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ORIGINAL ARTICLE

Retrospective Study

Mood Spectrum Model: Evidence reconsidered in the light of DSM-5

Antonella Benvenuti, Mario Miniati, Antonio Callari, Michela Giorgi Mariani, Mauro Mauri, Liliana Dell'Osso

Antonella Benvenuti, Mario Miniati, Antonio Callari, Michela Giorgi Mariani, Mauro Mauri, Liliana Dell'Osso, Department of Clinical and Experimental Medicine, University of Pisa, 56100 Pisa, Italy

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Correspondence to: Antonella Benvenuti, MD, Department of Clinical and Experimental Medicine, University of Pisa, Via Roma 67, 56100 Pisa, Italy. antonellabenvenuti@virgilio.it
Telephone: +39-050-999616
Fax: +39-050-2219787

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Abstract

AIM: to investigate studies conducted with the Mood Spectrum Structured Interviews and Self-Report versions (SCI-MOODS and MOODS-SR).

METHODS: We conducted a review of studies published between 1997 and August 2014. The search was performed using Pubmed and PsycINFO databases. Analysis of the papers followed the inclusion and exclusion criteria recommended by the PRISMA Guidelines, namely: (1) articles that presented a combination of at least two terms, "SCI-MOODS" [all fields] or "MOODS-SR" [all fields] or "mood spectrum" [all fields]; (2) manuscript in English; (3) original articles; and (4) prospective or retrospective original studies (analytical or descriptive), experimental or quasi-experimental studies. Exclusion criteria were: (1) other study designs (case reports, case series, and reviews); (2) non-original studies including editorials, book reviews and letters to the editor; and (3) studies not specifically designed and focused on SCI-MOODS or MOODS-SR.

RESULTS: The search retrieved 43 papers, including 5 reviews of literature or methodological papers, and 1 case report. After analyzing their titles and abstracts, according to the eligibility criteria, 6 were excluded and 37 were chosen and included. The SCI-MOODS and the MOODS-SR have been tested in published studies involving 52 different samples across 4 countries (Italy, United States, Spain and Japan). The proposed mood spectrum approach has demonstrated its usefulness mainly in 3 different areas: (1) Patients with the so-called "pure" unipolar depression that might manifest hypomanic atypical and/or sub-threshold aspects systematically detectable with the mood questionnaire; (2) Spectrum features not detected by other instruments are clinically relevant, because they might manifest in waves during the lifespan, sometimes together, sometimes alone, sometimes reaching the severity for a full-blown disorder, sometimes interfering with

other mental disorders or complicating the course of somatic diseases; and (3) Higher scores on the MOODS-SR factors assessing "psychomotor disturbances", "mixed instability" and "suicidality" delineate subtypes of patients characterized by the more severe forms of mood disorders, the higher risk for psychotic symptoms, and the lower quality of life after the remission of the full-blown-episode.

CONCLUSION: The mood spectrum model help researchers and clinicians in the systematic assessment of those areas of psychopathology that are still neglected by the Diagnostic and Statistical Manual of Mental Disorders 5 classification.

Key words: Mood disorders; Dimensional; Categorical; Unipolar; Spectrum; Bipolar; Diagnostic and Statistical Manual of Mental Disorders 5

Core tip: Data emerging from the proposed mood spectrum approach suggest the existence of a continuum from "pure mania" to "pure depression", without a clear cut-off between the two realms. As a whole, the experience with the mood spectrum model enforces past and recent claims towards the need for a unitary dimensional approach to mood disorders.

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INTRODUCTION

The boundaries of mood disorders have expanded during the last two decades as a consequence of the growing interest in the atypical, subclinical and/or sub-threshold forms of unipolar and bipolar disorders[1,2]. Efforts were initially devoted to the identification of atypical and sub-threshold forms of depression (Depressive Spectrum)[3,4]. Subsequently, the manic/hypomanic side was explored[1,5,6] giving a new impulse to the literature on mood disorders in general.

An enlargement of the manic dimension of mood disorders was thus proposed, aiming to identify those bipolar syndromes that, not fitting in the classic categorical description of Diagnostic and Statistical Manual of Mental Disorders (DSM), have led to an over-diagnosis of "pure" unipolar forms[7]. However, the unipolar/bipolar dichotomy was still maintained as nuclear to all the proposed theoretic constructs.

At the beginning of the 90's, in an attempt to define "soft indicators of bipolarity", the focus was shifted on affective temperaments[8]. Over the following years, clinicians and researchers of the University of Pisa, Italy, and of the Universities of Pittsburgh, Columbia (New York) and California (San Diego), promoted the "Spectrum Project Collaborative Group" (SPCG) whose aim was to create and validate instruments able to recognize the wide halo of phenomenology surrounding the "core" features of each DSM mood category and overcome the classic unipolar/bipolar dichotomy[9].

The SPCG research agenda was based upon the empirical observation that a wide range of signs and features not included in the DSM might run completely overlooked or simply be considered not relevant from a clinical point of view. Conversely, a growing body of evidence indicated the clinical relevance of sub-threshold or atypical presentations of mood disorders and the potential usefulness of a dimensional assessment[9].

The SPCG proposed that life-long sub-threshold mood dysregulations represented the constitutional foundation of both full-blown manic and depressive episodes. The "SCI-MOODS" and the "its self-report version" (MOODS-SR) were developed to assess this wide area of phenomenology. The SCI-MOODS was the first version of the questionnaire, the MOODS-SR being its self-report version. The same authors constructed a MOODS-SR last-month version. All the versions were developed in parallel in English and Italian with a back translation and a subsequent validation for internal consistency and inter-rater reliability. The instruments consisted of 161 items coded as present or absent for one or more periods of at least 3-5 d through the subject's lifetime or over the past week or month[10]. The MOODS-SR was originally composed of four domains: (1) The Neurovegetative domain, assessing disturbances and rhythmic changes in feelings, eating attitudes, sexual activity and sleep, including rhythmic variations in affective and sub-affective symptoms; (2) the Energy levels domain, assessing changes in everyday activities, with special attention devoted to work, hobbies and social life; (3) the mood Domain, exploring the whole realm of depressive and manic symptoms, signs and sub-threshold manifestations of mood dysregulations; and (4) The cognitive domain, assessing changes in the cognitive realm that occur together with mood dysregulations[11].

The potential implications and the conceptual and methodological advantages of the proposed mood spectrum model have been already described[9-12]. However, at that time, evidence from clinical studies using the SCI-MOODS and the MOODS-SR was limited. The aim of this paper is to review and summarize the studies conducted with the SCI-MOODS and the MOODS-SR over the past 15 years and reconsider the evidence in the light of the DSM-5.

MATERIALS AND METHODS

We conducted a review of studies published between

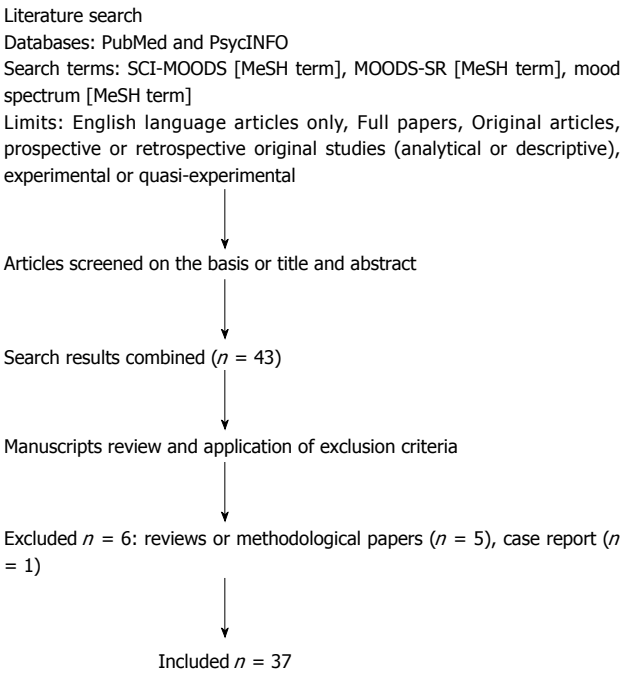

Figure 1 Flow diagram of study selection. SCI-MOODS: Mood Spectrum Structured Interview; MOODS-SR: MOODS Spectrum self-report version.

1997 (year of the first publication regarding the proposed mood spectrum approach) and August 2014. The search was performed using Pubmed and PsycINFO databases. Analysis of the articles followed inclusion and exclusion criteria derived from the ones recommended by the PRISMA Guidelines[13]. We included the following: (1) articles that presented a combination of at least two terms, namely "SCI-MOODS" [all fields] or "MOODS-SR" [all fields] or "mood spectrum" [all fields]; (2) manuscript in English; (3) original articles; and (4) prospective or retrospective original studies (analytical or descriptive), experimental or quasi-experimental. Exclusion criteria were as follows: (1) other study designs, such as case reports, case series, and reviews; (2) non-original studies including editorials, book reviews and letters to the editor; and (3) studies not specifically designed and focused on SCI-MOODS or MOODS-SR.

We utilized a flow diagram (Figure 1) to summarize the total number of screened papers and the number of those included in the review process, as suggested by the PRISMA Guidelines[13]. No extraction forms for the data extraction process were used, mainly because the studies on the proposed mood spectrum model were conducted in different fields and with different aims, as described in detail in the paragraphs of the result section. Two authors completed a formal training in reviewing data and performing meta-analyses, independently from this manuscript (AC and MGM).

Initially, the search retrieved 43 papers, including 5 reviews of literature or methodological papers, and 1 case report. After analyzing their titles and abstracts, according to the eligibility criteria, 6 were excluded and 37 were chosen and included in the final sample (Figure 1).

Statistical analysis

No new data have been added in this paper. No new analyses or meta-analyses were performed. The description of statistical methods used in any study can be found in the related papers.

RESULTS

The SCI-MOODS and the MOODS-SR have been tested in published studies involving 52 samples across 4 countries (Italy, United States, Spain and Japan) (see Table 1).

The SCI-MOODS and the MOODS-SR: Validity and reliability

The first two studies with the SCI-MOODS tested its validity and reliability. The reliability of the interview was proved to be excellent: the inter-rater reliability of domains ranged between 0.93 and 0.94, and the internal consistency of domains ranged between 0.79 and 0.92. In terms of discriminant validity, patients with mood disorders had significantly higher total and MOODS domain scores than controls, and patients with a bipolar disorder scored significantly higher on the manic component than patients with unipolar depression[10,14]. Subsequently, the self-report version of the questionnaire, the MOODS-SR, was developed and validated[11]. The results of the validation study were partially replicated by Ghouse *et al*[15]. Berrocal *et al*[16] validated a Spanish version of the MOODS-SR. A Swedish version of the questionnaire is currently undergoing the validation process.

A second step was the attempt to give the MOODS-SR a post-hoc structure with a factor analysis. The aim of the factor analysis was to determine, with a statistical approach, factors able to differentiate the pure dimensions of the depressive and the manic realm. The first study focused on the factor structure of mania-hypomania. The MOODS-SR was administered to a sample of 617 patients with a bipolar I disorder, diagnosed with the SCID-I. A classical exploratory factor analysis, based on a tetra choric matrix, was carried out on the 68 items of the manic/hypomanic component, followed by an Item Response Theory (IRT)-based factor analytic approach and by an IRT-based bi-factor analysis. Five factors of the manic/hypomanic component were identified: "Psychomotor Activation", "Mixed Instability", "Spirituality/Mysticism/Psychoticism", "Mixed Irritability" and "Euphoria". This approach permitted to subtype two clinical phenotypes of mania: the "pure mania", characterized by typical, atypical and sub-threshold symptoms of euphoria and psychomotor activation, and the "mixed mania", characterized by instability and irritability[17]. In a second study, the clinical features of 598 patients

Table 1 Mood Spectrum Structured Interview and Mood Spectrum Self-Report version studies

Ref.	Subjects	Design	Diagnostic criteria	Instruments	Results
Fagiolini *et al*[10]	491 (141 students, 116 gastrointestinal pts, 112 pts with BPD, 122 pts with recurrent MDEs)	Validation study (Italy)	DSM-IV	SCID-I, SCI-MOODS	Good discriminant validity and internal consistency
Dell'Osso *et al*[11]	41 (21 pts with MDEs or BPD *vs* 20 controls)	Validation study (Italy)	DSM-IV	SCID-I, SCI-MOODS, MOODS-SR	Good reliability of the self-report version (MOODS-SR) of the SCI-MOODS. Intraclass correlation coefficients ranged from 0.88 to 0.97
Veltri *et al*[34]	91 pts with TMD *vs* 26 TMD-free subjects	Open study (Italy)		Helkimo's Clinical Dysfunction Index (CDI), MOODS-SR	Total scores of depressive domains significantly higher in moderate or severe dysfunctional than in TMD-free and mild dysfunctional pts
Cassano *et al*[18]	213 (117 pts with recurrent MDEs in remission and 106 pts with BP-I)	Open study (Italy)	DSM-IV	MINI, SCI-MOODS	Patients with recurrent UP depression endorsed a substantial number of manic/hypomanic symptoms over their lifetimes
Manfredini *et al*[35]	85 subjects (34 bruxers *vs* 51 non-bruxers)	Open Study (Italy)	DSM-IV	MOODS-SR, PAS-SR	Significant differences between bruxers and controls emerged for the presence of both depressive and manic symptoms in MOODS-SR
Manfredini *et al*[36]	131 subjects screened for temporomandibular disorder (TMD)	Open study (Italy)	DSM-IV	MOODS-SR, PAS-SR, assessment for TMD	Significantly higher prevalence of both mood and panic-agoraphobic symptoms in myofascial pain pts than in the other diagnostic groups (TMD-free, disc displacement and joint disorders)
Manfredini *et al*[37]	20 pts with myofascial pain, 18 pts with temporomandibular joint pain-TMJ, 22 pts with combined pain *vs* 25 pts with non-painful TMD *vs* 29 TMD-free subjects	Open study (Italy)	DSM-IV	MOODS-SR, PAS-SR, assessment for TMD	Patients with painful TMD scored significantly higher than comparison groups in all MOODS-SR depressive domains
Cassano *et al*[19]	39 pts with Borderline PD + BPD *vs* 21 pts with Borderline PD	Open study (Italy)	DSM-IV	SCID-I, MOODS-SR, SCID-II	Lifetime manic-hypomanic mood dysregulations correlated with psychotic spectrum features in borderline patients
Benvenuti *et al*[45]	103 (70 pts with BP-I, 24 pts with BP-II, 4 pts with SA, 5 pts with BPD-NOS	Open study (United States)	DSM-IV	SCID-I, MOODS-SR, W-SAS, PAS-SR	WSAS scores on current depressive, manic, and panic spectrum total scores showed a highly significant "depressive spectrum" effect
Dell'Osso *et al*[30]	92 pts with Rheumatoid Arthritis	Open study (Italy)	DSM-IV	HAQ, MOS-SF36, MOODS-SR	Lifetime mood depressive spectrum was related with impaired HRQoL levels
Manfredini *et al*[38]	105 controls with bruxing behaviors	Open study (Italy)	DSM-IV	MOODS-SR	Prevalence of mood psychopathology was significantly higher in bruxers. Significant differences between bruxers and non-bruxers emerged in total MOODS-SR scores
Koukopoulos *et al*[57]	24 pts with Unipolar Depression *vs* 15 pts with BP-II	Open study (Japan)	DSM-IV	SCI-MOODS	Patients with BP-II disorder tended to show apparently quick disappearance of depressive symptoms
Ghouse *et al*[15]	71 (49 with MDEs or BPD or GAD, 22 controls)	Validation study (Spanish)	DSM-IV	SCID-I, BDI, MOODS-SR, Clinician-Administered Rating Scale for Mania	MOODS-SR good internal consistency and test-retest reliability. Significant positive correlations between depressive sub-domains and BDI and between manic-hypomanic subdomains and CARS for Mania
Piccinni *et al*[32]	92 pts with Rheumatoid Arthritis	Open study (Italy)	DSM-IV	MOS-SF36, MOODS-SR, PAS-SR	Significant worsening of all MOS SF-36 scores related to higher scores of the depressive domains of MOODS-SR
Benvenuti *et al*[20]	90 (25 pts with Borderline PD, 16 pts with BPD, 19 pts with MDE, 30 controls)	Open study (Spanish)	DSM-IV	SCID-I, MOODS-SR	No statistical significance for any (sub) domain considered between patients with BPD and Bipolar Disorder
Manfredini *et al*[39]	47 subjects (17 pts with BPD, 14 pts with MDEs, 16 controls)	Open study (Italy)	DSM-IV	SCID-I, SCI-MOODS-SR	Allopregnanolone/progesterone levels correlate with mixed features
Berrocal *et al*[16]	598 pts with MDE	Open study (Italy + United States)	DSM-IV	SCID-I, MOODS-SR	Central role of depressed mood, psychomotor retardation and suicidality. The factors "Drug/Illness related depression", "Psychotic features" and the neurovegetative dysregulation were identified

Cassano *et al*[17]	617 pts with BPD	Open study (Italy + United States)	DSM-IV	SCID-I, MOODS-SR	9 factors initially identified, 5 of them (Psychomotor Activation, Mixed Instability, Spirituality/Mysticism/Psychoticism, Mixed Irritability, Euphoria) subsequently retained
Dell'Osso *et al*[27]	130 (65 pts with PTSD *vs* 65 controls)	Open study (Italy)	DSM-IV	SCID-I, MOODS-SR	Statistically significant and positive associations were found between the presence of manic/hypomanic and depressive symptoms and the likelihood of suicidal ideation or attempts
Dell'Osso *et al*[29]	167 pts with fibromyalgia	Open study (Italy)	DSM-IV	SCID-I, MOS-SF36, FIQ, MOODS-SR	A high rate of lifetime manic symptoms was related to the Pain Visual Analogic Scale of the FIQ and the FIQ total scores and to the "bodily pain", and to the physical and mental component scores of the MOS SF-36
Mauri *et al*[41]	316 pts with MDEs	Depression Phenotype Study: Randomized (Italy + United States)	DSM-IV	SCID-I, MOODS-SR, HAM-D	In patients who reached remission from an MDE according to the Hamilton Rating Scale for Depression, scores on the depressive component of the MOODS-SR predicted relapses in the subsequent 6 mo
Benazzi *et al*[51]	222 pts with MDEs	Depression Phenotype Study: Randomized (Italy + United States)	DSM-IV	SCID-I, MOODS-SR	Association between the manic/hypomanic component of the MOODS-SR and the polymorphisms of the 5-HTTLPR was moderated by gender
Miniati *et al*[42]	312 pts with MEDs (78 with a history of emotional/physical abuse, EPA)	Depression Phenotype Study: Randomized (Italy + United States)	DSM-IV	SCID-I, SCID-II, HRSD, QIDS, MOODS-SR	Patients with a history of EPA did not differ from those without on HAM-D scores at baseline. The two groups differed on factors: "dep. Mood", "psychomotor retardation", "drug and illness-related depression", and "neurovegetative symptoms"
Frank *et al*[44]	226 pts with MDEs	Depression Phenotype Study: Randomized (Italy + United States)	DSM-IV	SCID-I, HAM-D, Q-LES-Q, WSAS, MOODS-SR, PAS-SR	Poor quality of life associated with the MOODS-SR factors "depressive mood" and "psychotic features" and the PAS-SR factors "separation anxiety" and "loss sensitivity". Functional impairment was associated with the MOODS-SR factor "psychomotor retardation" and the PAS-SR factor "fear of losing control"
Dell'Osso *et al*[28]	48 (25 pts with PTSD *vs* 23 controls)	Open study (Italy)	DSM-IV	SCID-I, IES, MOODS-SR	PTSD pts showed a significant decrease in TSPO density. TSPO density correlated with the number of lifetime manic/hypomanic spectrum symptoms
Bazzichi *et al*[31]	110 (60 pts with fibromyalgia *vs* 50 pts with Rheumatoid Arthritis)	Open study (Italy)	DSM-IV	MOODS-SR (OTHERS?)	FM pts showed significantly higher scores than RA patients in "mood depressive", "cognition depressive" domains and in total depressive component
Miniati *et al*[43]	318 pts with MDEs	Depression Phenotype Study: Randomized (Italy + United States)	DSM-IV	SCID-I, HAM-D, MOODS-SR, PAS-SR, SHY-SR	Participants with lower scores on the MOODS-SR "psychomotor activation" factor experienced more rapid remission with SSRI
Fagiolini *et al*[46]	291 pts with MDEs	Depression Phenotype Study: Randomized (Italy + United States)	DSM-IV	SCID-I, SCID-II, HRSD, QIDS, MOODS-SR	Compared to low scorers, participants with high scores on the LPR factor had greater severity of depression and more bipolarity indicators
Dell'Osso *et al*[24]	103 (53 pts with complicated grief *vs* 50 controls)	Open study (Italy)	DSM-IV	SCID-I, ICG, ASA-27, W-SAS, MOODS-SR	Patients with CG reported significantly higher scores on the MOODS-SR, ASA-27, and WSAS with respect to controls. The scores on the ASA-27 were significantly associated with the MOODS-SR depressive and manic components
Apfelbaum *et al*[22]	50 pts with complicated grief	Open study (Italy)	DSM-IV	SCID-I, ICG, MOODS-SR	MOODS-SR depressive and rhythmicity/vegetative items were associated with increased suicidal ideation and attempts, while sub-threshold manic items with suicidal ideation
Rucci *et al*[52]	1158 pts with MDEs or BPD	Open study (Italy + United States)	DSM-IV	SCID-I, MOODS-SR	MOODS-SR psychomotor activation factor identified subgroups with an increasing likelihood of bipolar disorder diagnosis
Dell'Osso *et al*[25]	116 (66 pts with PTSD, 22 pts with complicated grief, 28 pts with PTSD+complicated grief)	Open study (Italy)		SCID-I, ICG, ASA-27, W-SAS, MOODS-SR	Patients with CG+PTSD or PTSD alone reported significantly higher scores on the manic component of the MOODS-SR

Dell'Osso *et al*[23]	389 subjects (156 with Mood Disorders, 54 pts with Panic Disorder, 79 pts with schizophrenia, 100 controls)	Open study (Italy)	DSM-Ⅳ-TR	BPRS, OBS-SR, MOODS-SR, SCID-I	Sexual obsessions more frequent in schizophrenia (54.4%), followed by mood disorders (35.9%), and independently associated with all aspects of suicidal behaviors
Hardoy *et al*[40]	1066 pregnant women	Prospective Study (Italy)	DSM-Ⅳ	SCID-I, EPDS, MOODS-SR	The prevalence of suicidality in women who had MmD during pregnancy was 26.4% and 34.1%, assessed with the MOODS-SR and the EPDS, respectively, while it was 18.4% (MOODS-SR) and 30.6% (EPDS) during the postpartum period
Berrocal *et al*[21]	63 pts with MDE, BPD, Cluster B PD, comorbid BPD and PD-B	Open Study (United States)	DSM-Ⅳ	MINI and SCID II, MOODS-SR, BI, TEMPS-A and IPDE	BD+PD-B pts showed a more severe type of emotional dysregulation. Patients with BD+PD-B comorbidity had an earlier onset and more severity in suicide attempts, hospitalizations and self-harm behaviors
Dell'Osso *et al*[26]	475 students	Open study (Italy)	DSM-Ⅳ	MOODS-SR, TALS-SR (Others?)	Significantly higher MOODS-SR domain scores were found in PTSD survivors compared to those without. The mood depressive, cognition depressive and energy manic MOODS-SR domains were associated with an increased likelihood of PTSD
Rucci *et al*[14]	139 (52 pts with BP-I, 32 pts with BP-II, 17 pts with BPD-NOS *vs* 38 controls)	Open Study (United States)	DSM-Ⅳ	MOODS-SR, SCID-I, GAF	BPD pts scored significantly higher than controls on the total MOODS-SR scores and all sub-domains. Comparisons across BD subtypes revealed statistically significant higher scores among BD I, BD II and BD NOS only for the total MOOD-SR scores and for mood mania and energy domains

SCID-I: Structured Clinical Interview for DSM Disorders (Axis I Disorders); SCID-II: Structured Clinical Interview for DSM Disorders (Axis II Disorders); SCI-MOODS: Structured Clinical Interview for the Mood Spectrum; MOODS-SR: Structured Clinical Interview for the Mood Spectrum (self report version); PAS-SR: Structured Clincal Interview for the Panic-Agoraphobic Spectrum (self report version); WSAS: Work and Social adjustment scale; HAQ: Health Assessment Questionnaire; MOS-SF36: Medical Outcome Study-Short form 36; CDI: Helkimo's Clinical Dysfunction Index; MINI: Mini International Neuropsychiatry Interview; BDI: Beck Depression Inventory; FIQ: Fibromyalgia Impact Questionnaire; HAM-D: Hamilton Rating Scale for Depression; QIDS: Quick Inventory for Depressive Symptomatology; Q-LES-Q: Quality of Life Enjoyment and Satisfaction Questionnaire; IES: Impact Event Scale; SHY-SR: Structured Clinical Interview for the Social Phobic Spectrum (self-report version); CGI: Clinical Global Impression; ASA-27: Adult Separation Anxiety (27 items); BPRS: Brief Psychiatric Rating Scale; OBS-SR: Structured Clinical Interview for the Obsessive-Compulsive Spectrum (self report version); EPDS: Edinburgh post-natal depression scale; BI: Bipolarity Index of Gary Sachs; TEMPS-A: Temperament Evaluation of Memphis-Pisa-Paris and San Diego (self-questionnaire version); IPDE: Identify, predict, decide and execute; TALS-SR: Structured Clinical Interview for the Post-traumatic stress spectrum (self report version); GAF: Global Assessment of functioning; TMD: Temporomandibular disorder.

with unipolar depression (UP) were assessed with the MOOD-SR lifetime version. In this case too, a classical exploratory factor analysis using tetra choric correlation coefficients and an IRT-based factor analysis approach were adopted to analyze the data on 74 items of the instrument that explore cognitive, mood and energy/activity features associated with depression. The factor analysis identified three factors describing the core aspects of depression ("depressive mood", "psychomotor retardation" and "suicidality") and 3 more factors: the "neuro-vegetative symptoms", the "Drug/Illness related depression" and the "psychotic features" factors[18].

The detection of the lifetime manic/hypomanic component in patients with "pure" unipolar depression

One of the aims behind the construction of the MOODS-SR was to create an instrument able to recognize soft and atypical manic/hypomanic features both in bipolar and unipolar patients. As originally hypothesized, the instrument identified mild hypomanic features among 117 patients with a DSM-Ⅳ diagnosis of remitted recurrent unipolar depression and 106 patients with a bipolar I disorder. The number of manic/hypomanic items endorsed was directly related to the number of depressive items in both diagnostic groups. A more important presence of the manic/hypomanic component was found among those patients who had a wider number of depressive symptoms through their lifetime. This direct correlation was somehow surprising for patients with the so-called "pure unipolar" form of depression. Moreover, the number of sub-threshold manic/hypomanic items was related to an increased likelihood of endorsing paranoid and delusional thoughts and/or suicidal ideation among patients who were diagnosed as affected by "pure" unipolar depression, according to the DSM-IV categorical approach[19].

The detection of lifetime mood spectrum signs and symptoms among patients with other DSM-IV diagnoses and/or somatic/physical conditions

Benvenuti *et al*[20] assessed patients with borderline personality disorder with and without a comorbid mood disorder. The depressive and the manic-hypomanic component of the mood spectrum were higher than in normal controls and significantly correlated with the presence of sub-threshold psychotic symptoms, as assessed with the the Structured Clinical Interview for the Psychotic Spectrum (SCI-PSY) also in those patients who did not meet criteria for a DSM-5 diagnosis for a mood disorder[20]. Patients with borderline personality disorder and a comorbid mood disorder showed an even stricter correlation between the manic/hypomanic component of the MOODS-SR and different domains and sub-domains of the SCI-PSY[20]. These results were partially replicated by Berrocal *et al*[21], in a following study with the Spanish version of the questionnaire[21]. In a more recent paper Apfelbaum *et al*[22] tested the MOODS-SR in patients with Bipolar disorders with and without a comorbid Cluster B personality disorder. The results of the study showed that patients with BD + PD-B comorbidity had an earlier onset and more severity in suicide attempts, hospitalizations and self-harm behaviors[22].

More recently Apfelbaum *et al*[22] and Dell'Osso *et al*[23-25] has explored the role of mood dysregulations in patients with complicated grief (CG) and/or Post Traumatic Stress Disorder (PTSD) without full-blown mood disorders[22-25]. The aims of these studies were to better characterize patients in the perspective of a more tailored treatment approach, and to identify vulnerability towards CG and PTSD. Patients were assessed with the MOODS-SR lifetime version. MOODS-SR scores were higher in patients with CG than in controls. Patients with CG in comorbidity with PTSD and patients with PTSD reported significantly higher scores on the manic component of the MOODS-SR than patients with CG alone[26,27]. Patients with PTSD and higher MOODS-SR scores showed a higher likelihood of suicidal ideation or attempts[28]. In a following study, the same research group tested the 18 kDa mitochondrial translocator protein (TSPO) density in a sample of patients with a non-war-related PTSD. The decrease of TSPO correlated with the manic/hypomanic component of the mood spectrum, suggesting a possible role of sub-threshold bipolar comorbidity in PTSD-related neurobiological dysregulations[29]. These studies proved the ability of the MOODS-SR to detect sub-threshold manic/hypomanic signs in psychiatric patients without a full-blown diagnosis of Bipolar Disorder. The manic/hypomanic dimension as assessed with the MOODS-SR was associated with greater severity, higher risk for a psychotic evolution and higher suicidal risk in patients without a mood disorder.

The MOODS-SR has proved its usefulness also in medical settings and in non-psychiatric samples. Patients with fibromyalgia showed a relationship between the MOODS-SR lifetime manic spectrum scores, severity of pain and health-related quality of life[30]. Not surprisingly, lifetime depressive spectrum symptoms negatively affected quality of life in patients with rheumatoid arthritis (RA) while sub-threshold manic features improved the subjective perception of health[31,32]. Sub-threshold depressive symptoms were over-represented in fibromyalgic patients as compared to RA patients[33,34]. The mood spectrum instruments were also utilized to detect subthreshold mood dysregulations among patients with temporo-mandibular disorders or bruxism[35-39]. Hardoy *et al*[40] tested the instrument among subjects during the premenstrual phase showing that mixed features correlate with levels of allopregnanolone and pro-gesterone.

Mauri *et al*[41] published a large study performed to assess suicidality in a non-clinical sample of 1066 subjects during the perinatal period and to report suicidality rates in women with major or minor depressive episode (MmD). Subjects were screened with the SCID, during the perinatal period and with the MOODS-SR. The period prevalence of suicidality was 6.9% (95%CI: 6.0-7.8) during pregnancy and 4.3% (95%CI: 3.4-5.2) during postpartum, assessed with the MOODS-SR, and was 12.0% (95%CI: 10.8-13.2) during pregnancy and 8.6% (95%CI: 7.4-9.8) during the postpartum period, assessed with the EPDS. The prevalence of suicidality in women who had MmD during pregnancy was 26.4% and 34.1%, assessed with the MOODS-SR and the EPDS, respectively, while it was 18.4% (MOODS-SR) and 30.6% (EPDS) during the postpartum period.

Sub-typing clinical phenotypes of Mood Disorders: The "Depression Phenotype Study"

The Depression phenotypes study was a multi-center study financed by NIMH grants (Grant number: MH65376; MH30915) and performed by the University of Pittsburgh and Pisa. Aim of the study was to identify the mediators and moderators of depression treatment outcomes. Patients with a non-psychotic major depressive episode were randomly assigned to a pharmacotherapeutic intervention (escitalopram) or to the Interpersonal Psychotherapy (IPT), an empirically validated manual-based treatment for major depression. If the initial treatment was not successful in bringing about remission (HAM-D < 7), subjects received the other treatment as add-on. Patients were administered several instruments including the MOODS-SR in its lifetime and last-month versions.

Miniati *et al*[42] showed that in patients who reached remission according to the Hamilton Rating Scale for Depression, scores on the depressive component of the MOODS-SR predicted relapses in the subsequent 6 mo. The same authors analyzed patients belonging to the

Depression phenotypes study with a history of emotional and physical abuse. The two groups differed on several mood spectrum factors, namely: "depressive mood", "psychomotor retardation", "drug and illness-related depression", and "neurovegetative symptoms"[43].

Patients with lower scores on the "psychomotor activation" factor of the MOODS-SR experienced a shorter time to remission when treated with SSRIs compared to IPT[43]. Subsequent analyses indicated that 7 of 9 (77.8%) patients who experienced hypomania during the study had psychomotor activation scores above the median ($\geqslant$ 5), suggesting that this factor might be useful for the identification of patients at high risk of switching[44].

Depressive mood, suicidality, psychomotor retardation, neurovegetative symptoms, and the psychotic features factors of the MOODS-SR resulted as non-specific predictors of longer time to remission when in monotherapy[44].

Benvenuti *et al*[45] assessed the quality of life and the functional impairment of those patients who reached remission in the above-mentioned sample. In a previous study Fagiolini *et al*[46] proved the usefulness of MOODS-SR in detecting depressive sub-threshold manifestations that cause functional impairment in a sample of patients with bipolar disorder in remission. Patients with unipolar depression showed a poorer quality of life associated with the MOODS-SR factors "depressive mood" and "psychotic features". Higher functional impairment was associated with the MOODS-SR factor "psychomotor retardation". These data confirmed the ability of the MOODS-SR in recognizing subtle signs and symptoms not detected by the usual rating scales (namely HAM-D), but which interfere with the subjective perception of quality of life and functioning.

These results confirmed the hypothesis that a better definition of clinical phenotypes should be a crucial factor in the decision-making process for more specific and effective treatment strategies for the so-called pure unipolar depression.

In a following study, the hypothesis that "retardation" could be at the same time an indicator of clinical severity of depression and a "validator" of a bipolar diathesis in unipolar patients was tested[47], in line with previous observations in this field[48-51].

Unipolar patients with higher scores on the lifetime psychomotor retardation factor of the MOODS-SR showed greater severity of depression and more bipolar indicators, namely: earlier age at onset, longer duration of illness, higher frequency of episodes, more lifetime suicide attempts and a positive family history of psychiatric disorders. These patients were also more likely to endorse sub-threshold bipolar features, as assessed by the MOODS-SR, such as "Mixed Irritability", "Mixed Instability" and "Creativity".

Starting from a neurobiological point of view, Rucci *et al*[52] analyzed the relationship between the polymorphisms of 5-HTTLPR genotype and the MOODS-SR manic-hypomanic component over the lifetime. The authors found that the association between the manic/hypomanic component of the MOODS-SR and the polymorphisms of the 5-HTTLPR was moderated by gender. Moreover, women with unipolar disorder and the "ss" genotype were characterized by a higher severity of depression[52].

The detection of subjects with the so-called "pure" Unipolar Depression who are at risk for a Bipolar Disorder: The Classification-Tree approach

An exploratory statistical approach based on a classification tree analysis was used with the aim to determine which combination of clinical, demographic, and psychopathological factors and corresponding cut-off scores could best discriminate patients with unipolar disorder from those with bipolar disorders. Data were extracted from a database of 1158 patients tested with the MOODS-SR in the United States and Italy between October 2001 and March 2008. Patients received a DSM-Ⅳ-TR diagnosis of unipolar or bipolar mood disorders as assessed with the SCID-I. The classification tree utilized 5 mania spectrum factors and 6 depression spectrum factors derived from the MOODS-SR in combination with demographic and clinical characteristics. The psychomotor activation factor, assessing the presence of thought acceleration, distractibility, hyperactivity and restlessness for 1 or more periods of at least 3 to 5 d in the lifetime, identified subgroups with an increasing likelihood of bipolar disorder diagnosis. Mixed instability and suicidality contributed to further sub-typing the sample into mutually exclusive groups, characterized by a different likelihood of a diagnosis of bipolar disorder. Only gender proved to be useful to improve the discrimination, among the overall set of demographic and clinical characteristics included in the analysis[53].

DISCUSSION

The MOODS-SR has demonstrated its usefulness in different fields. Patients with the so-called unipolar depression manifest hypomanic atypical and/or sub-threshold aspects that are detectable with the mood questionnaire. Spectrum features, as assessed with the MOODS-SR, might manifest in waves during the lifespan, presenting sometimes together, sometimes alone, sometimes reaching the severity for a full-blown disorder, sometimes interfering with other mental disorders or complicating the course of somatic diseases. Higher scores on the factors assessing psychomotor disturbances, mixed instability and suicidality delineate specific subtypes of patients characterized by a more severe form, a higher risk for psychotic symptoms, and a lower quality of life after remission.

Clinical observations have shown that psychomotor

activation and irritability characterized mixed depression in 33% to 47% of patients with mood disorders[54-56]. On the other hand, some of the DSM-5 mixed features are rarely present in mixed states[57]. As a whole, the new classification does not clarify the overlap between unipolar and bipolar depression[58]. The DSM-5 authors added a "mixed features" specifier in patients with manic, hypomanic and depressive episode, thus recognizing the importance of soft bipolar signs in depressive patients and the typical instability of these manifestations (symptoms have to be present "nearly" every day). This notwithstanding, DSM-5 considers as "mixed features" only those sub-threshold symptoms of depression and mania that do not overlap. This definition permits the inclusion of seven symptoms as representative of "mixed features". As a result, psychomotor agitation, irritability and distractibility have been excluded, leading to a clinical construct that does not fit the whole realm of clinical reality[57,59]. Our studies with the MOODS-SR performed on unipolar patients confirmed and highlighted the complexity of the mixed dimension. The whole realm of the manic/hypomanic manifestations could appear in patients with unipolar depression and their assessment during the entire lifetime is crucial for their definition.

As a whole, the experience with our instruments enforces past and recent claims towards the need for a dimensional approach to mood disorders[2,5,60,61].

Thus, data emerging from the mood spectrum approach suggest the existence of a continuum from "pure mania" to "pure depression", without a clear cut-off between the two realms, confirming the need for a probabilistic approach towards mood disorders[60,62].

Several observations already highlighted the need of a more refined assessment of the broader area of psychopathology surrounding the core features of mood disorders in a dimensional manner. For example, studies with the Multidimensional Assessment of Thymic States (MAThyS) focused on the processes of inhibition/activation in 5 different dimensions (emotional reactivity, cognition speed, psychomotor function, motivation and sensory perception)[63], while the TEMPS-A[64] assessed the classical Akiskal' s affective temperaments[65,66]. Conversely, the DSM-5 task force for mood disorders decided that the unipolar/bipolar dichotomy would better fit for a diagnostic manual, which major aim is to help clinicians and researchers in the diagnostic process. The authors of the DSM-5 undoubtedly made an effort towards the "dimensional" realm, enlarging the too strictly designed categories of the DSM-Ⅳ, adding a number of subcategories and several specifiers for each diagnosis. The implementation of mood disorders with the "other specified" and "unspecified" categories represents an attempt to give clinical significance to atypical and sub-threshold manifestations of mood disorders. The description of previously neglected features (such as hopelessness) among the diagnostic criteria of depression moves in the same direction. This effort towards a more refined description of mood dimensions enlarged the number of subcategories (now 14) through a complex combination of coded courses and severity specifiers mimicking a dimensional rating.

As far as we know, the MOODS-SR is the only instrument exploring the "core" criterion diagnostic symptoms and their associated features, as well as the wide range of symptoms surrounding the typical features of mania and depression, in a unitary format. Findings suggest that the mood spectrum approach is able to offer clinicians a more clinically meaningful assessment of psychopathology than the established measures of manic and depressive severity. We propose the SCI-MOODS as an advance in clinical and research methodology. Unfortunately, even if the change in DSM-5 pointed-out for a more subtle definition of mood disorders a wide area of mood spectrum psychopathology is still neglected. The dimensional revolution in DSM-5 did not happen. Recalling Zenone's paradox, we can continuously reduce the distance between subcategories but we will never create a continuum. As a consequence a wide realm of psychopathology is still unexplored, unrecognized and not yet coded. The mood spectrum approach could help in the assessment of these neglected features by filling the DSM-5 gaps of the categorical approach.

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COMMENTS

Background

The "Mood Spectrum" model is here used to refer to the broad range of manifestations of a DSM 5 disorder from "core" symptoms to the sub-threshold and/or atypical signs. Spectrum manifestations may be present during, between, or even in the absence of, an episode of full-blown disorder. The authors have developed a structured clinical interview and a self-report version to assess the mood spectrum (SCI-MOODS, MOODS-SR) and to evaluate the whole range of depressive and manic symptoms along a "continuum" (unipolar/bipolar) model. The proposed spectrum model is complementary to the categorical approach of Diagnostic and Statistical Manual of Mental Disorders 5.

Research frontiers

The spectrum approach, complementing the Diagnostic and Statistical Manual of Mental Disorders 5, should help the clinician and the researcher in the identification of specific subgroup of patients more likely to respond to specific treatment approaches. Moreover, the goal is to provide an instrument useful for genetic and neuro-imaging researches targeted to specific clinical phenotypes of mood disorders.

Innovations and breakthroughs

Data emerging from the mood spectrum approach suggest the existence of a continuum from "pure mania" to "pure depression", without a clear cut-off between the two realms, confirming the need for a probabilistic approach towards mood disorders.

Applications

To better understand the clinical variability within the same DSM 5 category of patients; To systematically assess the presence of lifetime manic/hypomanic

symptoms among patients diagnosed as "pure" unipolar according to the categorical approach; To improve patient-therapist communication, using a systematic definition of the clinical phenotype of each patient; To better delineate the outcome measures; To improve the sub-typing of patients for research and treatment purposes.

Terminology

Mood Spectrum assessment is based on DSM criterion symptoms as a starting point, and extends the categorical description to encompass a halo of surrounding clinical phenomena, namely: associated features described in the DSM, atypical symptoms, maladaptive behavioral traits and temperamental features that do not appear in the DSM.

Peer-review

This is a well-conducted review of studies and the table is useful and informative. The manuscript including abstract is well written and structured clearly.

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