group; furthermore, in the latter group, there were significantly more BD-I cases than BD-II and cyclothymic disorder, as opposed to the nonMxD group, in which no BD-I cases occurred (Table 1).

MxD and nonMxD groups did not differ significantly in their scores on the HAM-D, HAM-A, EPDS, CGI-S, and GAF rating scales, but MxD scored significantly higher on the YMRS and the BPRS, as analyzed through Welch's t-test (Table 1). The two groups did not differ significantly for their scores on the five temperament dimensions of the TEMPS. MxD scored significantly higher than nonMxD on the KMDRS total scale and on each of the KMDRS-6 Subjective Feelings of Irritability and KMDRS-12 Suicidal Impulsiveness items (Table 1). These results were further strengthened by ANOVA 1-way (Tables 2 and 3). Total KMRDS scores correlated with those of the YMRS and of the BPRS but not with EPDS, HAM-A or GAF scores (Supplementary Table 1, see Supplement). Women with higher KMDRS were more severe [according the CGI-S] when looking at the entire sample, but significance was lost when analyzing each group, probably due to sample size reduction. The correlation between KMDRS and HAM-D was driven by the nonMxD sample.

MxD and nonMxD groups did not differ significantly in comorbidities or drug treatment they received, either considering individual drugs or pooling drug classes.

3.2. Predictive validity, sensitivity, specificity, and factor analysis of the KMDRS

To test the predictive validity of the KMDRS, we conducted logistic regression with total KMDRS as the independent variable and positivity for MxD as the dependent variable. Results are shown in Supplementary Table 2 (in Supplement) and were considered satisfactory. To test sensitivity and specificity of the KMDRS, we performed ROC analysis and determined AUC (Fig. 1; Supplementary Table 3). The overall AUC was 0.744 (SE = 0.78). The optimal cutoff value was 13 (correctly classified = 62.22%), corresponding to a sensitivity of 68% and a specificity of 58%. Significance was $p < 0.006$). Overall, data were considered satisfactory.

PCA identified three factors, with items loading positive on all factors. Five items loaded on Factor 1, five on Factor 2, and four on Factor 3. Two items loaded on more than one factor, i.e., item KMDRS-4 Emotional lability on factors 2 and 3 and item KMDRS-10 Muscular tension loaded on factors 3 and 1. Only higher lod scores were retained. Factor 1, which we called Outward expressions of feelings/excitement (5 items) explained 32.05% of total variance; Factor 2, named Dysphoric impulsiveness/Aggressiveness (5 items) explained 11.85% of total variance, and Factor 3, called Tension/Pressure (4 items) explained 10.76% of the total variance. The three factors combined explained 54.66% of cumulative variance. Table 4 shows the lod scores of each item entering into each factor. Nine iterations were needed for rotation to converge using the Oblimin method with Kaiser normalization.

4. Discussion

In this study we aimed to identify clinical and sociodemographic variables distinguishing MxD from nonMxD. Beyond expected differences in current diagnoses, with BD associated with the former and MDD with the latter, we identified three psychometric scale scores to be associated with MxD, i.e., the YMRS, the BPRS, and the KMDRS. To the best of our knowledge, this is the first study using scales specifically aimed to assess mixed symptoms during the perinatal period. We recommend the combined use of all these scales in people with bipolar diathesis, so to detect MxD.

Given the restrictions of the DSM-5 mixed specifier, we adopted a MxD definition suggested by literature to possess face validity superior to that of the DSM-5 for mixed depression (A. Koukopoulos et al., 2005; A. Koukopoulos et al., 2007; Angst et al., 2011; A. Koukopoulos et al., 2013; A. Koukopoulos and Sani, 2014; Sani et al., 2014b; Perugi et al., 2015; Mazzarini et al., 2018). To apply this specifier in a MDE case, the DSM-5 requires at least three hypomanic or manic symptoms which do not overlap with major depression symptoms. In cases of mixed? mania or hypomania, the presence of at least three depressive symptoms is required during the hypomanic or manic episodes. In our clinical practice, we have seen the 3rd and 4th criteria (namely, more talkative than usual or pressure to keep talking, and flight of ideas or subjective experience that thoughts are racing) frequently in MxD, but the other five criteria are extremely rare, if ever present. Symptoms like psychic and motor agitation, racing or crowded thoughts, irritability or unprovoked feelings of rage, talkativeness, mood lability and insomnia are symptoms of nervous excitability and constitute the essence of mixed affective episodes. In this study, we found the KMDRS-6 Subjective Feelings of Irritability item to be significantly more frequently reported among MxD women. Irritability was found to be higher in postpartum than in non-postpartum women and was related to depression in both (Williamson et al., 2015). The best fit for the KMDRS was a three-factor solution, in contrast to the two-factor of the scale by Cavanagh et al. (2009). However, the two scales are conceptually

Table 1
Sociodemographic and baseline clinical measures in our sample.

Parameter	Total group (N = 45)	MxD (N = 19)	nonMxD (N = 26)	Test: t/χ^2	p MxD vs. nonMxD
Age, in years (± SD)	36.84 (± 4.743)	36.21(± 5.493)	37.31 (± 4.164)	0.582	0.450
Highest educational level					
Primary, N (%)	0 (0)	0 (0)	0 (0)		
Middle school, N (%)	1 (2.22)	1 (5.3)	0 (0)		
High school, N (%)	19 (42.22)	10 (52.6)	9 (34.6)	1.1432	0.285
College/ University, N (%)	25 (55.56)	8 (42.1)	17 (65.4)		
With stable partner					
Yes, N (%)	41 (91.11)	17 (89.5)	24 (92.3)	0.0401	0.841
No, N (%)	4 (8.89)	2 (10.5)	2 (7.7)		
Professional status					
Employed, N (%)	39 (86.67)	17 (89.5)	22 (84.6)	0.0009	0.976
Unemployed, N (%)	6 (13.33)	2 (10.5)	4 (15.4)		
Nationality					
Italian N (%)	38 (84.44)	18 (94.7)	20 (76.9)	1.4692	0.225
Other N (%)	7 (15.56)	1 (5.3)	6 (23.1)		
Psychiatric history					
Negative N (%)	15 (33.33)	5 (26.3)	10 (38.5)	0.2847	0.594
Positive N (%)	30 (66.67)	14 (73.7)	16 (61.5)		
Diagnosis					
MDD N (%)	22 (48.89)	5 (26.3)	17 (65.4)	5.2334	**0.022**
BD spectrum N (%)	23 (51.11)	14 (73.7)	9 (34.6)		
BD-I N (%)	9 (39.14)	9 (47.4)	0 (0)	26.122	**0.0026**[§]
BD-II N (%)	7 (30.43)	3 (15.8)	4 (15.4)		
Cyclothymic N (%)	7 (30.43)	2 (10.5)	5 (19.2)		
Type of onset (lifetime)					
Perinatal N (%)	20 (44.44)	8 (57,9)	12 (53,8)	0.0011	0.973
Nonperinatal N (%)	25 (55.56)	11 (42,1)	14 (46,2)		
Period of perinatal onset of current episode					
Pregnancy N (%)	16 (35.56)	6 (31,6)	10 (38,5)	0.026	0.872
Postpartum N (%)	29 (64.44)	13 (68,4)	16 (61,5)		
HAM-D (± SD)	17.4 (6.96)	18.16 (9.06)	16.85 (5.04)	0.5692	0.5741
HAM-A (± SD)	17.71 (7.02)	18.89 (8.05)	16.85 (6.18)	0.9235	0.3627
YMRS (± SD)	6.64 (7.34)	10.89 (9.28)	3.54 (3.00)	3.3276	**0.0034**
BPRS (± SD)	33.7 (8.692)	37.84 (10.345)	30.62 (5.742)	8.962	**0.005**
EPDS (± SD)	19.23 (5.38)	20.14 (6.04)	18.80 (5.213)	0.287	0.598
CGI-S (± SD)	3.89 (1.03)	4.26 (1.24)	3.62 (0.75)	1.9984	0.0558
GAF (± SD)	57.27 (9.24)	55.63 (11.39)	58.46 (7.31)	0.9497	0.3504
TEMPS Depressive (± SD)	9.78 (4.726)	7.36 (5.048)	11.08 (4.069)	2.645	0.012
TEMPS Cyclothymic (± SD)	8.93 (5.131)	8.21 (6.658)	9.31 (4.193)	0.407	0.527
TEMPS Hyperthymic (± SD)	5.58(3.761)	5.79 (4.543)	5.46 (3.361)	0.066	0.799
TEMPS Irritable (± SD)	6.20(4.404)	8.36 (5.183)	5.04 (3.504)	2.417	0.022
TEMPS Anxious (± SD)	12.15 (6.183)	9.57 (7.122)	13.54 (5.248)	4.037	0.052
KMRS-1 (± SD)	0.8 (0.76)	1 (0.75)	0.65 (0.75)	1.5462	0.1303
KMRS-2 (± SD)	1.16 (0.77)	1.32 (0.82)	1.04 (0.72)	1.1904	0.2419
KMRS-3 (± SD)	1.24 (0.65)	1.42 (0.69)	1.12 (0.59)	1.5300	0.1350
KMRS-4 (± SD)	0.98 (0.92)	1.32 (0.95)	0.73 (0.83)	2.1689	0.0370
KMRS-5 (± SD)	2.2 (1.24)	2.42 (1.43)	2.04 (1.08)	0.9731	0.3378
KMRS-6 (± SD)	0.87 (0.97)	1.42 (0.96)	0.46 (0.76)	3.6099	**0.0010**
KMRS-7 (± SD)	0.84 (1.36)	1.53 (1.58)	0.35 (0.94)	2.9017	0.0073
KMRS-8 (± SD)	1.29 (0.87)	1.58 (1.02)	1.08 (0.69)	1.8497	0.0746
KMRS-9 (± SD)	1.69 (0.82)	1.95 (0.78)	1.5 (0.81)	1.8806	0.0675
KMRS-10 (± SD)	0.89 (1.01)	1 (1.05)	0.81 (0.98)	0.6166	0.5413
KMRS-11 (± SD)	1.73 (1.10)	1.74 (1.10)	1.73 (1.12)	0.0299	0.9763
KMRS-12 (± SD)	0.18 (0.58)	0.42 (0.84)	0 (0)	4.4832	**<0.0001**
KMRS-13 (± SD)	0.31 (0.60)	0.37 (0.76)	0.27 (0.45)	0.5117	0.6130
KMRS-14 (± SD)	0.31 (0.63)	0.53 (0.84)	0.15 (0.37)	1.8454	0.0779
KMRS-Total (± SD)	14.47 (7.04)	18 (8.07)	11.88 (4.89)	2.9352	**0.0067**

All significant p values surviving Bonferroni correction ($p < 0.00833$ for HAM-D, HAM-A, YMRS, BPRS, EPDS, CGI-S, and GAF, $p < 0.01$ for the TEMPS, and $p < 0.00357$ for the KMDRS items) in **bold** characters. [§]BD-I vs. BD-II + Cyclothymic Disorder, Fisher's exact test. ***Abbreviations:*** BD, bipolar disorder; BPRS, Brief Psychiatric Rating Scale; EPDS, Edinburgh Postnatal Depression Scale; GAF, Global Assessment of Functioning; CGI-S, Clinical Global Impressions-severity of the BP version; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; KMDRS, Koukopoulos' Mixed Depression Rating Scale; MDD, major depressive disorder; MxD, mixed depression; nonMxD, nonmixed depression; SD, standard deviation; TEMPS, Temperament Evaluation of Memphis, Pisa, Paris and San Diego-Autoquestionnaire; YMRS, Young Mania Rating Scale. t-Values refer to Welch's Two-Sample t-test for continuous variables; chi-square with Yates' correction.

different and each item is scored 0–3 or 0–6 the former, while in the latter, each item, corresponding to a dimension placed on a continuum, is scored from −4 to +4. The lack of ability of the DSM-5 to detect is underlined by the fact that another large study of perinatal depression chose to use a RDoC approach (Insel et al., 2010); this study assessed retrospectively the onset of symptoms and assessed current depressive psychopathology by using cross-sectionally the EPDS (Putnam et al., 2017). They identified through factor analysis five subtypes of perinatal depression, i.e., severe anxious depression, moderate anxious depression, anxious anhedonia, pure anhedonia, and resolved depression. Although this study did not specifically focus on MxD, we may hypothesize that the first two subtypes contained a significant portion of

Table 2
ANOVA1way for YMRS, HAM-D, HAM-A, BPRS, GAF, EPDS, CGI-S, KMDRS, by MxD and nonMxD.

		Sum of squares	df	Mean squares	F	*p*
HAM-D	Between-groups	18.889	1	18.889	.385	.538
	Within-groups	2111.911	43	49.114		
	Total	2130.800	44			
HAM-A	Between-groups	46.070	1	46.070	.933	.339
	Within-groups	2123.174	43	49.376		
	Total	2169.244	44			
YMRS	Between-groups	594.060	1	594.060	14.381	**.000**
	Within-groups	1776.251	43	41.308		
	Total	2370.311	44			
BPRS	Between-groups	573.320	1	573.320	8.962	**.005**
	Within-groups	2750.680	43	63.969		
	Total	3324.000	44			
EPDS	Between-groups	8.606	1	8.606	.287	.598
	Within-groups	599.257	20	29.963		
	Total	607.864	21			
CGI-S	Between-groups	4.606	1	4.606	4.734	.035
	Within-groups	41.838	43	.973		
	Total	46.444	44			
GAF	Between-groups	87.917	1	87.917	1.030	.316
	Within-groups	3668.883	43	85.323		
	Total	3756.800	44			
KMDRS	Between-groups	410.546	1	410.546	9.981	**.003**
	Within-groups	1768.654	43	41.131		
	Total	2179.200	44			

Abbreviations: BPRS, Brief Psychiatric Rating Scale; df, degrees of freedom; EPDS, Edinburgh Postnatal Depression Scale; GAF, Global Assessment of Functioning; CGI-S, Clinical Global Impressions-severity of the BP version; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; KMDRS, Koukopoulos' Mixed Depression Rating Scale; YMRS, Young Mania Rating Scale; all significant results in **bold** characters, $p < 0.00625$ after Bonferroni correction.

patients that would be adequately captured by the KMDRS.

The importance of identifying correctly MxD in the perinatal period resides in the fact that MDE could be mistreated with the institution of antidepressant drug treatment, should the mixed nature of symptoms go undiagnosed. When taking antidepressant treatment, women with underlying bipolarity may become nervous, irritable, and develop psychic agitation and racing thoughts. Literature now suggests that the use of antidepressants in this population could result in an emergence of manic or mixed symptoms and higher risk of suicide (Rihmer et al., 2016). In fact, one of the KMDRS items which we found to discriminate MxD from nonMxD women was KMDRS-12 Suicidal Impulsiveness. Perinatal suicide and suicidal ideation are still neglected (Arachchi et al., 2019) and unresolved issues (Knasmüller et al., 2019). Although suicide attempts occur less frequently during pregnancy and postpartum, compared to the nonperinatal period (Mota et al., 2019), such rates are still substantial (Vawda, 2018).

These considerations could have important implications in treatment choice and outcomes, especially at a time when erroneous treatment may be particularly harmful, as prolonging or mistreating mood episodes can negatively affect the baby's development (Poobalan et al., 2007).

Similarly, affective temperaments may be associated with future development of psychopathology in the offspring (Şair et al., 2019). The TEMPS is infrequently used in the perinatal period and is mostly directed at assessing infant/child temperament. Using the TEMPS, we found no significant differences, but a larger sample could have allowed for some differences to emerge.

The failure to diagnose underlying bipolarity implies that many women will receive inadequate treatment. Half of the women suffering from treatment-resistant postpartum depression have undiagnosed BD. Comorbidities with anxiety or OCD spectrum disorders may cover-up underlying BD diagnosis.

Monotherapy with antidepressant agents in patients belonging to the bipolar spectrum could trigger rapid cycling, hypo/manic episodes or increase treatment-resistance (Kukopulos et al., 1983; O'Hara and Wisner, 2014; Miller et al., 2004)., Instead, antipsychotics, antiepileptics, lithium and/or electroconvulsive therapy should be preferred (Centorrrino et al., 2005; Koukopoulos et al., 2007; Bersani et al., 2013; Sani et al., 2017; Perugi et al., 2019).

Among the changes introduced by the DSM-5, we should note that the course specifier "with peripartum onset" can now be applied to the index or most recent depressive, manic or hypomanic episode in MDD, BD-I and BD-II if the episode arises during pregnancy or within the first 4 postpartum weeks (American Psychiatric Association, 2013).

Hopefully, the inclusion of the "peripartum specifier" in the DSM-5 will probably increase attention and awareness on prepartum onset of mood disorders, thus increasing clinical screening and monitoring during pregnancy. Furthermore, the inclusion of hypomanic episodes in the peripartum specifier will draw attention to the excitatory dimension in the perinatal period.

On the other hand, a limitation to basic and clinical research is set by the tendency of the DSM-5 to lump episodes with onset during pregnancy with those presenting during postpartum. The issue of the heterogeneity of pre- and postpartum onset should be investigated thoroughly in future studies, which might possibly disclose interesting etiopathogenetic and neurobiological differences. Furthermore, it is possible that the different onset, i.e., during pregnancy or after birth, could be a useful outcome indicator for future pregnancies. The postpartum onset of depression is in fact more often associated with BD, compared to a depressive episode that has its onset during pregnancy (Azorin et al., 2012; Sharma and Kahn, 2010). Differences in severity between late pregnancy-onset and postpartum onset depressions were also recorded in the context of the large Postpartum Depression: Action Towards Causes and Treatment (PACT) Consortium, with the former being more often found in the resolved depression phenotype at assessment (Putnam et al., 2017). We did not find differences between MxD and nonMxD women in terms of the time of onset relative to delivery, but this may be due to our small sample size.

From a clinical viewpoint, we consider the peripartum specifier time frame of four postpartum weeks too restrictive, considering how many new mothers hesitate to seek medical attention and often do so *after* the first postpartum month (Munk-Olsen et al., 2012; Sharma and Mazmanian, 2014).

The perinatal period is not only a high-risk time for depressive episodes, but also for hypomanic, manic, or mixed episodes. Thus, patients should be carefully evaluated to recognize a possible bipolar diathesis. Diagnostic evaluation, even for women who present with depression, should always include questions related to hypomanic and manic symptoms or past episodes (Viguera et al., 2011; Meltzer-Brody and Stuebe, 2014).

4.2. Limitations

The cross-sectional design and the small sample size are the major limitations of our study.

In summary, this study demonstrated that the KMDRS, the BPRS and the YMRS distinguished between MxD and nonMxD in perinatal women; we suggest that these scales should be used in women developing mood symptoms during this period. However, the latter two of these scales did not detect mixed symptoms. The KMDRS showed good construct and content validity and fair convergent validity with the YMRS in a peripartum sample; hence, it appears to constitute a useful tool to assess MxD in this population. Its factor analysis points to a three-factor structure explaining most of the variance. The data we obtained here in a perinatal population with depression should be confirmed in longitudinal studies; our findings might possibly generalize to nonpregnant or other specific populations.

Table 3
ANOVA1way of KMDRS scores: comparison between MxD ($N = 19$) and nonMxD groups ($N = 26$).

		Sum of squares	df	Mean squares	F	*p*
KMDRS-1 Expression of Suffering	Between-groups	1.315	1	1.315	2.368	.131
	Within-groups	23.885	43	.555		
	Total	25.200	44			
KMDRS-2 Vivacious Facial Expression	Between-groups	.844	1	.844	1.448	.235
	Within-groups	25.067	43	.583		
	Total	25.911	44			
KMDRS-3 Amount of Speech	Between-groups	1.026	1	1.026	2.552	.118
	Within-groups	17.285	43	.402		
	Total	18.311	44			
KMDRS-4 Emotional Lability	Between-groups	3.757	1	3.757	4.863	.033
	Within-groups	33.221	43	.773		
	Total	36.978	44			
KMDRS-5 Psychomotor Activity	Between-groups	1.607	1	1.607	1.053	.310
	Within-groups	65.593	43	1.525		
	Total	67.200	44			
KMDRS-6 Subjective Feelings of Irritability	Between-groups	10.107	1	10.107	13.977	**.001**
	Within-groups	31.093	43	.723		
	Total	41.200	44			
KMDRS-7 Overt Expression of Irritability	Between-groups	15.290	1	15.290	9.869	.0036
	Within-groups	66.621	43	1.549		
	Total	81.911	44			
KMDRS-8 Racing or Crowded Thoughts	Between-groups	2.767	1	2.767	3.903	.055
	Within-groups	30.478	43	.709		
	Total	33.244	44			
KMDRS-9 Inner Tension	Between-groups	2.197	1	2.197	3.442	.070
	Within-groups	27.447	43	.638		
	Total	29.644	44			
KMDRS-10 Muscular Tension	Between-groups	.406	1	.406	.396	.532
	Within-groups	44.038	43	1.024		
	Total	44.444	44			
KMDRS-11 Initial and Middle Insomnia	Between-groups	.000	1	.000	.000	.986
	Within-groups	52.800	43	1.228		
	Total	52.800	44			
KMDRS-12 Suicidal Impulsiveness	Between-groups	1.946	1	1.946	6.625	**.014**
	Within-groups	12.632	43	.294		
	Total	14.578	44			
KMDRS-13 Sexuality	Between-groups	.108	1	.108	.299	.587
	Within-groups	15.536	43	.361		
	Total	15.644	44			
KMDRS-14 Psychotic Symptoms	Between-groups	1.523	1	1.523	4.062	.050
	Within-groups	16.121	43	.375		
	Total	17.644	44			
KMDRS Total	Between-groups	410.546	1	410.546	9.981	**.0030**
	Within-groups	1768.654	43	41.131		
	Total	2179.200	44			

All significant values in **bold** characters, at the $p < 0.00357$ level, after Bonferroni correction. ***Abbreviations:*** df, degrees of freedom; KMDRS, Koukopoulos' Mixed Depression Rating Scale; MxD, mixed depression; nonMxD, nonmixed depression.

Conclusions

Women with mixed symptoms had higher CGI and BPRS scores, which could mean that MxD represented a more severe type of depression in our sample. Most of the cases identified by the KMDRS as mixed would not have been classified as such if we had strictly applied DSM-5 criteria. The application of the KMDRS criteria in the assessment of mixed symptoms could be helpful in detecting MxD in the peripartum period, ultimately improving management.

Authorship statement

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Furthermore, each author certifies that this material or similar material has not been and will not be submitted to or published in any other publication before its appearance in the Journal of Affective Disorders.

Authorship contributions Please indicate the specific contributions made by each author (list the authors' initials followed by their surnames, e.g., Y.L. Cheung). The name of each author must appear at least once in each of the three categories below.

Category 1 Conception and design of study: Alexia E. Koukopoulos, Lavinia De Chiara, Gabriele Sani, Gloria Angeletti; acquisition of data: Delfina Janiri, Alessio Simonetti, Giovanni Manfredi; analysis and/or interpretation of data: _Giorgio D. Kotzalidis, Alessio Simonetti, Lavinia De Chiara.

Category 2 Drafting the manuscript: Alexia E. Koukopoulos, Lavinia De Chiara, Giorgio D. Kotzalidis; revising the manuscript critically for important intellectual content: Gabriele Sani, Gloria Angeletti, Giovanni Manfredi, Alessio Simonetti, Delfina Janiri.

Category 3 Approval of the version of the manuscript to be published (the names of all authors must be listed):

Alexia **E. Koukopoulos, L**avinia **De Chiara, A**lessio **Simonetti, G**eorgios **D. Kotzalidis, D**elfina **Janiri, G**iovanni **Manfredi, G**loria **Angeletti, G**abriele **Sani**

Role of the funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

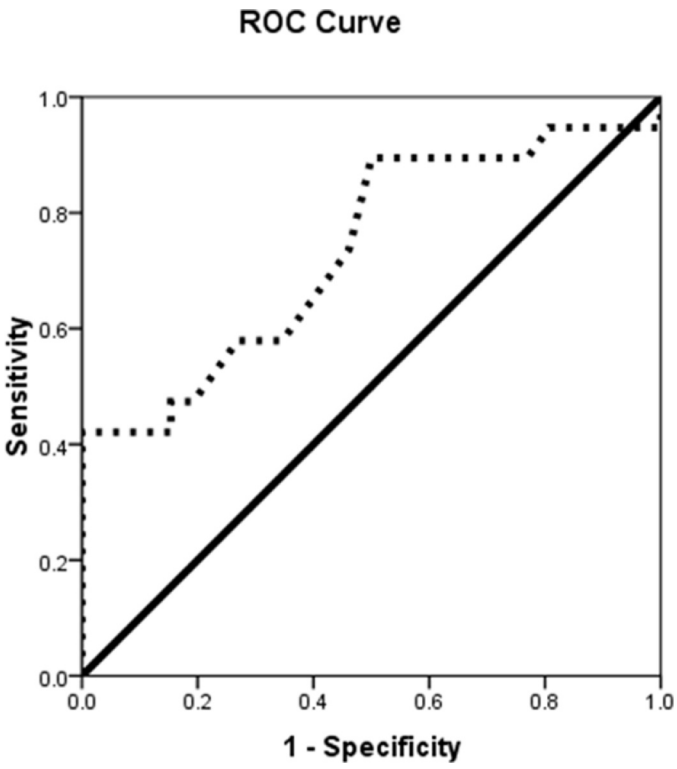

Fig. 1. ROC curve of the KMDRS and its AUC.
Continuous line, reference; dotted line, AUC.

Table 4
Factor-structure analysis of the KMDRS.

	Factors		
	1	2	3
KMDRS Vivacious facial expression (2)	**.801**		
KMDRS Expression of suffering (1)	**.715**		
KMDRS Psychomotor activity (5)	**.731**		
KMDRS Amount of speech (3)	**.462**		
KMDRS Initial and middle insomnia (11)	**.384**		
KMDRS Overt expression of irritability and anger (7)		**.835**	
KMDRS Subjective feelings of irritability and unprovoked anger (6)		**.770**	
KMDRS Suicidal impulsiveness (12)		**.679**	
KMDRS Emotional lability (4)		**.511**	.492
KMDRS Sexuality (13)		**.518**	
KMDRS Crowded and/or accelerated/ thinking (8)			**.824**
KMDRS Psychotic symptoms (14)			**.719**
KMDRS Inner tension (9)			**.719**
KMDRS Muscular tension (10)	.352		**.610**

Abbreviations: KMDRS, Koukopoulos' Mixed Depression Rating Scale. Items entering in a factor in **bold** characters.
Extraction Method: Principal Component Analysis.
Rotation Method: Oblimin with Kaiser Normalization.
a. Rotation converged in 9 iterations.

Conflicts of interest

All authors declare no conflict of interest.

Ethics approval

Specified in text. **Consent to participate**. Yes (specified in the text). **Consent for publication**. Yes (specified in the text)

Data statement

Statement on availability of data and material. Data available through request to first, last, and corresponding authors.

Author statement. authors' contributions

Alexia E. Koukopoulos, Gloria Angeletti and Lavinia De Chiara designed the study, saw patients, and provided the first draft, Alessio Simonetti and Georgios D. Kotzalidis performed statistical analyses and wrote the Methods, Delfina Janiri, Giovanni Manfredi, Gloria Angeletti, and Georgios D. Kotzalidis wrote the Results and Discussion section, and Gabriele Sani, Delfina Janiri, Alessio Simonetti, Georgios D. Kotzalidis, and Alexia E. Koukopoulos supervised the writing of the manuscript and corrected it. All authors contributed to and have approved the final manuscript.

Declaration of Competing Interest

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Acknowledgments

We appreciate the help of our secretary Ms. Tatiana Renzi for providing us useful tips for completing our manuscript. We are also grateful to Ms Mimma Ariano, Ms Ales Casciaro, Ms Teresa Prioreschi, and Ms Susanna Rospo, Librarians of the Sant'Andrea Hospital, School of Medicine and Psychology, Sapienza University, Rome, for rendering precious bibliographical material accessible.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.08.080.

References

Akiskal, H.S., Benazzi, F., 2003. Family history validation of the bipolar nature of depressive mixed states. J. Affect. Disord. 73 (1–2), 113–122. https://doi.org/10.1016/s0165-0327(02)00330-0.

Akiskal, H., .S, Benazzi, F., 2005. Psychopathologic correlates of suicidal ideation in major depressive outpatients: is it all due to unrecognized (bipolar) depressive mixed states? Psychopathology 38 (5), 273–280. https://doi.org/10.1159/000088445. Epub 2005 Sep 21.

Akiskal, H.S., Benazzi, F., Perugi, G., Rihmer, Z., 2005a. Agitated "unipolar" depression re-conceptualized as a depressive mixed state: implications for the antidepressant-suicide controversy. J. Affect. Disord. 85 (3), 245–258. https://doi.org/10.1016/j.jad.2004.12.004.

Akiskal, H.S., Akiskal, K.K., Haykal, R.F., Manning, J.S., Connor, P.D., 2005b. TEMPS-A: progress towards validation of a self-rated clinical version of the Temperament Evaluation of the Memphis, Pisa, Paris, and San Diego Autoquestionnaire. J. Affect. Disord. 85 (1–2), 3–16. https://doi.org/10.1016/j.jad.2004.12.001.

Altinbas, K., Ozerdem, A., Prieto, M.L., Fuentes, M.E., Yalin, N., Ersoy, Z., Aydemir, O., Quiroz, D., Oztekin, S., Geske, J.R., Feeder, S.E., Angst, J., Frye, M.A., 2014. A multinational study to pilot the modified hypomania checklist (mHCL) in the assessment of mixed depression. J. Affect. Disord. 152–154, 478–482. https://doi.org/10.1016/j.jad.2013.07.032. Epub 2013 Aug 23.

American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders, 4th Edition-Text Revision (DSM-IV-TR™). American Psychiatric Association, Washington, DC.

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5™). American Psychiatric Association Publishing, Inc., Arlington, VA.

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 (8), 791–798. https://doi.org/10.1001/archgenpsychiatry.2011.87.

Arachchi, N.S.M., Ganegama, R., Husna, A.W.F., Chandima, D.L., Hettigama, N., Premadasa, J., Herath, J., Ranaweera, H., Agampodi, T.C., Agampodi, S.B., 2019. Suicidal ideation and intentional self-harm in pregnancy as a neglected agenda in maternal health; an experience from rural Sri Lanka. Reprod. Health 16 (1), 166. https://doi.org/10.1186/s12978-019-0823-5. Epub Nov 15, 2019.

Azorin, J.-.M., Angst, J., Gamma, A., Bowden, C.L., Perugi, G., Vieta, E., Young, A., 2012. Identifying features of bipolarity in patients with first-episode postpartum depression: findings from the international BRIDGE study. J. Affect. Disord. 136 (3), 710–715. https://doi.org/10.1016/j.jad.2011.10.003. Epub 2011 Nov 1.

Bersani, F.S., Girardi, N., Sanna, L., Mazzarini, L., Santucci, C., Kotzalidis, G.D., Sani, G., De Rossi, P., Raccah, R.N., Caltagirone, S.S., Battipaglia, M., Capezzuto, S., Bersani, G., Girardi, P., 2013. Deep transcranial magnetic stimulation for treatment-resistant bipolar depression: a case report of acute and maintenance efficacy. Neurocase 19 (5), 451–457. https://doi.org/10.1080/13554794.2012.690429. Epub 2012 Jul 24.

Bottlender, R., Sato, T., Kleindienst, N., Strauss, A., Möller, H.-.J., 2004. Mixed depressive features predict maniform switch during treatment of depression in bipolar I disorder. J. Affect. Disord. 78 (2), 149–152. https://doi.org/10.1016/s0165-0327(02)00265-3.

Cassidy, F., Carroll, B.J., 2001. The clinical epidemiology of pure and mixed manic episodes. Bipolar Disord. 3 (1), 35–40. https://doi.org/10.1034/j.1399-5618.2001.030105.x.

Cavanagh, J., Schwannauer, M., Power, M., Goodwin, G.M., 2009. A novel scale for measuring mixed states in bipolar disorder. Clin. Psychol. Psychother. 16 (6), 497–509. https://doi.org/10.1002/cpp.633.

Çelik, S.B., Bucaktepe, G.E., Uludağ, A., Bulut, İ.U., Erdem, Ö., Altınbaş, K., 2016. Screening mixed depression and bipolarity in the postpartum period at a primary health care center. Compr. Psychiatry 71, 57–62. https://doi.org/10.1016/j.comppsych.2016.07.013. Epub 2016 Aug 4.

Centorrino, F., Fogarty, K.V., Sani, G., Salvatore, P., Cimbolli, P., Baldessarini, R.J., 2005. Antipsychotic drug use: mcLean Hospital, 2002. Hum. Psychopharmacol 20 (5), 355–358. https://doi.org/10.1002/hup.700.

Cox, J.L., Holden, J.M., Sagovsky, R., 1987. Detection of postnatal depression. Development of the 10-item Edinburgh postnatal depression scale. Br. J. Psychiatry 150 (6), 782–786. https://doi.org/10.1192/bjp.150.6.782.

Endicott, J., Spitzer, R.L., Fleiss, J.L., Cohen, J., 1976. The global assessment scale. A procedure for measuring overall severity of psychiatric disturbance. Arch. Gen. Psychiatry 33 (6), 766–771. https://doi.org/10.1001/archpsyc.1976.01770060086012.

First, M.B., Spitzer, R.L., Gibbon, M.L., Williams, J.B.W., 2002. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version. New York State Psychiatric Institute, New York City, NY.

First, M.B., Williams, J.B.W., Carg, R.S., Spitzer, R.L., 2016. Structured Clinical Interview for DSM-5®-Clinician Version (SCID-5-CV). American Psychiatric Association Publishing, Washington DC.

Goldberg, J.F., 2015. Mixed depression: a farewell to differential diagnosis? J. Clin. Psychiatry 76 (3), e378–e380. https://doi.org/10.4088/JCP.14com09578.

Grant, B.F., Stinson, F.S., Hasin, D.S., Dawson, D.A., Chou, S.P., Ruan, W.J., Huang, B., 2005. Prevalence, correlates, and comorbidity of bipolar I disorder and axis I and II disorders: results from the National Epidemiologic Survey on alcohol and related conditions. J. Clin. Psychiatry 66 (10), 1205–1215. https://doi.org/10.4088/jcp.v66n1001.

Guy, W., 1976. ECDEU Assessment manual for psychopharmacology (DHEW publication No.(ADM) 76-338). U.S. Dept. of health, education, and welfare, public health service, alcohol, drug abuse, and mental health administration, national institute of mental health, psychopharmacology research branch. Div. Extramural Res. Progr. 217–222 028 CGI Clinical Global Impressions.

Hamilton, M., 1959. The assessment of anxiety states by rating. Br. J. Med. Psychol. 32 (1), 50–55. https://doi.org/10.1111/j.2044-8341.1959.tb00467.x.

Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23 (Feb), 56–62. https://doi.org/10.1136/jnnp.23.1.56.

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D.S., Quinn, K., Sanislow, C., Wang, P., 2010. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am. J. Psychiatry 167 (7), 748–751. https://doi.org/10.1176/appi.ajp.2010.09091379.

Kessing, L.V., 2004. Gender differences in the phenomenology of bipolar disorder. Bipolar Disord 6 (5), 421–425. https://doi.org/10.1111/j.1399-5618.2004.00135.x.

Kessing, L.V., 2008. The prevalence of mixed episodes during the course of illness in bipolar disorder. Acta Psychiatr. Scand. 117 (3), 216–224. https://doi.org/10.1111/j.1600-0447.2007.01131.x. Epub 2008 Jan 30.

Koukopoulos, A., Sani, G., 2014. DSM-5 criteria for depression with mixed features: a farewell to mixed depression. Acta Psychiatr. Scand. 129 (1), 4–16. https://doi.org/10.1111/acps.12140. Epub 2013 Apr 19.

Koukopoulos, A., Albert, M.J., Sani, G., Koukopoulos, A.E., Girardi, P., 2005. Mixed depressive states: nosologic and therapeutic issues. Int. Rev. Psychiatry 17 (1), 21–37. https://doi.org/10.1080/09540260500064744.

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. https://doi.org/10.1111/j.1600-0447.2007.00963.x.

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 (1), 3–5. https://doi.org/10.1192/bjp.bp.112.124404.

Koukopoulos, A.E., Angeletti, G., Sani, G., Janiri, D., Manfredi, G., Kotzalidis, G.D., De Chiara, L., 2020. Perinatal mixed affective state: wherefore art thou? Psychiatr. Clin. North Am 43 (1), 113–126. https://doi.org/10.1016/j.psc.2019.10.004. Epub 2019 Nov 27.

Kraepelin, E., 1899. Psychiatrie. Ein Lehrbuch für Studierende und Ärzte, 6. Auflage, I. Band, Allgemeine Psychiatrie. II-Die Erscheinungen des Irreseins, Ss 101–239; II. Band, Klinische Psychiatrie. IX. Das manisch-depressive Irresein, Ss. 359–425(Mischzustände, Ss. 394–398). Verlag von Johann Ambrosius Barth, Leipzig.

Knasmüller, P., Kotal, A., König, D., Vyssoki, B., Kapusta, N., Blüml, V., 2019. Maternal suicide during pregnancy and the first postpartum year in Austria: findings from 2004 to 2017. Psychiatry Res. 281, 112530. https://doi.org/10.1016/j.psychres.2019.112530. Epub 2019 Aug 23.

Kukopulos, A., Caliari, B., Tundo, A., Minnai, G., Floris, G., Reginaldi, D., Tondo, L., 1983. Rapid cyclers, temperament, and antidepressants. Compr. Psychiatry 24 (3), 249–258. https://doi.org/10.1016/0010-440x(83)90076-7.

Maina, G., Rosso, G., Aguglia, A., Bogetto, F., 2014. Recurrence rates of bipolar disorder during the postpartum period: a study on 276 medication-free Italian women. Arch. Womens Ment. Health 17 (5), 367-372. https://doi.org/10.1007/s00737-013-0405-4.

Maj, M., 2015. "Mixed" depression: drawbacks of DSM-5 (and other) polythetic diagnostic criteria. J. Clin. Psychiatry 76 (3), e381–e382. https://doi.org/10.4088/JCP.14com09487.

Maj, M., Pirozzi, R., Magliano, L., Bartoli, L., 2003. Agitated depression in bipolar I disorder: prevalence, phenomenology, and outcome. Am. J. Psychiatry 160 (12), 2134–2140. https://doi.org/10.1176/appi.ajp.160.12.2134.

Maj, M., Pirozzi, R., Magliano, L., Fiorillo, A., Bartoli, L., 2006. Agitated "unipolar" major depression: prevalence, phenomenology, and outcome. J. Clin. Psychiatry 67 (5), 712–719. https://doi.org/10.4088/jcp.v67n0504.

Mazzarini, L., Kotzalidis, G.D., Piacentino, D., Rizzato, S., Angst, J., Azorin, J.M., Bowden, C.L., Mosolov, S., Young, A.H., Vieta, E., Girardi, P., Perugi, G., Group, BRIDGE-II-Mix Study, 2018. Is recurrence in major depressive disorder related to bipolarity and mixed features? Results from the BRIDGE-II-Mix study. J. Affect. Disord 229, 164–170. https://doi.org/10.1016/j.jad.2017.12.062. Epub 2018 Jan 2.

Meltzer-Brody, S., Stuebe, A., 2014. The long-term psychiatric and medical prognosis of perinatal mental illness. Best Pract. Res. Clin. Obstet. Gynaecol. 28 (1), 49–60. https://doi.org/10.1016/j.bpobgyn.2013.08.009. Epub 2013 Aug 27.

Miller, C.J., Klugman, J., Berv, D.A., Rosenquist, K.J., Ghaemi, S.N., 2004. Sensitivity and specificity of the Mood Disorder Questionnaire for detecting bipolar disorder. J. Affect. Disord. 81 (2), 167–171. https://doi.org/10.1016/S0165-0327(03)00156-3.

Mota, N.P., Chartier, M., Ekuma, O., Nie, Y., Hensel, J.M., MacWilliam, L., McDougall, C., Vigod, S., Bolton, J.M., 2019. Mental disorders and suicide attempts in the pregnancy and postpartum periods compared with non-pregnancy: a population-based study. Can. J. Psychiatry 64 (7), 482–491. https://doi.org/10.1177/0706743719838784. Epub 2019 Mar 20.

Munk-Olsen, T., Laursen, T.M., Meltzer-Brody, S., Mortensen, P.B., Jones, I., 2012. Psychiatric disorders with postpartum onset: possible early manifestations of bipolar affective disorders. Arch. Gen. Psychiatry 69 (4), 428–434. https://doi.org/10.1001/archgenpsychiatry.2011.157. Epub 2011 Dec 5.

Murray, D., Cox, J.L., 1990. Screening for depression during pregnancy with the Edinburgh depression scale (EPDS). J. Reprod. Infant Psychol. 8 (2), 99–107. https://doi.org/10.1080/02646839008403615.

O'Hara, M.W., Wisner, K.L., 2014. Perinatal mental illness: definition, description and aetiology. Best Pract. Res. Clin. Obstet. Gynaecol. 28 (1), 3–12. https://doi.org/10.1016/j.bpobgyn.2013.09.002. Epub 2013 Oct 7.

Overall, J.E., 1974. The brief psychiatric rating scale in psychopharmacology research. In: Pichot, P. (Ed.), Psychological Measurements in Psychopharmacology. Modern Problems in Pharmacopsychiatry 7. Karger Verlag, BaselCH, pp. 67–78 S.

Overall, J.E., Gorham, D.R., 1962. The brief psychiatric rating scale. Psychol. Rep. 10 (June), 799–812. https://doi.org/10.2466/pr0.1962.10.3.799.

Perugi, G., Angst, J., Azorin, J.M., Bowden, C.L., Mosolov, S., Reis, J., Vieta, E., Young, A.H., 2015. Mixed features in patients with a major depressive episode: the BRIDGE-II-MIX study. J. Clin. Psychiatry 76 (3), e351–e358. https://doi.org/10.4088/JCP.14m09092.

Perugi, G., De Rossi, P., Fagiolini, A., Girardi, P., Maina, G., Sani, G., Serretti, A., 2019. Personalized and precision medicine as informants for treatment management of bipolar disorder. Int. Clin. Psychopharmacol. 34 (4), 189–205. https://doi.org/10.1097/YIC.0000000000000260.

Pompili, M., Girardi, P., Tatarelli, R., Iliceto, P., De Pisa, E., Tondo, L., Akiskal, K.K., Akiskal, H.S., 2008. TEMPS-A (Rome): psychometric validation of affective temperaments in clinically well subjects in mid- and south Italy. J. Affect. Disord. 107 (1–3), 63–75. https://doi.org/10.1016/j.jad.2007.07.031. Epub 2007 Sep 19.

Poobalan, A.S., Aucott, L.S., Ross, L., Smith, W.C., Helms, P.J., Williams, J.H., 2007. Effects of treating postnatal depression on mother-infant interaction and child development: systematic review. Br. J. Psychiatry 191, 378–386. https://doi.org/10.1192/bjp.bp.106.032789.

Prieto, M.L., Youngstrom, E.A., Ozerdem, A., Altinbas, K., Quiroz, D., Aydemir, O., Yalin, N., Geske, J.R., Feeder, S.E., Angst, J., Frye, M.A., 2015. Different patterns of manic/hypomanic symptoms in depression: a pilot modification of the hypomania checklist-32 to assess mixed depression. J. Affect. Disord. 172, 355–360. https://doi.org/10.1016/j.jad.2014.09.047. Epub 2014 Oct 13.

Putnam, K.T., Wilcox, M., Robertson-Blackmore, E., Sharkey, K., Bergink, V., Munk-Olsen, T., Deligiannidis, K.M., Payne, J., Altemus, M., Newport, J., Apter, G., Devouche, E., Viktorin, A., Magnusson, P., Penninx, B., Buist, A., Bilszta, J., O'Hara, M., Stuart, S., Brock, R., Roza, S., Tiemeier, H., Guille, C., Epperson, C.N., Kim, D., Schmidt, P., Martinez, P., Di Florio, A., Wisner, K.L., Stowe, Z., Jones, I., Sullivan, P.F., Rubinow, D., Wildenhaus, K., Meltzer-Brody, S., 2017. Clinical phenotypes of perinatal depression and time of symptom onset: analysis of data from an international consortium. Lancet Psychiatry 4 (6), 477–485. https://doi.org/10.1016/S2215-0366(17)

30136-0. Epub 2017 May 3.
Rihmer, Z., Gonda, X., Rihmer, A., Döme, P., 2016. Antidepresszívum-rezisztens depresszió és a bipoláris spektrum kapcsolata - diagnosztikai és terápiás szempontok [Antidepressant-resistant depression and the bipolar spectrum – diagnostic and therapeutic considerations–Hungarian]. Psychiatr. Hung. 31 (2), 157–168. URI. http://real.mtak.hu/id/eprint/40243.
Rusner, M., Berg, M., Begley, C., 2016. Bipolar disorder in pregnancy and childbirth: a systematic review of outcomes. BMC Pregnancy Childbirth 16 (1), 331. https://doi.org/10.1186/s12884-016-1127-1.
Şair, Y.B., Sevinçok, D., Kutlu, A., Çakaloz, B., Sevinçok, L., 2019. The affective temperament traits and pregnancy-related depression in mothers may constitute risk factors for their children with attention deficit and hyperactivity disorder. J. Obstet. Gynaecol. 1–6. https://doi.org/10.1080/01443615.2019.1679741. [Epub ahead of print Dec 8 2019].
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. https://doi.org/10.1159/000358808. Epub 2014 Jun 19.
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. https://doi.org/10.1016/j.jad.2014.03.054. Epub 2014 Apr 12.
Sani, G., Perugi, G., Tondo, L., 2017. Treatment of bipolar disorder in a lifetime perspective: is lithium still the best choice? Clin. Drug Investig 37 (8), 713–727. https://doi.org/10.1007/s40261-017-0531-2.
Sani, G., Vöhringer, P.A., Barroilhet, S.A., Koukopoulos, A.E., Ghaemi, S.N., 2018. The Koukopoulos Mixed Depression Rating Scale (KMDRS): an International Mood Network (IMN) validation study of a new mixed mood rating scale. J. Affect. Disord. 232, 9–16. https://doi.org/10.1016/j.jad.2018.01.025. Epub 2018 Feb 16.
Sato, T., Bottlender, R., Schröter, A., Möller, H.-J., 2003. Frequency of manic symptoms during a depressive episode and unipolar 'depressive mixed state' as bipolar spectrum. Acta Psychiatr. Scand. 107 (4), 268–274. https://doi.org/10.1034/j.1600-0447.2003.00051.x.
Shansis, F.M., Reche, M., Capp, E., 2016. Evaluating response to mood stabilizers in patients with mixed depression: a study of agreement between three different mania rating scales and a depression rating scale. J. Affect. Disord. 197, 1–7. https://doi.org/10.1016/j.jad.2016.02.064. Epub 2016 Mar 3.
Shapiro, S.S., Wilk, M.B., 1965. Analysis of variance test for normality (complete samples). Biometrika 52, 591–611. https://doi.org/10.1093/biomet/52.3-4.591.
Sharma, V., Kahn, M., 2010. Identification of bipolar disorder in women with postpartum depression. Bipolar Disord. 12 (3), 335–340. https://doi.org/10.1111/j.1399-5618.2010.00809.x.
Sharma, V., Mazmanian, D., 2014. The DSM-5 peripartum specifier: prospects and pitfalls. Arch. Womens Ment. Health 17 (2), 171–173. https://doi.org/10.1007/s00737-013-0406-3. Epub 2014 Jan 12.
Sharma, V., Khan, M., Corpse, C., Sharma, P., 2008. Missed bipolarity and psychiatric comorbidity in women with postpartum depression. Bipolar Disord 10 (6), 742–747. https://doi.org/10.1111/j.1399-5618.2008.00606.x.
Sharma, V., Xie, B., Campbell, M.K., Penava, D., Hampson, E., Mazmanian, D., Pope, C.J., 2014. A prospective study of diagnostic conversion of major depressive disorder to bipolar disorder in pregnancy and postpartum. Bipolar Disord. 16 (1), 16–21. https://doi.org/10.1111/bdi.12140. Epub 2013 Oct 16.
Spearing, M.K., Post, R.M., Leverich, G.S., Brandt, D., Nolen, W., 1997. Modification of the clinical global impressions (CGI) Scale for use in bipolar illness (BP): the CGI-BP. Psychiatry Res. 73 (3), 159–171. https://doi.org/10.1016/S0165-1781(97)00123-6.
Suppes, T., Mintz, J., McElroy, S.L., Altshuler, L.L., Kupka, R.W., Frye, M.A., Keck, P.E.Jr., Nolen, W.A., Leverich, G.S., Grunze, H., Rush, A.J., Post, R.M., 2005. Mixed hypomania in 908 patients with bipolar disorder evaluated prospectively in the Stanley Foundation Bipolar Treatment Network: a sex-specific phenomenon. Arch. Gen. Psychiatry 62 (10), 1089–1096. https://doi.org/10.1001/archpsyc.62.10.1089.
Tohen, M., Jacobs, T.G., Grundy, S.L., McElroy, S.L., Banov, M.C., Janicak, P.G., Sanger, T., Risser, R., Zhang, F., Toma, V., Francis, J., Tollefson, G.D., Breier, A., 2000. Efficacy of olanzapine in acute bipolar mania: a double-blind, placebo-controlled study. Olanzapine HGGW Study Group. Arch. Gen. Psychiatry 57 (9), 841–849. https://doi.org/10.1001/archpsyc.57.9.841.
Vawda, N.B.M., 2018. Suicide attempts during pregnancy in South Africa. S. Afr. J. Psychiatr. 24, 1154. https://doi.org/10.4102/sajpsychiatry.v24i0.1154. eCollection Apr 16, 2018.
Ventura, J., Lukoff, D., Nuechterlein, K.H., Liberman, R.P., Green, M., Shaner, A., 1993. Appendix 1: brief Psychiatric Rating Scale (BPRS) Expanded version (4.0) scales, anchor points and administration manual. Int. J. Meth. Psychiatr. Res. 3, 227–244.
Vieta, E., Grunze, H., Azorin, J.M., Fagiolini, A., 2014. Phenomenology of manic episodes according to the presence or absence of depressive features as defined in DSM-5: results from the IMPACT self-reported online survey. J. Affect. Disord. 156, 206–213. https://doi.org/10.1016/j.jad.2013.12.031. Epub 2014 Jan 1.
Viguera, A.C., Whitfield, T., Baldessarini, R.J., Newport, D.J., Stowe, Z., Reminick, A., Zurick, A., Cohen, L.S., 2007. Risk of recurrence in women with bipolar disorder during pregnancy: prospective study of mood stabilizer discontinuation. Am. J. Psychiatry 164 (12), 1817–1824. https://doi.org/10.1176/appi.ajp.2007.06101639.
Viguera, A.C., Tondo, L., Koukopoulos, A.E., Reginaldi, D., Lepri, B., Baldessarini, R.J., 2011. Episodes of mood disorders in 2,252 pregnancies and postpartum periods. Am. J. Psychiatry 168 (11), 1179–1185. https://doi.org/10.1176/appi.ajp.2011.11010148. Epub 2011 Jul 28.
Welch, B.L., 1947. The generalization of "Student's" problem when several different population variances are involved. Biometrika 34 (1–2), 28–35. https://doi.org/10.1093/biomet/34.1-2.28.
Weygandt, W., 1899. Über die Mischzustände des manischdepressiven Irreseins. J.F. Lehmann, München.
Williamson, J.A., O'Hara, M.W., Stuart, S., Hart, K.J., Watson, D., 2015. Assessment of postpartum depressive symptoms: the importance of somatic symptoms and irritability. Assessment 22 (3), 309–318. https://doi.org/10.1177/1073191114544357. Epub 2014 Jul 24.
Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: reliability, validity and sensitivity. Br. J. Psychiatry 133 (5), 429–435. https://doi.org/10.1192/bjp.133.5.429.