

MIXED STATES: A “NEW” NOSOGRAPHIC ENTITY

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SUMMARY

Objective: Mixed states represent a controversial topic in the current psychiatry. The definitions and the diagnostic criteria have changed over the past years. The new DSM-5 classification will have a substantial impact in several fields: epidemiology, diagnosis, treatment, research, education, and regulations.

Methods: We reviewed the latest literature by using the key words “mixed states” and “agitated depression” on the PubMed.

Results: Although there is a great expectation about the validity of the new DSM-5 mixed states diagnosis, little is known about its application on large population study but the formulation of less restrictive and more specific criteria for the diagnosis of mixed states represent a starting point for future researches, mainly in consideration of the fact that previous classifications consider the MS a superposition of manic and depressive symptoms, underestimating the clinical complexity and the wider phenomenologic variability of these conditions.

Conclusions: Clinical trials need to address treatment effects according to the presence or absence of mixed features in consideration of the fact that replacing in the bipolar spectrum patients that traditionally are considered to be affected by unipolar depression, represent a topical research hypothesis and has a practical remarkable importance in the appropriate therapeutic choice.

Key words: mixed states - agitated depression - mood disorders - DSM-5

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BACKGROUND

According to the literature, the Mixed States (MS) remain a nosologic dilemma, a diagnostic challenge and a neglected area of therapeutic research (Dell’Osso et al. 1991, Akiskal 1992, Perugi et al. 1997, Cassidy et al. 2000, Cassidy et al. 2001, Pacchiarotti et al. 2011, 2013, Vieta et al. 2013, Vampini & Nifosi 2014) although the correct identification of these MS has important implications for clinical practice (Perugi et al. 2014).

Actually, there are few existing psychometric scales that measure the mixed dimension (Berk et al. 2007); consequently, further studies and specific diagnostic criteria are needed to ascertain psychometric measurements for the mixed component (Pacchiarotti et al. 2013, Perugi et al. 2014).

Until now, the DSM-IV-TR criteria for mixed episode did not allow an adequate understanding of a vast majority of bipolar patients with mixed (hypo) manic-depressive features (Pacchiarotti et al. 2011) due to the fact that the approach to the MS was mainly categorical and very restrictive (Pacchiarotti et al. 2013).

The MS in the DSM-IV-TR are basically defined as the combination of mania and major depression co-occurring in the same period (Perugi et al. 2013); this definition has been reviewed in the new DSM-5, that proposes a mixed categorical-descriptive approach in the effort for overcome the deriving problems of the restrictive definition in the DSM-IV-TR (Vampini & Nifosi 2014); in fact, at least in the most severe forms, MS appears to represent more than a superposition of

affective symptoms of opposite polarity (Vampini & Nifosi 2014).

Nevertheless, the latest literature doesn’t point out a univocal point of view.

Although some authors (Vieta et al. 2013) suggest that the new classification will capture subthreshold non-overlapping symptoms of the opposite pole, other authors (Koukopoulos et al. 2014) try to demonstrate that the DSM-5 proposal has weak scientific basis and does not identify a large number of mixed depressive states.

Perugi et al. (Perugi et al. 2014) indicate that the combinatory model might be more appropriate for the definition of less severe MS, in which mood symptoms are prominent and clearly identifiable; on the contrary, in the most severe MS, characterized by psychosis, severe emotional, perceptual and motor disturbances, the association with depressive and manic features could be not easily recognized and these conditions might be confused with a number of other psychiatric disorders, including borderline personality disorder, delusional depression, schizophrenia, and organic mental disorder (Akiskal et al. 1987, Koukopoulos et al. 1992, Swann et al. 2013).

Therefore, it would be important to distinguish mixed states from these conditions so that treatments (e.g., antidepressants), which might worsen their symptomatology, would be utilized with due caution (Akiskal et al. 2005) and treatments that might be particularly effective (e.g., mood stabilizers and ECT) would not go underutilized (Perugi et al. 2014).

EVOLUTION OF THE CONCEPT OF MIXED STATES

The first modern psychiatrist that described mixed states systematically was Johann Christian August Heinroth (1773–1843), who categorized mental disorders as exaltations (“hyperthymias”), depressions (“asthenias”), and mixed states of exaltation and weakness (“hypo-asthenias”), further divided into mixed mood, mental, and volition disorders (Heinroth 1818).

Subsequently, Emil Kraepelin (1856–1926) observed that mood, thought and volition could increase (manic) or decrease (depression) in an independent manner (Perugi et al. 1997, Angst et al. 2000, Marneros 2001, Marneros & Goodwin 2005, Swann et al. 2013).

On the basis of the different combinations of these independent oscillations, Kraepelin distinguished schematically the following subtypes for the MS: 1. Agitated depression, characterized by depressed mood and psychomotor agitation; 2. Manic stupor, where elation and the sensation of augmented capacity and power go together with psychomotor and ideational inhibition; 3. Depression with flight of ideas, characterized by depressed mood and psychomotor inhibition associated with the acceleration of thought; 4. Unproductive mania, with elation and psychomotor agitation associated with thought retardation; 5. Depressive-anxious mania, with a mood deflection associated with irritability, intolerance and reactivity; 6. Inhibited mania, with elation, distractibility, flight of ideas associated with motor inhibition (Perugi et al. 1997a).

In addition, Kraepelin described some MS specific features such as the tendency to chronicity, the frequent presence of psychotic aspects (Vampini & Nifosi 2014) and mainly, he proposed that MS were driven by a sort of hyperarousal and, consequently, they can be considered as a severe form of bipolar disorder (Swann et al. 2013).

After that, Wilhelm Weygandt, a pupil and a colleague of Kraepelin, published the first book on MS, “On the mixed states of Manic-Depressive Insanity” (Weygandt 1899), in which introduced the term “agitated depression” (Swann et al. 2013), stating the basis of a differentiation between mania with depressive features, now called “mixed” or “dysphoric mania” and depression with manic features, named “agitated depression”.

In fact, Kraepelin (1921) (Akiskal et al. 2005) initially excluded this syndrome from his broad rubric of manic-depression, but based on follow-up of such cases by another student, Georges Dreyfus, he reclassified them as mixed states.

Although the classification proposed by Kraepelin has been criticized in the past for its schematic approach, now has regained value in consideration of its correspondence to the clinical reality (Swann et al. 2013).

MIXED STATES CRITERIA: PROPOSALS

The definition of mixed states in the different editions of the DSM has suffered from several changes: in the first edition of the DSM (1952) (American Psychiatric Association 1952) the term “manic depressive reaction, mixed type” was used rather loosely, while the second edition (1968) (American Psychiatric Association 1968) required that “manic and depressive symptoms appeared almost simultaneously” in order to diagnose “mixed” manic-depressive. In the DSM-III (1980) (American Psychiatric Association 1980) and DSM-III-R (1987) (American Psychiatric Association 1987), the diagnosis of bipolar disorder, mixed, required the “full symptomatic picture of both manic and major depressive episodes, intermixed or rapidly alternating every few days”, whereas in the DSM-IV (1994) (American Psychiatric Association 1994) and the DSM-IV-TR (2000) (American Psychiatric Association 2000), the term “mixed episode” was introduced and required that criteria were met for both manic and depressive episodes each day for at least 1 week, that either socio-professional and/or everyday life impairment or psychosis be present, and that medical conditions and drugs do not account for symptoms (Pacchiarotti et al. 2011, Vampini & Nifosi 2014).

The ICD-10 classification (World Health Organization 1992) provides a less rigid description; in fact it considers the possibility of having depression with mixed hypomanic features. Anyway, it requires that two sets of opposite symptoms occur for the most part of the current episode, as in the DSM-IV TR (Vampini & Nifosi 2014).

Several authors, evaluating large cohorts of patients, have proposed a new nosology for the MS based on different criteria that proceed from an intermediate categorical definition to wider dimensional approaches (Vampini & Nifosi 2014).

Berner et al. (Berner et al. 1983) proposed specific criteria (Vienna Research Criteria), which delineate a mixed affective subtype defined by a sustained instability characterized by a “persistent presence of a drive state contradictory to the mood state and/or the emotional resonance” (Perugi et al. 2001) and associated with perception disorders, sensation of external disturbance and depersonalization (Vampini & Nifosi 2014).

McElroy et al. (McElroy et al. 1992, 1995) defined the dysphoric mania by the presence of three or more symptoms of major depression during a full manic or hypomanic episode by DSM-III-R criteria (McElroy et al. 1992) and Cassidy et al. (Cassidy et al. 2000, Cassidy & Carroll 2001) stated that the definition of mixed mania requires that subjects meet the full DSM-III-R criteria for mania and have two or more of the following six symptoms: depressed mood, anhedonia, guilt, suicidality, fatigue and anxiety; in contrast to the DSM-III-R definition, non-specific items, such as

psychomotor agitation, have been deleted and anxiety has been included (Cassidy & Carroll 2001). These criteria are named Cincinnati Criteria.

Akiskal (Akiskal 1992) described mixed states in Bipolar Disorder I, II and III, delineating the clinical aspects of the different presentations and the associated prognostic factors.

The Pisa-San Diego criteria (Perugi et al. 1997, 2001) are based on the presence of a state of sustained (at least 2 weeks) emotional instability and/or perplexity in which depressive and manic symptoms are simultaneously present in a fluctuating manner in 2 or more of five areas such as mood, thought flow, thought content, perceptual disturbance and motility associated with 2 or more temperament characteristics.

Koukopoulos et al. (Koukopoulos et al. 2014) criticize the DSM definition of mixed states and point out that the concepts of agitation and psychomotor excitement is the key point, not DSM-defined manic symptoms for the mixed depressive state or "agitated depression".

Finally, it has also been proposed in research, specific cut-offs in symptom scales should be incorporated (i.e., a score ≥ 10 on the Hamilton Depression Rating Scale for a hypomanic mixed episode, or a Schedule for Affective Disorders and Schizophrenia score ≥ 8 for a depressive mixed episode) (Swann et al. 2013).

CRITICS TO THE NOSOLOGY

The DSM-IV TR indicates, as an exclusion criterion, that the mixed symptomatology doesn't derive from the effects of drugs or a medical condition but it is difficult to evaluate if a mixed episode is the consequence of a brain injury, of a drug abuse and/or toxicity (Vampini et al. 2014) in consideration of the fact that these conditions are frequently reported in the personal histories of these patients (Perugi et al. 2001, McElroy 2008); furthermore this approach addressed depressive and manic episodes separately, regarding mixed states as subtypes of these episodes rather than in terms of episode components (like Kraepelin) or underlying mechanisms (like Berner) (Swann et al. 2013).

In addition, the ICD-10 classification provides for the mixed state diagnosis the presence of at least a previous affective episode; consequently it doesn't take in consideration that a mixed episode is often the first expression of the mood disorder (McElroy et al. 1992, 1995, Cassidy et al. 2000, Cassidy & Carroll 2001).

These restrictive bidimensional criteria undermine the existence of subsyndromal mixed states, and obscure the fact that, in clinical practice, the most prevalent clinical presentation of mixed episodes is the presence of few concomitant symptoms of the opposite polarity (Perugi et al. 1997, Akiskal et al. 1998, Perugi et al. 2001, Goldberg et al. 2009, Swann et al. 2009).

Consequently, one current challenge is to develop models in which reliably observable clinical characteristics can drive research on the mechanisms and treatments of these states (Swann et al. 2013).

THE DSM-5 MIXED STATES

In DSM-5, mood episodes will be defined as being manic, major depressive, or hypomanic, and the mixed episode as defined in DSM-IV-TR will be removed; in fact, the updated DSM-5 proposes a "with mixed features" specifier to be applied when at least three opposite symptoms are present during a mood episode and it could be referred to manic episodes in BD I; hypomanic episodes in BD I and II; and Mood Depressive Episodes (MDEs) experienced in BD I, BD II, BD not otherwise specified (BD-NOS), and major depressive disorder (MDD). This decision arises from the manifest need to capture subthreshold nonoverlapping symptoms of the opposite pole and to better account for the highly prevalent subsyndromal presentations that, under DSM-IV-TR classification, do not meet the criteria for any of the 3 bipolar diagnoses (Nusslock 2011, Pacchiarotti et al. 2011).

This new classification seems to outdo the unipolar-bipolar dichotomy and is linked to Kraepelin's concept of a "mood spectrum" that varies from unipolar depression to pure mania at its extremes (Kraepelin 1899, Akiskal et al. 2000, Perugi & Akiskal 2005, Angst et al. 2010); this seems to be in line with several studies showing a frequency of patients with Major Depressive Disorder (MDD) with at least one manic symptom ranging from 22% to 50% and with at least three manic symptoms ranging from 7% to 23% (Nusslock 2011, DSM web site 2012) (similar proportions were found among depressive bipolar I (BP I) and bipolar II (BPII) patients: more than half experienced at least one manic symptom, and 10–16% experienced at least three manic symptoms).

The Mood Disorders Work Group also accepted that mixed depressive patients are likely to belong to bipolar spectrum according to their socio-demographic and clinical characteristics (Koukopoulos et al. 2014).

Nonetheless, some authors (Sato et al. 2003, Maj et al. 2006, Goldberg et al. 2009) did not find any of the proposed DSM-5 symptoms as diagnostically relevant for identifying depression with mixed features; others (Murru et al. 2011) underline that the new DSM-5 approach doesn't clarify the boundary between BD and the correlated diagnosis (i.e. the schizoaffective disorder). Furthermore, some authors observe that the problem of the "unipolar-bipolar dichotomy" remains unresolved because a depressive episode with mixed features is still considered a MDD and consequently, not included in the bipolar spectrum (Moreno et al. 2012).

MIXED STATES. FROM DYSPHORIC MANIA TO AGITATED DEPRESSION: CLINIC AND EPIDEMIOLOGY

Mixed states are characterized by a complex symptomatological picture that includes severe anxiety and prolonged affective instability related to emotional

perplexity, psychotic experiences and grossly disorganized behaviour (Perugi & Akiskal 2005), irritability, impulsivity and psychomotor agitation (Marneros & Goodwin 2005); these are the specific and typical characteristics of the MS and lead to the hypothesis of their autonomy as the "third polarity" of mood disorders (Cohen et al. 1988, Perugi et al. 1997, Freeman & McElroy 1999).

In general, MS are associated with earlier age at first hospitalization and longer duration of illness (Cassidy & Carroll 2001, Baldassarini et al. 2010, Valenti et al. 2011), with an increased relapse risk (Kessing 2008, Baldassarini et al. 2010), a overall morbidity 1.6-times higher in bipolar patients with an initial mixed state than in bipolar patients with a first purely manic episode (Baldassarini et al. 2010), an increased risk of developing future mixed episodes (Kessing 2008, Baldassarini et al. 2010), a higher prevalence of substance use (González-Pinto et al. 2007) and other comorbidities (Goldberg & McElroy 2007), a higher risk of suicide (González-Pinto et al. 2007, Henry et al. 2007, Goldberg et al. 2009, Swann et al. 2009, González-Pinto et al. 2010, Valenti et al. 2011), lower recovery rates in the long-term (Azorin et al. 2009), and lower response to antidepressant drugs (ADs) (Goldberg et al. 2007, Frye et al. 2009, Valenti et al. 2011)

In addition, MS patients are affected from major depression 6.5 times more often than the BD patients and had 69% more dysthymia during follow-up than BD patients presenting with an initial manic episode (Baldassarini et al. 2010).

Thus, the combination of components of manic and depressive states is associated with a more severe form of BD with a worse course of illness and higher rates of comorbid conditions (Vieta & Valenti 2013).

Several studies have focused attention on manic states co-existing with full or partial depressive features that is generally called "manic mixed states (MMS)", "dysphoric mania" or "mixed mania" (Akiskal et al. 2005, Golberg et al. 2009, Swann et al. 2013) and variously considered as a subtype of mania (Murphy & Beigel 1974), a more severe manic state (Post et al. 1989) or a transitional state between mania and depression (Bunney et al. 1972).

Swann et al. (Swann et al. 2013, 2013a) reviewed the most recent literature and identify that anxiety, 1 depressive component, irritability/hostility, and one component of psychosis, as well as the classic elevation of mood and psychomotor activation symptoms of mania are common to mixed mania.

Some distinctive features of mixed mania compared with pure mania and mixed depressive states have been found: greater prevalence in females, ranging from 63% to 69% using most definitions (Cassidy et al. 2008), more functional impairment (Rosa et al. 2009), more frequent comorbidity with obsessive-compulsive disorder (Mc Elroy et al. 1995) or substance abuse and more common past, current and recent suicidality

(Dilsaver et al. 1994, Goldber et al. 1998); as for the prognostic aspects, mixed mania presents more past mixed episodes of longer duration, high probability of a MS at onset with a higher risk of a future mixed episode (Perugi et al. 2001, Cassidy et al. 2008, Kessing 2008, Azorin et al. 2009, Baldassarini et al. 2010, Gonzalez-Pinto et al. 2010, Valenti et al. 2011, Martin-Carrasco et al. 2012); regarding the age of onset, the majority of studies report that mixed mania occur at a younger age than pure episodes (Cassidy & Carroll 2001, Perugi & Akiskal 2005, Benazzi 2008, Goldberg et al. 2009, Gonzalez-Pinto et al. 2011, Valenti et al. 2011, Azorin et al. 2012).

Contrary to mixed mania, the existence of depressive mixed states (DMS), characterized by a complete major depressive episode with manic symptoms, are not officially recognized within the current nosology (Perugi et al. 2001) and have been ignored in the literature for a long time (Vampini & Nifosi 2014).

According to the clinical descriptive observations, the symptomalogical profile of DMS is characterized by an "agitated depression", often with psychotic features, irritability/aggressivness, psychomotor agitation, increased talkativeness, hypersexuality, distractibility and flight of ideas/racing thoughts (Akiskal & Mallya 1987, Koukopoulos et al. 1992, Koukopoulos & Koukopoulos 1999, Swann et al. 2013a).

Similar to mixed mania, mixed depressive patients differ from pure bipolar depressives in that they are more likely to show a mixed state at the first episode; have more severe episodes of longer duration; have less interepisodic remission; have more rapid cycling; have higher recurrence rates of depressive or hypomanic episodes; have more previous mixed episodes; and have more incongruent psychotic features, suicide attempts, and alcohol abuse (Perugi et al. 2001, Akiskal et al. 2005, Goldberg et al. 2009, Azorin et al. 2012).

In addition, the majority of studies agree that there is no sex difference in the prevalence of mixed depression (Perugi et al. 2001, Benazzi 2003, Akiskal et al. 2005, Azorin et al. 2012,); as for the age of onset, mixed depression occur at a younger age than pure episodes (Cassidy and Carroll 2001, Perugi and Akiskal 2005, Benazzi 2008, Goldberg et al. 2009, Gonzalez-Pinto et al. 2011, Valenti et al. 2011, Azorin et al. 2012).

Perugi et al. (Perugi et al. 2000) observed that DMS are often confused with other psychiatric disorders (such as schizophrenia, psychotic depression or borderline personality disorder); consequently, they are inadequately treated with high probability of resistance to treatment and/or destabilization of the BD.

Furthermore, they revealed that major depression was more common among the relatives of depressive mixed states. In effect, depressive mixed states, like manic mixed states, arise from a bipolar diathesis, yet they are distinguished from them by higher familial load for depression.

As for the epidemiological aspects, mixed states are common in the context of BD (Akiskal et al. 2000), but a direct consequence of the several definitions is that the reported prevalence rate varies significantly between studies (Vieta & Valenti 2013). For mixed manic states, the recognized overall mean global prevalence is 31% (McElroy et al. 1992), but the prevalence based on the narrow definitions of ICD-10 and DSM-III/IV is reported to be between 6.7% and 28%, and is up to 66% when using broader definitions (Cassidy et al. 2008).

In a cross-sectional multicenter study, Vieta and Morralla (Vieta & Morralla 2010) reported 9% prevalence according to ICD-10 criteria, 13% prevalence according to DSM-IV-TR criteria, 17% according to Cincinnati criteria, and 23% by clinicians' assessment.

Predominantly depressive mixed states have been studied less, but the reported rates also vary, between 20% and 70%, depending on the use of narrow or broad definitions (Benazzi 2008, Goldberg et al. 2009, Azorin et al. 2012).

Consequently, more studies focused on the clinical features and the diagnostic aspects of MS are needed to overcome the diagnostic difficulties.

DIAGNOSTIC ASPECTS

Until now, many researchers have studied the clinical characteristics of MS in order to better recognize this disorder.

Swann et al. (Swann et al. 2013), on the basis of a literature review, state that, regardless of the dominant polarity, characteristics of mixed states emerge with two or three symptoms of opposite polarity.

Depressive symptoms that characterize mixed manic episode included dysphoric mood, anxiety, excessive guilt and suicidality (Cassidy et al. 1998).

Mixed manic episodes seem to be similar to agitated depressive episodes with more severe agitation, irritability and cognitive impairment (Swann et al. 1993).

The symptoms characterizing mixed manic episodes include increased mood lability and irritability, less grandiosity, euphoria, pressure of speech, and decreased need for sleep compared to non-mixed episodes (Cassidy et al. 1998).

In addition, anxiety appears to be a core symptom of mixed manic episodes (Cassidy 2010); in fact, in mania, high anxiety scores are associated with depression scores (González-Pinto et al. 2007, Swann et al. 2009) and it seems to emerge with two depressive symptoms in mixed mania (Swann et al. 2009).

As for the course of the disorder, early onset of illness emerged with three or more depressive symptoms in the context of mixed mania (Swann et al. 2009).

The same consideration is valid for suicidal behaviour (Goldberg et al. 1998); in fact mixed mania combines the hopelessness of depression with the impulsivity and hyperactivity of mania.

As for the manic features associated with a major depressive episode, Sato et al. (Sato et al. 2003) decidedly affirmed that euphoria and grandiosity, the first two diagnostic criteria proposed by DSM-5, were too rare to be considered diagnostically important in mixed depressive clinical pictures.

Dysphoria, defined as a constellation of symptoms such as inner tension, irritability, aggressive behaviour and hostility, was ascertained in 73.3% of patients with a mixed state (Bertschy et al. 2008). Similarly, Olgiati et al. (Olgiati et al. 2006) found that dysphoria, together with psychotic symptoms and reduced need for sleep, was an independent predictor of agitated depression in a multivariate model.

Some authors (Maj et al. 2003, Akiskal et al. 2005, Benazzi 2005, Pae et al. 2012) reported that the most frequent symptoms found in DMS were irritability (Maj et al. 2003, Pae et al. 2012), racing thoughts/ flight of ideas (Maj et al. 2003), psychomotor agitation, talkativeness (Maj et al. 2003, Perlis et al. 2012), distractibility (Maj et al. 2003) and increased energy/ decreased sleep (Perlis et al. 2012) with different percentages.

Furthermore, according to Pacchiarotti et al. (Pacchiarotti et al. 2011) irritability and psychomotor agitation are the strongest predictors of suicide attempts (Balázs et al. 2006, El-Mallakh et al. 2008) in these patients.

Koukopoulos et al. (Koukopoulos & Sani 2014) observed the clinical utility of using a different set of symptoms, other than DSM-5 criteria, to characterize mixed depression and that these symptoms should not be called 'manic/hypomanic' symptoms but excitatory symptoms, following Griesinger's use of the phrase 'excitation of the psychic processes' (Griesinger 1861).

A recent factor analysis (Pacchiarotti et al. 2013) of manic, depressive, and mixed episodes in BD I inpatients identified a specific mixed factor dimension that the authors termed "mixicity," which distinguishes mixed episodes from pure manic and depressive episodes. This dimension includes the items anxiety, tension, suicidality, motor hyperactivity, and excitement; is unrelated to depressed mood; and does not include psychomotor retardation. This "mixicity" dimension was found to be associated with predominant depressive polarity, more lifetime mixed episodes, worse course of illness, and a higher frequency of previous antidepressant use. Moreover, the "mixicity" factor was associated with an anxious temperament and a premorbid temperament mainly characterized by anxiety and tension, supporting the hypothesis that mixed episodes result from an admixture of inverse temperamental factor to a manic syndrome, as proposed by some authors (Akiskal 1992, Perugi & Akiskal 2005); in fact Akiskal et al. (Akiskal et al. 1998), in an attempt to explain the development of mixed states, hypothesized that mixed states arise from the intrusion of an affective episode into an opposite temperament or one with a high degree of chronic instability, such as cyclothymic temperament.

This dimensional pattern of an anxious–excited arousal is not in agreement with some of the symptoms needed to define a manic episode with mixed features in DSM-5. Dysphoria is included, but psychomotor retardation is also a possible symptom, and anxiety is not explicitly included in the DSM-5 definition.

Consequently, further research is needed to understand in large sample of inpatients and outpatients what are the real predictors of the mixed states disease.

THERAPEUTIC IMPLICATIONS

It is largely recognized that mixed manic/depressive presentations in BD have a poorer pharmacological response compared with pure episodes (Benazzi 2008, Cassidy et al. 2008, Gonzalez-Pinto et al. 2011), and combination therapy is often required (Gonzalez-Pinto et al. 2007).

According to the latest literature (Pacchiarotti et al. 2013), patients with MS have more past antidepressant treatment, especially SSRIs, and increased antidepressant (AD) use during the six months preceding the index episode.

Akiskal et al. (Akiskal et al. 2005) proposed that mixed depressive episodes should not be treated with antidepressants because of increased activation and risk for suicidality; in fact the FDA has listed some features of mixed depression, like irritability, psychomotor agitation, and bipolarity, among the possible precursors of AD-related suicidality (FDA 2011). It has been advanced that agitation, dysphoria, and other characteristics of the mixed state might provide the energy needed to support suicidal actions (Koukopoulos et al. 2005). It is worthy to note that previous studies showed that the reports of increased risk of suicidal behaviour in some depressed patients on AD treatment might be related to the psychomotor activation/agitation as a part of an unrecognized mixed state (Akiskal et al. 2005).

Furthermore, it could be speculated that the excessive use of ADs in these patients worsen the clinical course of a depressive mixed state (Koukopoulos et al. 2007, Pacchiarotti et al. 2011) causing increased agitation and insomnia, the occurrence of psychotic symptoms and the emergence of suicidal ideas or impulses.

In summary, antidepressants without mood-stabilizing treatments have limited efficacy and the potential for harm in MS (Akiskal et al. 2005, Swann et al. 2013); anyway, patients with mixed states have a poorer long-term prophylactic response to treatment in general (González-Pinto et al. 2011). Given the high risk for suicidal behaviour in mixed states, many authors (McElroy et al. 1992, Swann et al. 1997, Golberg et al. 1998a) studied the role of lithium in patients susceptible to mixed states and discover that, although lithium is effective on impulsivity and suicidality, the prophylactic treatment is less effective in mixed mania than the pure episode (McElroy et al. 1992, Swann et al. 1997,

Golberg et al. 1998a); on the contrary valproate seems to be effective in the treatment of mixed mania (McFarland et al. 1990, Calabrese et al. 1992, Cassidy et al. 2000, Bowden et al. 2006, Smith et al. 2010).

As for antipsychotic drugs, the second generation drugs are efficacious, both in monotherapy and in combination with mood stabilizers (Muralidharan et al. 2013).

THE ADDED VALUE OF THE RESEARCH

Although there is a great expectation about the validity of the new DSM-5 mixed states diagnosis, little is known about its application on large population study.

The new DSM-5 classification will have a substantial impact in several fields: epidemiology, diagnosis, treatment, research, education, and regulations. The new concept is data-driven and maybe it could overcome the problems derived from the extremely narrow definition in the DSM-IV-TR (Vieta & Valenti 2013). Contemporary, the formulation of less restrictive and more specific criteria for the diagnosis of mixed states represent a starting point for future researches (Perugi et al. 1997a, Vampini & Nifosi 2014), mainly in consideration of the fact that previous classifications consider the MS a superposition of manic and depressive symptoms, underestimating the clinical complexity and the wider phenomenologic variability of these conditions.

In fact, according to McElroy hypothesis (McElroy et al. 1995), if dysphoric mania (and agitated depression too) proved to be a separate affective state rather than a stage-related or transitional state, it could be argued that triangular model of mood disorder may be more appropriate than bipolar model; in this context, agitated depression would represent severe depression with mild mania and dysphoric mania would represent severe depression with severe mania; furthermore, other forms of MS may represent transitional disturbances between the extremes of agitated depression and dysphoric mania of greater and lesser severity, according to the Kraepelin's concept of "Bipolar Spectrum" (Kraepelin 1899).

As a consequence, clinical trials also need to address treatment effects according to the presence or absence of mixed features (Vieta & Valenti 2013); in fact replacing in the bipolar spectrum patients that traditionally are considered to be affected by unipolar depression, represent a topical research hypothesis and has a practical remarkable importance in the appropriate therapeutic choice (Vampini & Nifosi 2014).

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References

1. Akiskal HS & Mallya G: Criteria for the "soft" bipolar spectrum: treatment implications. *Psychopharmacol Bull* 1987; 23:68-73.
2. Akiskal HS: The distinctive mixed states of Bipolar I, II and III. *Clin Neuropharmacol* 1992; 15, Pt. A.
3. Akiskal HS, Hantouche EG, Bourgeois ML, Azorin JM, Sechter D, Allilaire JF et al.: Gender, temperament, and the clinical picture in dysphoric mixed mania: findings from a French national study (EPIMAN). *J Affect Disord* 1998; 50:175-186.
4. Akiskal HS, Bourgeois ML, Angst J, Post R, Moller H & Hirschfeld R: Re-evaluating the prevalence of and diagnostic composition within the broad clinical spectrum of bipolar disorders. *J Affect Disord* 2000; 59(Suppl. 1):S5–S30.
5. Akiskal HS, Benazzi F, Perugi G & Rihmer Z: Agitated "unipolar" depression re-conceptualized as a depressive mixed state: Implications for the antidepressant-suicide controversy. *J Affect Disord* 2005; 85:245-258.
6. American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*. First Edition. Washington, DC, 1952.
7. American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*. DSM-II. Washington, DC, 1968.
8. American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*. DSM-III. Washington, DC, 1980.
9. American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*. DSM-III-R. Washington, DC, 1987.
10. American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*. DSM-IV. Washington, DC, 1994.
11. American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed., Text Revision (DSM-IV-TR). Washington, DC, 2000.
12. Angst J & Sellaro R: Historical perspectives and natural history of bipolar disorder. *Biol Psychiatry* 2000; 48:445-457.
13. Angst J, Cui L, Swendsen J, Rothen S, Cravchik A, Kessler RC et al.: Major depressive disorder with subthreshold bipolarity in the National Comorbidity Survey Replication. *Am J Psychiatry* 2010; 167:1194–1201.
14. Azorin JM, Aubrun E, Bertsch J, Reed C, Gerard S & Lukasiewicz M: Mixed states vs. pure mania in the French sample of the EMBLEM study: results at baseline and 24 months - European mania in bipolar longitudinal evaluation of medication. *BMC Psychiatry* 2009; 9:33.
15. Azorin JM, Kaladjian A, Adida M, Fakra E, Belzeaux R, Hantouche E et al.: Self-assessment and characteristics of mixed depression in the French national EPIDEP study. *J Affect Disord* 2012; 143: 109–117.
16. Baldessarini RJ, Salvatore P, Khalsa M & Tohen M: Dissimilar morbidity following initial mania versus mixed-states in type-I bipolar disorder. *J Affect Disord* 2010; 126:299–302.
17. Benazzi F: The role of gender in depressive mixed state. *Psychopathology* 2003; 36:213-217.
18. Benazzi F: Family history validation of a definition of mixed depression. *Compr Psychiatry* 2005; 46:159–166.
19. Benazzi F: Reviewing the diagnostic validity and utility of mixed depression (depressive mixed states). *European Psychiatry* 2008; 23:40–48.
20. Berk M, Malhi GS, Cahill C, Carman AC, Hadzi-Pavlovic D, Hawkins MT et al.: The Bipolar Depression Rating Scale (BDRS): its development, validation and utility. *Bipolar Disord* 2007; 9:571-579.
21. Berner P, Gabriel E & Katschnig H: *Diagnostic criteria for schizophrenic and affective psychoses*. Vienna: World Psychiatric Association, 1983.
22. Bertschy G, Gervasoni N, Favre S, Liberek C, Ragama-Pardos E, Aubry JM et al.: Frequency of dysphoria and mixed states. *Psychopathology* 2008; 41:187–193.
23. Bowden CL, Swann AC, Calabrese JR, Rubenfaer LM, Wozniak PJ, Collins MA et al.: A randomized, placebo-controlled, multicentre study of divalproex sodium extended release in the treatment of acute mania. *J Clin Psychiatry* 2006; 67:1501-10.
24. Bunney WE, Murphy DL, Goodwin FK & Borge GF: The 'Switch Process' in manic-depressive illness. I. A systematic study of sequential behavioral changes. *Arch Gen Psychiatry* 1972; 27:295–302.
25. Calabrese JR, Markovitz PJ, Kimmel SE & Wagner SC: Spectrum of efficacy of valproate in 78 rapid-cycling bipolar patients. *J Clin Psychopharmacol* 1992; 12:53S-6.
26. Cassidy F, Murry E, Forest K & Carroll BJ: Signs and symptoms of mania in pure and mixed episodes. *J Affect Disord* 1998; 50:187–201.
27. Cassidy F, Ahearn E, Murry E, Forest K & Carroll BJ: Diagnostic depressive symptoms of the mixed bipolar episode. *Psychol Med* 2000; 30:403-411.
28. Cassidy F & Carroll BJ: The clinical epidemiology of pure and mixed manic episodes. *Bipolar Disord* 2001; 3:35-40.
29. Cassidy F, Yatham LN, Berk M & Grof P: Pure and mixed manic subtypes: a review of diagnostic classification and validation. *Bipolar Disord* 2008; 10:131–143.
30. Cassidy F: Anxiety as a symptom of mixed mania: implications for DSM-5. *Bipolar Disord* 2010; 12:437–439.
31. Cohen S, Khan A & Robison J: Significance of mixed features in acute mania. *Compr Psychiatry* 1988; 29:421-6.
32. Dell'Osso L, Placidi GF, Nassi R, Freer P, Cassano GB & Akiskal HS: The Manic-Depressive Mixed State: Familial, Temperamental and Psychopathologic Characteristics in 108 Female Inpatients. *Eur Arch Psychiatry Clin Neurosci* 1991; 240:234-239.
33. Dilsaver SC, Chen YW, Swann AC, Shoaib AM & Krajewski KJ: Suicidality in patients with pure and depressive mania. *Am J Psychiatry* 1994; 151:1312–1315.
34. DSM web site, available at: <http://www.dsm5.org/proposedrevision/pages/proposedrevision.aspx?rid=483#> (last access: October 2012).
35. El-Mallakh RS, Ghaemi SN, Sagduyu K, Thase ME, Wisniewski SR, Nierenberg AA et al.: STEP-BD investigators. Antidepressant-associated chronic irritable dysphoria (ACID) in STEP-BD patients. *J Affect Disord* 2008; 111:372–377.
36. FDA-US Food and Drug Administration Public Health Advisory 2007. Antidepressant Use in Children, Adolescents, and Adults Assessed on the WorldWideWeb on 21-8-2011. <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm096273.htm>

37. Freeman MP & McElroy SL: Clinical picture and etiologic models of mixed states. *Psychiatr Clin North Am* 1999; 22:535–46.
38. Frye MA, Helleman G, McElroy SL, Altshuler LL, Black DO, Keck Jr. PE et al.: Correlates of treatment-emergent mania associated with antidepressant treatment in bipolar depression. *Am J Psychiatry* 2009; 166:164–172.
39. Goldberg JF, Garno JL, Leon AC, Kocsis JH & Portnera L: Association of recurrent suicidal ideation with non-remission from acute mixed mania. *Am J Psychiatry* 1998; 155:1753–1755.
40. Goldberg JF, Garno JL, Leon AC, Kocsis JH & Portnera L: Rapid titration of mood stabilizers predicts remission from mixed or pure mania in bipolar patients. *J Clin Psychiatry* 1998a; 59:151–8.
41. Goldberg JF & McElroy SL: Bipolar mixed episodes: characteristics and comorbidities. *J Clin Psychiatry* 2007; 68:e25.
42. Goldberg JF, Bowden CI, Thase ME, Miklowitz DJ, Marangell LB, Calabrese JR et al.: Manic symptoms during depressive episodes in 1380 patients with bipolar disorder: findings from the STEP-BD. *Am J Psychiatry* 2009; 166:173–181.
43. González-Pinto A, Aldama A, Mosquera F & González Gómez C: Epidemiology, diagnosis and management of mixed mania. *CNS Drugs* 2007; 21:611–626.
44. González-Pinto A, Aldama A, Mosquera F & González Gómez C: Epidemiology, diagnosis and management of mixed mania. *CNS Drugs* 2007; 21:611–626.
45. Gonzalez-Pinto A, Alberich S, Barbeito S, Alonso M, Vieta E, Martínez-Aran A et al.: Different profile of substance abuse in relation to predominant polarity in bipolar disorder: the Vitoria long-term follow-up study. *J Affect Disord* 2010; 124:250–255.
46. González-Pinto A, Barbeito S, Alonso M, Alberich S, Haidar MK, Vieta E et al.: Poor long-term prognosis in mixed bipolar patients: 10-year outcomes in the Vitoria prospective naturalistic study in Spain. *J Clin Psychiatry* 2011; 72:671–676.
47. Griesinger W. *Pathologie und Therapie der psychischen Krankheiten*, 2nd edn. Stuttgart: Adolf Krabbe Verlag, 1861.
48. Heinroth JCA. *Lehrbuch der Störungen des Seelenlebens oder der Seelenstörungen und ihrer Behandlung - aus rationaler Sicht*. Leipzig, Vogel, 1818.
49. Henry C, M'Bailara K, Desage A, Gard S, Misdrahi D & Vieta E: Towards a reconceptualization of mixed states, based on an emotional-reactivity dimensional model. *J Affect Disord* 2007; 101:35–41.
50. Kessing LV: The prevalence of mixed episodes during the course of illness in bipolar disorder. *Acta Psychiatr Scand* 2008; 117:216–224.
51. Koukopoulos A, Faedda G, Proietti R, D'Amico S, de Pisa E & Simonetto C: Mixed depressive syndrome. *Encéphale* 1992; 18 (Spec No 1):19–21.
52. Koukopoulos A & Koukopoulos A: Agitated depression as a mixed state and the problem of melancholia. *Psychiatr Clin North Am* 1999; 22:547–564.
53. Koukopoulos A, Albert MJ, Sani G, Koukopoulos AE & Girardi P: Mixed depressive states: nosologic and therapeutic issues. *Int Rev Psychiatr* 2005; 17:21–37.
54. Koukopoulos A, Sani G, Koukopoulos AE, Manfredi G, Pacchiarotti I & Girardi P: Melancholia agitata and mixed depression. *Acta Psychiatr Scand* 2007; 115:50–57.
55. Koukopoulos A & Sani G: DSM-5 criteria for depression with mixed features: a farewell to mixed depression. *Acta Psychiatr Scand* 2014; 129:4–16.
56. Kraepelin E: *Psychiatrie. Ein Lehrbuch für Studierende und Ärzte, Klinische Psychiatrie*. Verlag von Johann Ambrosius Barth, Leipzig, Germany, 1899.
57. Marneros A: Origin and development of concepts of bipolar mixed states. *J Affect Disord* 2001; 67:229–240.
58. Marneros A & Goodwin F: *Bipolar Disorders: mixed states, rapid cycling and atypical forms*. Cambridge, UK: Cambridge University Press, 2005.
59. Martín-Carrasco M, González-Pinto A, Galan JL, Ballesteros J, Maurino J & Vieta E: Number of prior episodes and the presence of depressive symptoms are associated with longer length of stay for patients with acute manic episodes. *Ann Gen Psychiatry* 2012; 11:7.
60. May M, Pirozzi R, Magliano L, Fiorillo A, Kleindienst N & Moller HJ: Evaluating the inter-episode stability of depressive mixed states. *J Affect Disord* 2004; 81:103–113.
61. McElroy SL, Keck PE Jr., Pope HG Jr., Hudson JI, Faedda GI & Swann AC: Clinical and Research Implications of the Diagnosis of Dysphoric or Mixed Mania or Hypomania. *Am J Psychiatry* 1992; 149:1633–1644.
62. McElroy SL, Strakowski SM, Keck PE Jr, Tugrul KL, West SA & Lonczak HS: Differences and Similarities in Mixed and Pure Mania. *Compr Psychiatry* 1995; 36:187–194.
63. McElroy SL: Understanding the complexity of bipolar mixed episodes. *J Clin Psychiatry* 2008; 69:e06.
64. McFarland BH, Miller MR & Straumfjord AA: Valproate use in the older manic patient. *J Clin Psychiatry* 1990; 51:479–81.
65. Moreno C, Hasin DS, Arango C, Oquendo MA, Vieta E, Liu S et al.: Depression in bipolar disorder versus major depressive disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Bipolar Disord* 2012; 14:271–282.
66. Muralidharan K, Ali M, Silveira LE, Bond DJ, Fountoulakis KN, Lam RW et al.: Efficacy of second generation antipsychotics in treating acute mixed episodes in bipolar disorder: a meta-analysis of placebo-controlled trials. *J Affect Disord* 2013; 150:408–414.
67. Murphy DL & Beigel A: Depression, elation, and lithium carbonate responses in manic patient subgroups. *Arch Gen Psychiatry* 1974; 31:643–648.
68. Murru A, Pacchiarotti I, Nivoli AM, Grande I, Colom F & Vieta E: What we know and what we don't know about the treatment of schizoaffective disorder. *Eur Neuropsychopharmacol* 2011; 21:680–90.
69. Nusslock R & Frank E: Subthreshold bipolarity: diagnostic issues and challenges. *Bipolar Disord* 2011; 13:587–603.
70. Olgiati P, Serretti A & Colombo C: Retrospective analysis of psychomotor agitation, hypomanic symptoms, and suicidal ideation in unipolar depression. *Depress Anxiety* 2006; 23:389–397.
71. Pacchiarotti I, Mazzarini L, Kotzalidis GD, Valenti M, Nivoli AMA, Sani G et al.: Mania and depression. Mixed, not stirred. *J Affect Disord* 2011; 133:105–113.
72. Pacchiarotti I, Nivoli AMA, Mazzarini L, Kotzalidis GD, Sani G, Koukopoulos A et al.: The symptom structure of

- bipolar acute episodes: In search for the mixing link. *J Affect Disord* 2013; 149:56-66.
73. Pae CU, Vöhringer PA, Holtzman NS, Thommi SB, Patkar A, Gilmer W et al.: Depression: a study of its phenomenology and relation to treatment response. *J Affect Disord* 2012; 136:1059–1061.
74. Perlis RH, Cusin C & Fava M: Proposed DSM-5 mixed features are associated with greater likelihood of remission in out-patients with major depressive disorder. *Psychol Med* 2012; 15:1–7.
75. Perugi G, Akiskal HS, Micheli C, Musetti L, Paiano A, Quilici C et al.: Clinical subtypes of bipolar mixed states: Validating a broader European definition in 143 cases. *J Affect Disord* 1997; 43:169-180.
76. Perugi G, Micheli C & Socci C: Aspetti nosologici e diagnostici degli stati misti. *NòOζ?* 1997a; 3:179-188.
77. Perugi G, Micheli C, Akiskal HS, Madaro D, Socci C, Quilici C et al.: Polarity of the first episode, clinical characteristics and course of manic-depressive illness: a systematic retrospective investigation of 320 bipolar bipolar patients. *Compr Psychiatry* 2000; 41:13-8.
78. Perugi G, Akiskal HS, Micheli C, Toni C & Madaro D: Clinical characterization of depressive mixed state in bipolar-I-patients: Pisa-San Diego collaboration. *J Affect Disord* 2001; 67:105-114.
79. Perugi G & Akiskal HS: Emerging concepts of mixed states: a longitudinal perspective. In: Marneros, A., Goodwin, F.K. (Eds.), *Emerging Concepts of Mixed States: A Longitudinal Perspective*. 2005, Cambridge University Press, Cambridge, UK, pp. 45–60.
80. Perugi G, Medda P, Reis J, Rizzato S, Giorgi Mariani M & Mauri M: Clinical subtypes of severe bipolar mixed states. *J Affect Disord* 2013; 151:1076-1082.
81. Perugi G, Medda P, Swann AC, Reis J, Rizzato S & Mauri M: Phenomenological subtypes of severe bipolar mixed states: a factor analytic study. *Compr Psychiatry* 2014; article in press.
82. Post RM, Rubinow DR, Uhde TW, Roy-Byrne PP, Linnoila M, Rosoff A et al.: Dysphoric mania, clinical and biological correlation. *Arch Gen Psychiatry* 1989; 46:353–358.
83. Rosa AR, Reinares M, Franco C, Comes M, Torrent C, Sanchez-Moreno J et al.: Clinical pre-dictors of functional outcome of bipolar patients in remission. *Bipolar Disord* 2009; 11:401–409.
84. Sato T, Bottlender R, Schroter A & Moller HJ: Frequency of manic symptoms during a depressive episode and unipolar “depressive mixed states” as bipolar spectrum. *Acta Psychiatr Scandinav* 2003; 107:268-274.
85. Smith LA, Cornelius VR, Azorin JM, Perugi G, Vieta E, Young AH et al.: Valproate for the treatment of acute bipolar depression: Systematic review and meta-analysis. *J Affect Disord* 2010; 122:1-9.
86. Swann AC, Secunda SK, Katz MM, Croughan J, Bowden CL, Koslow SH et al.: Specificity of mixed affective states: clinical comparison of dysphoric mania and agitated depression. *J Affect Disord* 1993; 28:81–89.
87. Swann AC, Bowden CL, Morris D, Calabrese JR, Petty F, Small J et al.: Depression during mania. Treatment response to lithium or divalproex. *Arch Gen Psychiatry* 1997; 54:37-42.
88. Swann AC, Steinberg JL, Lijffijt M & Moeller GF: Continuum of depressive and manic mixed states in patients with bipolar disorder: quantitative measurement and clinical features. *World Psychiatry* 2009; 8:166-172.
89. Swann AC, Lafer B, Perugi G, Frye MA, Bauer M, Bahk WM 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; 170:31-42.
90. Swann AC, Suppes T, Ostacher MJ, Eudicone JM, McQuade R, Forbes A 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* 2013a; 144:59–64.
91. Valentii M, Pacchiarotti I, Rosa AR, Bonnin CM, Popovic D, Nivoli AMA et al.: Bipolar mixed episodes and anti-depressants: a cohort study of bipolar I patients. *Bipolar Disord* 2011; 13:145–154. doi:10.1111/j.1399-5618.2011.00908.x.
92. Vampini C & Nifosi F: Gli stati misti bipolari: evoluzione del concetto e implicazioni per la cura e la ricerca. (Bipolar mixed states: evolution of the concept and implications for the treatment and research). *J Psychopathol* 2014; 20:92-106.
93. Vieta E & Morralla C: Prevalence of mixed mania using 3 definitions. *J Affect Disord* 2010; 125:61-73.
94. Vieta E & Valenti M: Mixed states in DSM-5: Implications for clinical care, education, and research. *J Affect Disord* 2013; 148:28-36.
95. Weygandt W: *Über die Mischzustände des manisch-depressiven Irreseins*. Munich, JF Lehmann, 1899.
96. World Health Organization. *International classification of diseases*. 10th ed. Geneva, 1992.

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