Psychopathology of Mixed States

Sergio A. Barroilhet, MD, PhD[a,b,*], S. Nassir Ghaemi, MD, MPH[b,c]

KEYWORDS

• Mixed states • Psychopathology • Factor structure • Conceptual models
• Mixed depression • Mixed mania

KEY POINTS

- Mixed states are not only a mixture of depressive and manic symptoms, but reflect manic and depressive symptoms combined with the core feature of psychomotor activation.
- Psychomotor activation is the core feature of mixed states, independent of polarity.
- Dysphoria (irritability/hostility) is the next most important feature of mixed states.
- Kraepelin and Koukopoulos provide conceptual models that fit the empirical data regarding mixed states well and are useful clinically.

INTRODUCTION

Mixed states pose a problem for the concept of bipolar illness. The term, *bipolar*, implies that mood varies between 2 opposite poles, mania and depression. Mixed states have been seen as transitional, and uncommon, phases between depression and mania.[1,2] Kraepelin, who emphasized course of illness rather than polarity of mood states in the diagnosis of manic-depressive insanity (MDI), argued that most mood episodes were neither depressive nor manic, but both at the same time, ie, mixed.[3] He did not emphasize polarity (depression vs mania) because he considered pure polarity (pure mania or pure depression) as infrequent, whereas mixed states were common. Influenced by Kraepelin's opponents in the Wernicke-Kleist-Leonhard school, the *Diagnostic and Statistical Manual of*

[a] Clínica Psiquiátrica Universitaria, Facultad Medicina Universidad de Chile, Santiago, Chile; [b] Department of Psychiatry, Tufts University, School of Medicine, Tufts Medical Center, Pratt Building, 3rd Floor, 800 Washington Street, Box 1007, Boston, MA 02111, USA; [c] Department of Psychiatry, Harvard Medical School, Harvard University, Boston, MA, USA
* Corresponding author. Clínica Psiquiatrica Universitaria, Av. La Paz 1003, Recoleta, Santiago, Chile.
E-mail address: sbarroilhet@hcuch.cl

Psychiatr Clin N Am 43 (2020) 27–46
https://doi.org/10.1016/j.psc.2019.10.003 **psych.theclinics.com**

Mental Disorders (Third Edition) (*DSM-III*) changed the emphasis of diagnosis of MDI from course of illness to polarity and replaced the MDI diagnosis with 2 offshoots: bipolar disorder and the newly invented major depressive disorder (MDD). Mixed states were legislated out of existence, being defined as simultaneous full manic and depressive episodes, a rare occurrence. Common mixed state symptoms like irritability or agitation became nosologically irrelevant. After 4 decades, the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) *(DSM-5*) introduced a mixed features specifier to MDD but still denied any diagnostic validity to core mixed features of psychomotor agitation and dysphoria.[4,5]

Despite this anti-Kraepelinian *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) ideology, the research literature in the past few decades has contradicted the Leonhardian viewpoint, finding that coexistence of manic and depressive symptoms is the rule more than the exception.[6,7] Mood states with mixed symptoms may be the most common presentation of bipolar illness[8] and also common in unipolar depression.[9–11] These studies challenge the current *DSM* nosology and suggest a need for further attention to the psychopathology of mixed states.

A prominent approach to the psychopathology of mixed states is through 2 methods: factor analysis and cluster analysis. In factor analysis, clinical symptoms are analyzed into underlying components. In cluster analysis, clinical symptoms are combined to identify homogenous patient subgroups.[12] A complementary approach is based on systematic clinical observation, producing hypotheses to test with factor and cluster analytical methods.

This article summarizes factor and cluster analytical studies of the psychopathology of mixed states and relates those results to clinical models of mixed states.

METHODS

This article updates a prior review of factor and cluster analytical studies conducted by the 2013 International Society for Bipolar Disorders Task Force on mixed states (**Tables 1** and **2**).[13] Searches were done in PubMed from 1998 to 2019 using combinations of relevant terms, “mixed, “mania”, “hypomania” “subtype”, “factor structure”, “factor analysis”, and “cluster analysis”, to explore structural analysis and cluster classification studies that included patients with mania and mixed mania. Likewise, for patients with depression and mixed depression, several searches were done in PubMed from 1998 to 2019 using combinations of relevant terms, “mixed depression”, ‘“mixed depressive state”, “depressive mixed state”, “mixed depressive syndrome”, “subtype”, “factor structure”, “factor analysis”, and “cluster analysis.” Additional bibliographic cross-referencing was conducted. Data on frequency of symptomatic domains were added as complementary information when found.

RESULTS

The results of this review are presented in 2 parts. The first summarizes factor and cluster analysis studies of empirical data on the psychopathology of mixed states. The second summarizes proposed clinical/conceptual models of mixed states. This discussion attempts to integrate the empirical factor analysis literature with proposed clinical/conceptual models.

Table 1
Symptomatic structure of pure and mixed manic episodes

Study	Sample	Measures	Factor Structure	Notes
Cassidy et al,[30] 1998	204 manic 33 mixed *DSM-III-R*	Rating scale derived by authors	Dysphoric mood,[a,b] psychomotor acceleration, psychosis, increased hedonia, irritable-aggression	Time of assessment: 2–5 d of admission Measure included mania depression, and psychosis items (20 items) Medication: as appropriate during inpatient stay Results did not change when removing mixed patients
Dilsaver & Shoaib,[24] 1999	48 manic 57 mixed RDC and *DSM-III-R*	SADS	Depressive state, sleep disturbance, manic state, and irritability-paranoia	Time of assessment: "before starting treatment"
Akiskal et al,[22] 2001	104 manic *DSM-IV*	MVAS-BP	Expansiveness Activation Psychomotor acceleration Anxiety depression Social desinhibition Sleep Anger	Based on $\geq$2 concurrent depressive symptoms 64.5% had pure mania and 35.5 had depressive mixed mania
Kumar et al,[38] 2001	100 manic ICD-10-DCR	SMS	Mania (psychomotor acceleration) Psychosis Irritability-aggression	Outpatients Patients with mixed mania were excluded Substance abuse excluded
Perugi et al,[23] 2001	153 manic *DSM-III-R*	CPRS	Depressive Irritable-agitated Euphoric-grandiose Accelerated-sleepless Paranoid-anxious	Time of assessment: within 7 d of admission Medication: as appropriate during inpatient stay Substance abuse excluded
Rossi et al,[19] 2001	124 manic *DSM-III-R*	BRMaS BRMeS	Activation-euphoric Depression Psychomotor retardation Hostility-destructiveness sleep disturbance	Time of assessment: within 3 d of admission

(*continued on next page*)

Table 1
(*continued*)

Study	Sample	Measures	Factor Structure	Notes
Swann et al,[31] 2001	162 manic or mixed RDC and *DSM-III-R*	SADS ADRS	Impulsivity, anxious pessimism,[b] hyperactivity, distressed appearance, hostility, psychosis	Inpatients, screened during washout of medication; 50% were delusional
Sato et al,[25] 2002	518 manic 58 mixed *DSM-IV*	SADS (37 symptoms)	Depressive mood, irritable aggression, insomnia, depressive inhibition, pure mania, lability/agitation, psychosis	Time of assessment: 1–5 d of admission Medication: as appropriate during inpatient stay
González-Pinto et al,[26] 2003, and González-Pinto et al,[15] 2004	78 manic 25 mixed SCID-I	YMRS HAM-D-21	Depression,[b] dysphoria, hedonism, psychosis, activation	Time of assessment: first day after admission Medication: patients on medication when assessed Substance abuse excluded
Akiskal et al,[18] 2003	104 manic *DSM-IV*	MSRS HAM-D-17	Disinhibition Hostility Deficit (lack of self-care) Psychosis Elation Depression Sexuality	Inpatients Sample: Consecutive admissions without selection
Harvey et al,[14] 2008	363 manic 71 mixed SCID-I	HAM-D-21 MRS (SADS)	Manic: energy/activity, lack of insight, depression, racing thoughts, and reduced sleep Mixed: 5-factor solution differed to energy/activity, judgment, elation, depression/thinking, and reduced sleep	Inpatients Substance abuse excluded
Picardi et al,[37] 2008	88 manic *ICD-10*	BPRS	Mania Disorganization Positive symptoms Dysphoria	Time of assessment: within 3 d of admission Sample: subsample of acute manic hospitalized patients, from a national multicenter sample in Italy

Gupta et al,[20] 2009	225 manic ICD-10-DCR	SMS	Psychosis, irritability/aggression, dysphoria,[a] accelerated thought stream, hedonia, hyperactivity	Sample: excluded patients if they had received a diagnosis of mixed affective disorder
Hanwella and de Silva,[36] 2011	131 manic ICD-10	YMRS	Irritable mania, elated mania, psychotic mania	Time of assessment: within 24 h of admission. Inpatients
Swann et al,[16] 2013	1535 manic 644 mixed *DSM-IV*	MADRS YMRS	Depression, mania, sleep disturbance, judgment/impulsivity, irritability/hostility	Time of assessment: before randomization. Sample: patients pooled from 6 RCT with aripiprazole Medication: no meds or in washout Substance abuse excluded (<3 mo)
Perugi et al,[27] 2013	202 mixed *DSM-IV*	HAM-D-18 YMRS	Depression, agitation/irritability/aggression, psychosis Anxiety, sleep disorder, anxiety/language-thought disorder, motor retardation/somatic symptoms/guilt	Time of assessment: first week of admission Sample: resistant inpatient derived for trial of ECT; 70% psychosis Factor analysis: considered 9 non-redundant items of YMRS, and 12 items of HAM-D-18
Perugi et al,[28] 2014	202 mixed *DSM-IV*	BPRS	Psychotic-positive symptoms, mania, disorientation–unusual motor behavior, depression Negative symptoms and anxiety	Time of assessment: first week of admission Sample: resistant inpatient derived for trial of ECT; 70% psychosis
Filgueiras et al,[21] 2014	117 manic *DSM-IV*	SADS-C	Depression, suicide, insomnia, mania, psychosis, anxiety	Time of assessment: first week of admission
Güclü et al,[17] 2015	96 manic SCID-I	YMRS MADRS SAPS	Increased, psychomotor activity, dysphoria,[a] psychosis	Time of assessment: within 3 d of admission Sample: only males High prevalence of alcohol and marijuana use
Shah et al,[29] 2017	50 manic or mixed *ICD-10* RDC	YMRS BPRS	Pure mania, dysphoric mania,[a] hostile mania, delirious mania	Unmedicated

Abbreviations: ADRS, Affective Disorder Rating Scale; BPRS, Brief Psychiatric Rating Scale; BRMaS, Bech–Rafaelsen Mania Scale; BRMeS, Bech–Rafaelsen Melancholia Scale; CPRS, Comprehensive Psychopathological Rating Scale; *DSM-III-R*, *Diagnostic and Statistical Manual of Mental Disorders* (Third Edition Revised); ECT, Electro-convulsive Therapy; HAM-D-21, Hamilton Depression Rating Scale, 21 items; HAM-D-18, Hamilton Depression Rating Scale, 18 items; HAM-D-17, Hamilton Depression Rating Scale, 17 items; *ICD-10*, *International Classification of Diseases, Tenth Revision*; ICD-10-DCR, International Classification of Diseases, Tenth Revision, Diagnostic Criteria for Research; MADRS, Montgomery–Åsberg Depression Rating Scale; MRS, Mania Rating Scale; MSRS, Beigel-Murphy Manic-State Rating Scale; MVAS-BP, Multiple Visual Analogue Scales of Bipolarity; RDC, Research Diagnostic Criteria; SADS, Schedule for Affective Disorders and Schizophrenia; SADS-C, Schedule for Affective Disorders and Schizophrenia (Changed); SAPS, Scale for the Assessment of Positive Symptoms; SCID-I, Structured Clinical Interview for *DSM-IV* Axis I Disorders; SMS, Scale for Manic States; YMRS, Young Mania Rating Scale.

[a] Dysphoria used as a synonym of depressive.

[b] Biphasic distribution.

Table 2
Symptomatic structure of depressive and mixed depressive episodes

Study	Sample	Measures	Factor Structure	Notes
Benazzi & Akiskal,[48] 2005	348 BP II MDE 254 UP MDE SCID	HIG	Psychomotor activation Irritability–mental activation	Depressed outpatients Excluded patients with substance abuse, borderline personality, or significant medical illness Unmedicated
Biondi et al,[51] 2005	380 UP MDE 143 UP MDE *DSM-IV*	Author-derived scale MMPI-2	Depression Anxiety Activation	Depressed outpatients Measure assessed a broad range of behavior, beyond conventional mood symptoms Excluded: bipolar unmedicated
Sato et al,[52] 2005	863 UP MDE 25 BP II MDE 70 BP I MDE *ICD-10*	AMDP system	Typical vegetative symptoms Depressive retardation/loss of feeling, hypomanic syndrome, anxiety, psychosis, depressive mood/ hopelessness	Depressive inpatients Medicated before admission Measured 43 symptoms of the AMDP
Benazzi,[49] 2008	441 BP II MDE 289 UP MDE 275 remitted BP II SCID	SCID (modified) HIG	Irritable mental overactivity Elevated mood, motor overactivity	Depressed outpatients Excluded patients with SUS, BPD, or significant medical illness Unmedicated
Frye et al,[50] 2009	172 BP I or II MDE SCID	YMRS	Motor/verbal activation Thought content/insight Aggressiveness Appearance	Moderate severity of depression

Abbreviations: AMDP, Association for Methodology and Documentation in Psychiatry; BP II, Bipolar Disorder, type II; HIG, hypomanía interview guide; *ICD-10*, *International Classification of Diseases, Tenth Revision*; MDE, Major Depressive Episode; MMPI-2, Minnesota Multiphasic Personality Inventory; SCID, Structured Clinical Interview for *DSM-IV*; UP, Unipolar; YMRS, Young Mania Rating Scale.

Part I: Factor and Cluster Analysis Studies of the Empirical Psychopathology of Mixed States

Factor analysis studies: pure and mixed mania

All manic episodes, whether pure or mixed, shared a similar multidimensional structure according to factor analysis (see **Table 1**). The 3 main components were manic, depressive, and non–mood-related symptoms (ie, psychomotor activation, dysphoria, psychosis, and anxiety).

Depression Contrary to common belief, pure mania was associated with an underlying depressive factor in most studies,[14–31] mainly depressed mood, guilt, and suicidality.[13,32] Depressive symptoms can be found in 12.8% to 29% of pure manic patients[15,32] and may rise to 30% to 40%, depending on the methodology.[33] This may be due to a lack of specificity of *DSM* and *International Classification of Diseases* (*ICD*) diagnostic criteria,[30] which are insufficient to rule out mixed mania, and, because of the low frequency of pure forms, as Kraepelin predicted. Using the mixed features specifier in *DSM-5*, incidence of depressive symptoms in patients with mania/hypomania rises to 24% to 34%.[34,35]

Dysphoria A dysphoria (irritability/hostility) factor presented as a consistent independent factor across most studies,[16,18–20,22–27,29–31,36–38] although sometimes it covaried with other symptoms like lack of insight[14,23,25,26] or increased motor activity.[17,19,21,23,27] This factor often is more frequent in mixed than pure mania,[8] though not in all studies.[15] It includes irritability, subjective and overt anger, uncooperativeness, impatience, suspiciousness, hostility, and aggression, and is present in 22.7% to 72% of manic patients.[32,39]

Psychomotor activation This factor showed a variable pattern, sometimes covarying with manic elation symptoms (ie, euphoria, increased self-esteem, and grandiosity)[16,17,19,21,22,24,28,31,37] or dysphoria,[13,17,23,27,36] and sometimes presenting as an independent factor.[14,18,20,26,30,38] Common symptoms were racing thoughts, distractibility, pressured speech, intrusiveness and increased contacts with other people, hyperactivity, and increased goal-directed activities. Sometimes a separate factor was expressed in the opposite dimension, with retarded or inhibited thought and inhibited drive and motor activities,[19,25,27] all of which were independent of depressive mood,[25] pointing to an inhibited mania subtype, as described by Kraepelin.

Anxiety The anxiety component of mania includes inner tension, somatic symptoms, worry, indecisiveness, and panic symptoms. It correlates with severity of depressive symptoms and in most studies loads in the depressive factor.[15,16,20,24,25,31] In some studies with more severely ill patients, it is present as an individual factor,[21,27] while also overlapping with other factors of language/thoughts or motor/agitation.[27] Hence, anxiety may be a marker of severity of mixed states, with a strong correlation with depression scores in manic subjects.[40] Although many studies do not measure anxiety directly, it appears that anxiety is present in 17% to 32% of manic patients.[32]

Psychosis In most studies, psychosis presented as an independent factor of mania,[17–21,25–28,31,32,36–38] characterized by hallucinations, delusions, paranoia (hypervigilance and suspiciousness), lack of insight, impaired self-care, and bizarre or disorganized behavior. Psychotic symptoms can be found in up to 70% of severely ill manic patients[27] and can present with equal frequency in pure and mixed

mania,[25,32] being more common in the manic than in the depressive pole.[13,27] It has been conceptualized as a marker of severity in pure and mixed manic patients.[13,36,41]

In contrast to abnormal thought content, abnormalities of thought process had no consistent role in manic states. In some studies, thoughts process loaded mainly with psychomotor symptoms,[26,30] whereas in other studies, it loaded with affective components of mania (euphoria, increased self-esteem, and grandiosity)[25,36] or even as an independent factor.[14,20]

Sleep disturbance Sleep symptoms loaded independently from mania or depression factors,[14,16,19,21,22,24,25] perhaps because patients experience insomnia in different ways; for example, some patients with manic insomnia lack insight into their decreased need for sleep and do not see it as a problem, whereas other insomniac patients without decreased need for sleep experience it as a subjectively painful state.[21]

Subtypes of pure and mixed mania

A majority of cluster studies demonstrated 4 consistent clusters of manic subtypes: euphoric, dysphoric, depressive, and psychotic manic states. A fifth possible group is mixed hypomania.

Euphoric mania Euphoric mania entails elevated mood, increased self-esteem or grandiosity, and increased energy and activity,[16,24,31] with little or no irritability/hostility,[16] anxiety, or psychosis.[24,31] Sleep disturbance may be present or not.[16] The main characteristic is the relative (although not complete) absence of depressive symptoms.[16,24]

Dysphoric mania In this subtype, classical manic symptoms are present with lower scores in manic hyperactivity.[24,31] There are high levels of distress and hostility[31] and high scores for depressed state, anxiety, and irritability/paranoia, compared with pure manic patients,[16,24] and more treatment refusal compared with other mixed or pure manic patients.[23] A severely ill subgroup demonstrates high anxiety (panic attacks), higher hyperactivity, and psychotic symptoms,[27] resembling Kraepelin's depressive-anxious mania.

Depressive mania In this subtype, the clinical picture of depressive mania tends to meet *DSM-5* criteria for mixed states. There is high psychomotor activation, with variable degrees of irritability and paranoia.[16] Depression is characteristically prominent.[16,17,24,25] Patients are prone to have a negative evaluation of self, have self-reproach, feel discouragement, suffer from psychic and somatic anxiety,[31] and experience emotional lability/agitation, which may increase suicidality.[17,25,42] Some patients show psychomotor inhibition with retarded thoughts and inhibited drive, along with emotional lability/agitation,[25] resembling Kraepelin's "excited depression," where depressive-anxious mood and thought inhibition are combined with agitation and restlessness.[27]

Depressive mania and dysphoric mania are different.[31,42] The latter has milder depressive symptoms and the former has more suicidality. These differences can be linked to baseline temperaments, depressive and irritable, respectively.[42] Some investigators see dysphoric mania as an intermediate state in a continuum between pure euphoric mania and depressive mania.[24] Bimodal distribution of the depressive factor in some studies support this view.[16,26,30,31]

Psychotic mania In this subtype, there is psychomotor activation along with psychotic features, ranging from impairment of judgment and insight[16] to overt delusions.[31]

Besides manic symptoms, such patients present little or no irritability/hostility (except in patients with substance abuse[17]) or depressive symptoms.[16,25,30,31] There is low frequency of rapid cycling[23,31,43] but more chronic residual manic and psychotic symptoms.[27]

Mixed hypomania The clinical picture of mixed hypomania has been little studied, with no factor analysis studies to date. The most frequent symptom is irritability, with or without depressive symptoms, the latter being more frequent among women.[44,45] Crowded thoughts may be more frequent compared with pure mania or depression.[46] Psychotic symptoms are not common. *DSM-5*–defined MDD with mixed features captures a clinical picture that is equivalent to mixed hypomania, not mixed depression.[4]

Factor analysis studies: pure and mixed depression

Manic symptoms are frequent in depressive episodes, whether unipolar or bipolar (see **Table 2**). Concurrent manic symptoms are present in 38.1% to 47% of cases of unipolar depression[9,10] and in 68.8% of cases of bipolar depression.[6] The specific manic symptoms that occur during depressive episodes are similar in both unipolar and bipolar depression, especially psychomotor agitation and racing/crowded thoughts.[4,6] Pure depression versus mixed depression is best distinguished by manic symptoms of irritability, language/thought disorder, rate and amount of speech, and increased psychomotor activity/energy.[47]

Table 2 summarizes factor analysis studies on this topic. A limiting factor was that no studies used both depressive and manic symptom scales in current depressive episodes. In general, psychomotor activation and dysphoria appear as the main underlying factors, explaining a major part of the variance.[48–50]

Psychomotor activation

Psychomotor activation was the strongest and most consistent factor present in mixed depression, whether unipolar or bipolar. In unipolar depression, it was present in 20% to 27% of cases and loaded on a factor characterized by motor overactivation[51] and agitation,[48,49] along with talkativeness,[48,49] acceleration of ideas, impulsiveness, and unstable mood.[51] It covaried with irritability and aggressiveness (dysphoria). In bipolar depression, the activation factor had the same symptomatic profile but with higher amount of increased energy and overactivation of thought process (racing thoughts and flight of ideas).[50] This factor included standard *DSM* manic symptoms except euphoria, increased self-esteem, or grandiosity.[48,49,52] Baseline psychomotor activation (racing thoughts, talkativeness, and increased activities) was related to antidepressant-induced mania.[50] As seen in factor analysis studies of mania and mixed mania, however, a separate factor expressed the opposite extreme of the dimension, with retarded and inhibited thinking, loss of emotion, perplexity, inhibited drive, social withdrawal, and objective retardation.[52]

Dysphoria Dysphoria also was present consistently in mixed depression, both unipolar and bipolar, with 40% to 73.3% prevalence[6,39] (vs 15%–17.5% in pure depression[39,53,54]). It is characterized by irritability[48,49] and increased risky activities.[48] Associated features that covaried with it were racing/crowded thoughts, distractibility, and psychomotor activation.[48,49] In unipolar depression, a composite factor included intolerance toward social rules, impulsiveness, sensitivity, and aggressiveness, but overtly disruptive aggressive behavior loaded in this factor only in bipolar depression.[50] Standard manic and psychotic symptoms were covariates of the dysphoria factor in unipolar depression.[51]

Psychosis Psychotic symptoms were present in up to 30.0% of subjects with unipolar and bipolar mixed depression,[9] including paranoia (vigilance, sensitivity, litigiousness, distrust, and suspicion), along with delusions of poverty, guilt, reference, and hypochondria[52] as well as lack of insight.[50] Psychosis covaried with psychomotor activation.[51]

Anxiety In unipolar mixed depression, the anxiety factor comprised apprehension, fear, preoccupation, and somatization,[51] along with somatic inner restlessness, complaints, somatic anxiety, and panic attacks.[52] Anxiety scores correlated strongly with manic scores.[40]

Phenomenology of depressive features in mixed depression The experience of the core depressive state in mixed depression was similar in both unipolar and bipolar types. It included sadness, demoralization, apathy, hopelessness, feeling of inadequacy, and suicidal ideation.[51,52] There also was a somatic factor comprising initial insomnia, interrupted sleep, shortened sleep, early waking, decreased appetite, tiredness, loss of vitality, and decreased sexual interest.[52] The latter study also identified a factor that included psychomotor inhibition with motor retardation, inhibited affectivity and drive, retarded thinking, and social withdrawal.[52]

Subtypes of pure and mixed depression

Available studies suggest 2 main clusters of depressive subtypes: an activated/hyperreactive cluster and a retarded/hyporeactive cluster.

Activated/hyperreactive mixed depression This subtype is characterized by psychomotor agitation, irritability, emotional lability, distractibility, and mood reactivity.[55] In bipolar depression, there is increased psychomotor activation with many plans and activities[56]; increased speech,[57] racing thoughts, and distractibility[56]; suicidal ideation; and psychotic symptoms.[57] This subtype of depression presents with emotional hyperreactivity, marked emotional lability,[56] somatic symptoms like appetite disturbance,[57] and enhanced sensory perception.[56] Psychomotor activation can lead to agitation[57] and suicide attempts.[56] A characteristic of this subtype is higher intensity and frequency of emotions like irritability, anger, panic, anxiety, and exaltation,[56,57] which previously have been labeled in the psychiatric literature with other terms, such as agitated depression or irritable-hostile depression.

Retarded/hyporeactive pure depression This other main subtype of depression, is characterized centrally by psychomotor retardation.[55] In bipolar depression, it is characterized by reduced energy[56,57] and more inhibition in thoughts process and motor activities[56] and loss of motivation,[56,57] diminished interests, reduced social engagement,[57] indecision,[56] and impaired concentration and memory.[57] In the affective domain, this subtype is characterized by anhedonia along with feelings of worthlessness, helplessness and hopelessness, depressed mood, anxiety, and guilt,[57] with notable affective flattening,[56,57] emotional hyporeactivity, sensorial numbness,[56] and sleep disturbances.[57] This clinical picture resembles classic melancholic depression.[58]

Threshold for diagnosis of mixed states

In contrast to *DSM-III* through *DSM-5*, there is no scientific rationale at all for the *DSM* requirement of 3 or 4 manic symptoms as the threshold for mixed episodes or mixed modifier definitions. Instead, the reviewed literature consistently and strongly supports a cutoff of 2 or 3 symptoms of the opposite polarity during a depressive or manic/hypomanic episode.[9,10,15,32] This threshold correlates with

diagnostic validators of differing course of illness, prognosis, comorbidities, and treatment response.

Part II: Clinical/Conceptual Models of Mixed States

Kraepelin/Weygandt model

Kraepelin acknowledged that mixed states were propelled by a mechanism similar to hyperarousal and emphasized the importance of course, distinguishing a transitional and an autonomous form. Following Weygandt, Kraepelin held that mixed states resulted from the combination of 3 independent domains—mood, thought, and volition—on an excitation-inhibition continuum. Different combinations of these domains constituted different subtypes of MDI. Accordingly, he described 8 mood states, 2 pure (pure mania and pure depression) and 6 mixed: depression with flight of ideas, exited or agitated depression, depressive/anxious mania, inhibited mania, mania with poverty of thoughts, and manic stupor.[59]

The most prevalent mixed states were depressive/anxious mania, excited or agitated depression, and depression with flight of ideas.[13] The first subtype was characterized by increased thought production and speed manifested externally in logorrhea and pressured speech, along with restlessness, high anxiety, and increased activities. Psychomotor excitation was prominent, and delusions of guilt, persecution and hypochondriac delusions were common. The second subtype was similar to the latter but with inhibition of thought. The third subtype consisted of depressive mood and inhibition of motor activity, including speech, but with abnormal thought processes. Patients could even become mute and rigid.[60]

Malhi and colleagues[12] proposed a revised formulation of the Kraepelin/Weygandt model, the activity-cognition-emotion (ACE) model. These 3 dimensions interact with each other. One can be primary but combine with other dimensions for secondary symptoms. Mixed states result from overactivation of one dimension along with inhibition of another. Dimensions can shift in occurrence and severity over time, accounting for myriad mixed state presentations.

Mentzos/Berner model

The Greek-German psychiatrist Stavros Mentzos defined mood states on 2 domains: *boost* (the underlying force behind the psychic process) and *mood* (the predominant affective tone that colored thoughts and conscienceless).[5,61] Pure forms would result from concordant boost and mood, whereas mixed states resulted from contradictory or quickly changing boost and mood.[5,59] Based on this structure, Berner explained mixed states as the "persistent presence of a drive state contradictory to the mood state and/or the emotional resonance."[62] Mixed states were classified in stable and unstable (ie, rapid cycling) forms and included diurnal variations and sleep disturbances as key aspects.[63] This group proposed a dysphoric dimension (morose, tense, and irritated mood) as a third field in mood disorders, distinguishable from mixed states[64] that also may mix with depression and mania.[65] Other investigators have proposed that the dysphoric syndrome (inner tension, irritability, aggressive behavior, and hostility) is the core marker of mixed states.[39]

Akiskal model

Akiskal proposed that mixed states were the result of interaction of a mood episode with a temperament in the opposite polarity, such as a depressive episode in a person with hyperthymic or cyclothymic temperament.[66,67] Likewise, pure depressive episodes occur when an episode aligns with temperamental predisposition (such as, euphoric mania in a person with hyperthymic temperament) or occurs in someone with no affective temperament at all (a depressive episode in a person with a

normal personality).[23,42,62] Empirical data to support this view include evidence that affective temperaments are more frequent in mixed than pure depressive or manic episodes.[68]

Koukopoulos model

Koukopoulos advocated for the Kraepelin and Akiskal models but saw depression as the effect of manic states, not an independent phenomenon. He followed Griesenger in the view that excitatory brain processes (producing mania) are the cause of inhibitory brain processes (producing depression).[69] The "primacy of mania"[70] hypothesis put forward by Koukopoulos holds that depressive symptoms in mixed states are caused by manic processes.[71] Furthermore, even pure depressive episodes are caused by prior manic episodes or symptoms (such as manic temperaments). His metaphor for this theory was that "mania is the fire, depression is the ash."

This theory explains why mixed states occur, not as an accident or coincidence but because they are the outcome of depressive symptoms fueled by mania. Therefore, because mania causes depression, it is mania that has to be prevented or treated directly, not depression.[71]

Clinically, Koukopoulos sees mixed depression as the presence of a depressive episode with psychomotor excitation, manifested as psychomotor agitation and/or marked rage. *DSM* manic symptoms may or may not be present.[4] As noted, his view is consistent with Akiskal's emphasis on affective temperaments, specifically those with manic features, that is, cyclothymic, hyperthymic, and irritable temperaments.

The following quotation from Koukopoulos and colleagues brings out his meaning: "When a sad or stressful event provokes a depressive reaction, or a seasonal or endogenous depression occurs in such a person, the psychic reaction is intense and exacerbates the depression itself. In turn, the emotional reaction heightens and unleashes this energy, which produces manic symptoms, such as restlessness and racing thoughts, while it also triggers anxiety and aggravates the depressive psychic pain. This tight interweaving of manic traits and depressive states of agitated depression makes it an authentic mixed state."[60]

DISCUSSION

A summary of the factor/cluster analytical studies reviewed is as follows: Besides mood-related factors of depression and mania, the core additional features of the mixed state are psychomotor activation and secondarily, in some subtypes, dysphoria. Those central features are more pronounced in mixed mania than in mixed depression but are present nonetheless in both mood states. These central features of mixed states are independent of illness polarity (ie, are similar in both unipolar and bipolar illness). Anxiety and psychosis reflect severity of the mixed state in both mania and depression and are not core features. Psychomotor inhibition, although sometimes present in some mixed states (ie, depressive mania) mainly is present in pure depression.

In classification studies, 4 main subtypes of manic states—euphoric, dysphoric, depressive, and psychotic—and 2 main subtypes of depressive states—activated/hyperreactive mixed depression and retarded/hyporeactive pure depression—were identified (**Fig. 1**).

Clinical/conceptual models acknowledge the multidimensionality of mood disorders and the myriad of possible presentations. Weygandt and Kraepelin saw mixed states as a combination of contradictory forces from 3 dimensions: mood, thought, and volition (recently reformulated in the ACE model as affect, emotion, and

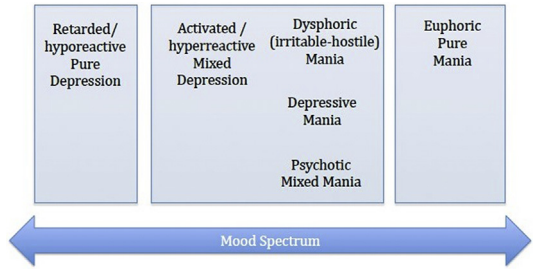

Fig. 1. Subtypes of mood states supported by cluster analysis studies. Note: the 6 subtypes of mood states supported by cluster analysis studies are individualized, and myriad intermediate forms may have not yet been captured given the lack of psychopathologic nuance of current instruments and limitations of studies.

cognition). Metzos and Berner underscored that an underlying alteration (drive or boost) at a physiologic level, contradictory to mood or emotional resonance, was the basis of mixed states. Akiskal held that mixed states were the result of mood episodes interacting with affective temperaments of the opposite pole. Koukopoulos highlighted the importance psychomotor excitation (with clinical presentation as rage and lability) as the crucial process causing subsequent depressive symptoms.

Importance of Psychomotor Activation

Frequently, psychomotor overactivation is interpreted in terms of *agitation* or *excitation*. Agitation to many clinicians implies observable physical activity, although it need not do so, because the concept of *psychic agitation*, without motor changes, also has existed for many years. Another term that is used confusedly is *psychomotor*. This term means either psychological or motor changes, not both psychological and motor changes. In other words, motor abnormalities are not necessary for the presence of psychomotor disturbance.

One approach to clarifying any confusion in terms is to prefer the term, *activation*, as Scott and colleagues[72] have proposed: as "a multilevel construct emerging from underlying physiologic change… measurable in objectively observed behavior (motor activity) and the related subjective experience of the overt behavior (energy)." Activation also broadly comprehends other less observable phenomena like fine motor movements, reaction times, and speech articulation and production[73] and is tightly related to thought production and flow[46,74] and to feelings, emotions, and volitions.[75,76] An apt metaphor may be voltage, the push that causes the charge to move in a functional system.

Correlation of Empirical Factor/Cluster Analytical Studies with Clinical/Conceptual Models

The empirical results, described previously, with emphasis on core features of psychomotor activation and dysphoria, are consistent with the clinical/conceptual models provided.

The Kraepelin/Weygandt model is consistent with the notion that psychomotor activation would drive affectivity (intensity, reactivity, and stability), thoughts or cognitions (speed, shifts, and quantity), and volition (impulsivity, intensity, and endurance or shifts of behavior). For each symptom domain, this psychomotor activation may

demonstrate in over-activation or over-deactivation (inhibition), presenting as mixed states when activation in some domains coincide with deactivation in other domains.

The Metzos/Berner model is consistent with the idea that a physiologic psychomotor activation is the underlying boost or voltage that creates a mixed state. The Akiskal model provides a rationale for propensity for psychomotor activation as being related to manic affective temperaments, although there is some evidence opposed to this view because sometimes mixed states appear to happen without affective temperaments.

The Koukopoulos model, like Metzos/Berner, views psychomotor excitation as primary and causative not only of mixed states but also depressive states. The Koukopoulos model not only fits the empirical factor analytical data but also is the only model that provides a conceptual rationale for those data, namely that manic states and depressive states go together, because the former cause the latter. This "primacy of mania" claim can be rephrased as the "primacy of psychomotor overactivation" if the core of mania is defined as psychomotor overactivation, as is shown to be the case in the factor analytical studies. This concept, that the central feature of mania is psychomotor overactivation and that the central feature of depression is psychomotor inhibition, also has been a central idea of classical European psychopathology, dating to Pinel and Kraepelin in the eighteenth and nineteenth centuries and forward to Binswanger, Jaspers, Schneider, and Kuhn in the twentieth century.[73,77] The concept of melancholia specifically was characterized by psychomotor inhibition as its central feature in this classical literature.[58] The Koukopoulos model is consistent with all the other models described as well, because underlying biology (Metzos/Berner) and/or temperament may predispose to manic symptoms (Akiskal). Of the 3 Kraepelinian domains, the Koukopoulos model emphasizes volition as primary (elevated activity).

In sum, all the models fit these empirical data somewhat, but the Kraepelin/Weygandt and Koukopoulos models seem to fit those data best, and integrate that evidence well into clinical experience and the traditional psychopathology literature.

Differential Diagnosis with Borderline Personality and Neurotic Depression

It often is stated that mixed states resemble borderline personality, due to mood instability. It also is important to distinguish mixed depression from other kinds of depression that are unrelated to manic-depressive illness. The most important depressive presentation that was not seen as part of manic-depressive illness used to be called *neurotic depression*. This concept has been legislated away by *DSM-III* and folded into the *DSM* concept of major depressive disorder.[78] **Table 3** provides some distinguishing features between mixed states of bipolar and unipolar depression, versus neurotic depression and borderline personality.[60,79]

The key clinical distinction is that psychomotor activation is primary and central to mixed states of MDI but absent in neurotic depression and more variable in borderline personality (sometimes present, sometimes not, and typically secondary to life events, unlike mixed states, where it can be spontaneous). Furthermore, there are other diagnostic differences of importance in genetics, course, and prognosis between MDI, neurotic depression and borderline personality, which must be taken into account, as described in **Table 3**.

Clinical Consequences

This review suggests some important clinical consequences. First, mixed states are not the result of opposing symptoms of only depression and mania but rather a

Table 3
Differential diagnosis of mixed states versus borderline personality/neurotic depression

Anxious Syndrome	Neurotic Depression	Mixed States
Psychomotor activation	• Secondary to life stressors and less present at baseline	• Primary, present at baseline, and not only with life stressors
Thought content and process	• Depressive, obsessive, or anxious ruminations with worry-based content • Analytical pattern of thinking that is constantly present or repetitive	• Racing thoughts, flight of ideas, and, more specifically, crowded thoughts
Arousal and tension	• Very emotionally reactive to painful life experiences • Feelings of apprehension, fearfulness, or impending doom • Feelings of worthlessness, pessimism	• Inner tension, restlessness • Overwhelming despair and sense of lack of power to do things
Genetics and course	• Absent manic-depressive genetics and chronic course • Extremely reactive to life events and stressors	• Strong manic-depressive genetics and episodic course • Sometimes reactive to life events and stressors but sometimes spontaneous
Dysphoric Syndrome	**Borderline Personality**	**Mixed States**
Hyperarousal	• Secondary to emotional tension • Hyper-reactivity triggered by interpersonal stressors	• Primary: somatic tension • Hyper-reactivity triggered from the somatic realm: very sensitive to noise, light, touch
Hostility	• Anger combined with fear • Experience of fragility • Attention oriented to the environment • Behavior oriented to receiving attention and help	• Rage combined with despair; no fear • Attention oriented inward, not to the external environment • Behavior oriented to end visceral discomfort and extreme tension
Suicidality	• Secondary: very reactive to interpersonal triggers • Parasuicidal behavior, with self-cutting and other self-harm • High frequency of low-lethality attempts	• Primary: less reactive to interpersonal triggers • Little to no parasuicidal behavior • High risk of impulsive suicidality with high-lethality attempts
Genetics and course	• Absent manic-depressive genetics and chronic course • Extremely reactive to life events and stressors	• Strong manic-depressive genetics and episodic course • Sometimes reactive to life events and stressors but sometimes spontaneous

combination of psychomotor activation and dysphoria with standard depressive or manic symptoms. Second, the *DSM*-based unipolar-bipolar ideology is questionable because mixed states are so frequent, and thus polarity is not a good basis for diagnosis.[80] Other depressive presentations, like neurotic depression and borderline

personality, can be distinguished from mixed states based on the role of psychomotor activation as well as other clinical features (like genetics and course of illness). Third, mixed states involving dimensional domains of affect, thought, and volition argue against *DSM*-based overly categorical approaches to diagnosis. Fourth, this review puts into doubt the conventional psychopharmacological treatment of mood conditions, with antidepressants for unipolar depression and mood stabilizers and antipsychotics for bipolar illness. Instead, because mixed states occur in both unipolar and bipolar illnesses, their treatments may be similar, with less emphasis on traditional antidepressants and more emphasis on treating psychomotor disturbance with lithium, some anticonvulsants, and dopamine-blocking agents.

DISCLOSURE

S.A. Barroilhet has no disclosures to report and no commercial or financial conflicts of interest. S.N. Ghaemi is currently employed at Novartis Institutes for Biomedical Research in Cambridge, Massachusetts.

REFERENCES

1. Schneider K, Sánchez-Pascual A. Psicopatología Clínica. Madrid: Fundación Archivos de Neurobiología; 1997.
2. Goodwin FK, Jamison KR. Manic-depressive illness: bipolar disorders and recurrent depression, vol. 1. New York: Oxford University Press; 2007.
3. Angst J, Marneros A. Bipolarity from ancient to modern times: conception, birth and rebirth. J Affect Disord 2001;67(1–3):3–19.
4. Koukopoulos A, Sani G. DSM-5 criteria for depression with mixed features: a farewell to mixed depression. Acta Psychiatr Scand 2014;129(1):4–16.
5. Tortorella A, Albert U, Nivoli AMA, et al. Mixed states: still a modern psychopathological syndrome? J Psychopathol 2015;21(4):332–40.
6. Goldberg JF, Perlis RH, Bowden CL, et al. Manic symptoms during depressive episodes in 1,380 patients with bipolar disorder: findings from the STEP-BD. Am J Psychiatry 2009;166(2):173–81.
7. Grunze H, Vieta E, Goodwin GM, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: acute and long-term treatment of mixed states in bipolar disorder. World J Biol Psychiatry 2018;19(1):2–58.
8. Solé E, Garriga M, Valentí M, et al. Mixed features in bipolar disorder. CNS Spectr 2017;22(2):134–40.
9. Perlis RH, Uher R, Ostacher M, et al. Association between bipolar spectrum features and treatment outcomes in outpatients with major depressive disorder. Arch Gen Psychiatry 2011;68(4):351–60.
10. Angst J, Azorin JM, Bowden CL, et al. Prevalence and characteristics of undiagnosed bipolar disorders in patients with a major depressive episode: the BRIDGE study. Arch Gen Psychiatry 2011;68(8):791–8.
11. Nusslock R, Frank E. Subthreshold bipolarity: diagnostic issues and challenges. Bipolar Disord 2011;13(7–8):587–603.
12. Malhi GS, Irwin L, Hamilton A, et al. Modelling mood disorders: an ACE solution? Bipolar Disord 2018;20(S2):4–16.
13. Swann AC, Lafer B, Perugi G, et al. Bipolar mixed states: an international society for bipolar disorders task force report of symptom structure, course of illness, and diagnosis. Am J Psychiatry 2013;170(1):31–42.

14. Harvey PD, Endicott JM, Loebel AD. The factor structure of clinical symptoms in mixed and manic episodes prior to and after antipsychotic treatment. Bipolar Disord 2008;10(8):900–6.
15. González-Pinto A, Aldama A, Pinto AG, et al. Dimensions of mania: differences between mixed and pure episodes. Eur Psychiatry 2004;19(5):307–10.
16. Swann AC, Suppes T, Ostacher MJ, et al. Multivariate analysis of bipolar mania: retrospectively assessed structure of bipolar I manic and mixed episodes in randomized clinical trial participants. J Affect Disord 2013;144(1–2):59–64.
17. Güclü O, Şenormancı Ö, Aydın E, et al. Phenomenological subtypes of mania and their relationships with substance use disorders. J Affect Disord 2015;174:569–73.
18. Akiskal HS, Azorin JM, Hantouche EG. Proposed multidimensional structure of mania: beyond the euphoric-dysphoric dichotomy. J Affect Disord 2003;73(1–2):7–18.
19. Rossi A, Daneluzzo E, Arduini L, et al. A factor analysis of signs and symptoms of the manic episode with Bech–Rafaelsen Mania and Melancholia Scales. J Affect Disord 2001;64(2–3):267–70.
20. Gupta SC, Sinha VK, Praharaj SK, et al. Factor structure of manic symptoms. Aust N Z J Psychiatry 2009;43(12):1141–6.
21. Filgueiras A, Nunes ALS, Silveira LAS, et al. Latent structure of the symptomatology of hospitalized patients with bipolar mania. Eur Psychiatry 2014;29(7):431–6.
22. Akiskal HS, Hantouche EG, Bourgeois ML, et al. Toward a refined phenomenology of mania: combining clinician-assessment and self-report in the French EPIMAN study. J Affect Disord 2001;67(1):89–96.
23. Perugi G, Maremmani I, Toni C, et al. The contrasting influence of depressive and hyperthymic temperaments on psychometrically derived manic subtypes. Psychiatry Res 2001;101(3):249–58.
24. Dilsaver SC, Shoaib AM. Phenomenology of mania: evidence for distinct depressed, dysphoric, and euphoric presentations. Am J Psychiatry 1999;156(3):426–30.
25. Sato T, Bottlender R, Kleindienst N, et al. Syndromes and phenomenological subtypes underlying acute mania: a factor analytic study of 576 manic patients. Am J Psychiatry 2002;159(6):968–74.
26. González-Pinto A, Ballesteros J, Aldama A, et al. Principal components of mania. J Affect Disord 2003;76(1):95–102.
27. Perugi G, Medda P, Reis J, et al. Clinical subtypes of severe bipolar mixed states. J Affect Disord 2013;151(3):1076–82.
28. Perugi G, Medda P, Swann AC, et al. Phenomenological subtypes of severe bipolar mixed states: a factor analytic study. Compr Psychiatry 2014;55(4):799–806.
29. Shah S, Aich TK, Subedi S. A factor analytical study report on mania from Nepal. Indian J Psychiatry 2017;59(2):196–201.
30. Cassidy F, Forest K, Murry E, et al. A factor analysis of the signs and symptoms of mania. Arch Gen Psychiatry 1998;55(1):27–32.
31. Swann AC, Janicak PL, Calabrese JR, et al. Structure of mania: depressive, irritable, and psychotic clusters with different retrospectively-assessed course patterns of illness in randomized clinical trial participants. J Affect Disord 2001;67(1–3):123–32.
32. Cassidy F, Murry E, Forest K, et al. Signs and symptoms of mania in pure and mixed episodes. J Affect Disord 1998;50(2):187–201.

33. Suppes T, Eberhard J, Lemming O, et al. Anxiety, irritability, and agitation as indicators of bipolar mania with depressive symptoms: a post hoc analysis of two clinical trials. Int J Bipolar Disord 2017;5(1):36.
34. Shim IH, Woo YS, Bahk W-M. Prevalence rates and clinical implications of bipolar disorder "with mixed features" as defined by DSM-5. J Affect Disord 2015;173:120–5.
35. McIntyre RS, Tohen M, Berk M, et al. DSM-5 mixed specifier for manic episodes: evaluating the effect of depressive features on severity and treatment outcome using asenapine clinical trial data. J Affect Disord 2013;150(2):378–83.
36. Hanwella R, de Silva VA. Signs and symptoms of acute mania: a factor analysis. BMC Psychiatry 2011;11(1):137.
37. Picardi A, Battisti F, de Girolamo G, et al. Symptom structure of acute mania: a factor study of the 24-item Brief Psychiatric Rating Scale in a national sample of patients hospitalized for a manic episode. J Affect Disord 2008;108(1):183–9.
38. Kumar R, Sinha BNP, Chakrabarti N, et al. Phenomenology of Mania - A factor analysis approach. Indian J Psychiatry 2001;43(1):46–51.
39. Bertschy G, Gervasoni N, Favre S, et al. Frequency of dysphoria and mixed states. Psychopathology 2008;41(3):187–93.
40. Swann AC, Steinberg JL, Lijffijt M, et al. Continuum of depressive and manic mixed states in patients with bipolar disorder: quantitative measurement and clinical features. World Psychiatry 2009;8(3):166–72.
41. Canuso CM, Bossie CA, Zhu Y, et al. Psychotic symptoms in patients with bipolar mania. J Affect Disord 2008;111(2–3):164–9.
42. Akiskal HS, Hantouche EG, Bourgeois ML, et al. Gender, temperament, and the clinical picture in dysphoric mixed mania: findings from a French national study (EPIMAN). J Affect Disord 1998;50(2–3):175–86.
43. Haro JM, van Os J, Vieta E, et al. Evidence for three distinct classes of 'typical', 'psychotic' and 'dual' mania: results from the EMBLEM study. Acta Psychiatr Scand 2006;113(2):112–20.
44. Benazzi F. Delineation of the clinical picture of Dysphoric/Mixed Hypomania. Prog Neuropsychopharmacol Biol Psychiatry 2007;31(4):944–51.
45. Suppes T, Mintz J, McElroy SL, et al. Mixed hypomania in 908 patients with bipolar disorder evaluated prospectively in the Stanley Foundation Bipolar Treatment Network: a sex-specific phenomenon. Arch Gen Psychiatry 2005;62(10):1089–96.
46. Weiner L, Ossola P, Causin J-B, et al. Racing thoughts revisited: a key dimension of activation in bipolar disorder. J Affect Disord 2019;255:69–76.
47. Miller S, Suppes T, Mintz J, et al. Mixed depression in bipolar disorder: prevalence rate and clinical correlates during naturalistic follow-up in the stanley bipolar network. Am J Psychiatry 2016;173(10):1015–23.
48. Benazzi F, Akiskal H. Irritable-hostile depression: further validation as a bipolar depressive mixed state. J Affect Disord 2005;84(2):197–207.
49. Benazzi F. A tetrachoric factor analysis validation of mixed depression. Prog Neuropsychopharmacol Biol Psychiatry 2008;32(1):186–92.
50. Frye MA, Helleman G, McElroy SL, et al. Correlates of treatment-emergent mania associated with antidepressant treatment in bipolar depression. Am J Psychiatry 2009;166(2):164–72.
51. Biondi M, Picardi A, Pasquini M, et al. Dimensional psychopathology of depression: detection of an 'activation' dimension in unipolar depressed outpatients. J Affect Disord 2005;84(2):133–9.

52. Sato T, Bottlender R, Kleindienst N, et al. Irritable psychomotor elation in depressed inpatients: a factor validation of mixed depression. J Affect Disord 2005;84(2–3):187–96.
53. Sato T, Bottlender R, Schröter A, et al. Frequency of manic symptoms during a depressive episode and unipolar 'depressive mixed state' as bipolar spectrum. Acta Psychiatr Scand 2003;107(4):268–74.
54. Maj M, Pirozzi R, Magliano L, et al. Agitated "unipolar" major depression: prevalence, phenomenology, and outcome. J Clin Psychiatry 2006;67(5):712–9.
55. Brancati GE, Vieta E, Azorin J-M, et al. The role of overlapping excitatory symptoms in major depression: are they relevant for the diagnosis of mixed state? J Psychiatr Res 2019;115:151–7.
56. Henry C, M'Baïlara K, Poinsot R, et al. Evidence for two types of bipolar depression using a dimensional approach. Psychother Psychosom 2007;76(6):325–31.
57. Chang JS, Ahn YM, Yu HY, et al. Exploring clinical characteristics of bipolar depression: internal structure of the bipolar depression rating scale. Aust N Z J Psychiatry 2009;43(9):830–7.
58. Parker G. Defining melancholia: the primacy of psychomotor disturbance. Acta Psychiatr Scand Suppl 2007;(433):21–30.
59. Marneros A. Origin and development of concepts of bipolar mixed states. J Affect Disord 2001;67(1):229–40.
60. Koukopoulos A, Sani G, Albert MJ, et al. Agitated depression: spontaneous and induced. In: Marneros A, Goodwin F, editors. Bipolar disorders: mixed states, rapid-cycling, and atypical forms. 1st edition. New York: Cambridge University Press; 2005. p. 157–86.
61. Maina G, Bertetto N, Boccolini FD, et al. The concept of mixed state in bipolar disorder: from Kraepelin to DSM-5. J Psychopathol 2013;19:287–95.
62. Perugi G, Akiskal HS. Emerging concepts of mixed states: a longitudinal perspective. In: Marneros A, Goodwin FK, editors. Bipolar disorders: mixed states, rapid-cycling, and atypical forms. 1st edition. New York: Cambridge University Press; 2005. p. 45–60.
63. Berner P, Gabriel E, Katschnig H, et al. Diagnostic criteria for schizophrenic and affective psychoses. Washington: World Psychiatric Press; 1983.
64. Berner P, Musalek M, Walter H. Psychopathological concepts of dysphoria. Psychopathology 1987;20(2):93–100.
65. Dayer A, Aubry JM, Roth L, et al. A theoretical reappraisal of mixed states: dysphoria as a third dimension. Bipolar Disord 2000;2(4):316–24.
66. Akiskal HS. The distinctive mixed states of bipolar I, II, and III. Clin Neuropharmacol 1992;15(Suppl 1 Pt A):632A–3A.
67. Akiskal HS, Pinto O. The evolving bipolar spectrum: prototypes I, II, III, and IV. Psychiatr Clin North Am 1999;22(3):517–34.
68. Iasevoli F, Valchera A, Di Giovambattista E, et al. Affective temperaments are associated with specific clusters of symptoms and psychopathology: a cross-sectional study on bipolar disorder inpatients in acute manic, mixed, or depressive relapse. J Affect Disord 2013;151(2):540–50.
69. Marneros A, Goodwin FK. Bipolar disorders: mixed states, rapid-cycling, and atypical forms. 1st edition. New York: Cambridge University Press; 2005.
70. Koukopoulos A, Ghaemi SN. The primacy of mania: a reconsideration of mood disorders. Eur Psychiatry 2009;24(2):125–34.
71. Ghaemi SN, Vohringer PA. Athanasios koukopoulos' psychiatry: the primacy of mania and the limits of antidepressants. Curr Neuropharmacol 2017;15(3):402–8.

72. Scott J, Murray G, Henry C, et al. Activation in bipolar disorders: a systematic review. JAMA Psychiatry 2017;74(2):189.
73. Sobin C, Sackeim HA. Psychomotor symptoms of depression. Am J Psychiatry 1997;154(1):4–17.
74. Carrol BJ. Psychopathology and neurobiology of manic-depressive disorders. In: Carrol BJ, Barrett JE, editors. Psychopathology and the brain. New York: Raven Press; 1991. p. 265–85.
75. Capponi R. Psicopatología y Semiología Psiquiátrica. Santiago, Chile: Editorial Universitaria; 1987.
76. Koukopoulos A, Koukopoulos A. Agitated depression as a mixed state and the problem of melancholia. Psychiatr Clin North Am 1999;22(3):547–64.
77. Day RK. Psychomotor agitation: poorly defined and badly measured. J Affect Disord 1999;55(2-3):89–98.
78. Ghaemi SN, Vohringer PA, Vergne DE. The varieties of depressive experience: diagnosing mood disorders. Psychiatr Clin North Am 2012;35(1):73–86.
79. Risco L, Herane A. Estados mixtos. In: Trastornos bipolares. 2nd edition. Santiago (Chile): Mediterráneo; 2006. p. 151–64.
80. Malhi GS, Berk M, Morris G, et al. Mixed mood: the not so united states? Bipolar Disord 2017;19(4):242–5.