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Preface: Mixed States: Beyond Depression and Mania

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Gabriele Sani and Alan C. Swann

History and Clinical Impact: Recognized and Overlooked Since (before) the Beginning of Psychiatry

Mixed States: Historical Impact and Evolution of the Concept

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Gabriele Sani and Alan C. Swann

Mixed states have been discussed for more than 2 millennia. The theoretic conception of the coexistence of presumably opposite symptoms of mood or of different psychic domains is well established, although obscured by the presumed separation between bipolar and depressive disorders. Moreover, the lack of response to treatments and severe psychopathology raise important issues requiring urgent solution. The aim of this article was to review the development of the concept of mixed states from the classic literature to modern nosologic systems and to claim for the need of a new paradigm to address the still-open issues about mixed states.

Clinical Characteristics and Diagnostic Challenges of Mixed Syndromes

Clinical Picture, Temperament, and Personality of Patients with Mixed States

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Mario Luciano, Delfina Janiri, Andrea Fiorillo, and Gabriele Sani

The construct of mixed states is a robust clinical entity with a high variability of prevalence according to different diagnostic criteria. Despite the changes over the years, current official diagnostic criteria still have poor clinical usefulness. Premorbid characteristics with a potential high clinical importance such as temperament, personality, and emotional reactivity are understudied in patients with mixed states and excluded from the current nosologic systems. The authors provide an overview of current nosography and clinical pictures of mixed states and discuss the role of temperament, personality, and emotional reactivity in mixed states.

Psychopathology of Mixed States

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Sergio A. Barroilhet and S. Nassir Ghaemi

Mixed states are frequent clinical pictures in psychiatric practice but are not well described in nosologic systems. Debate exists as to defining mixed states. We review factor and cluster analytical studies and prominent clinical/conceptual models of mixed states. While mania involves standard manic symptoms and depression involves standard depressive symptoms, core additional features of the mixed state are, primarily, psychomotor activation and, secondarily, dysphoria. Those features are more pronounced in mixed mania than in mixed depression but are present in both.

Diagnosis, Clinical Features, and Implications of Agitated Depression

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Gaia Sampogna, Valeria Del Vecchio, Vincenzo Giallonardo, Mario Luciano, and Andrea Fiorillo

Agitated “unipolar” depression is a clinical entity characterized by excitement together with depressed mood during the same episode. The clinical picture of agitated “unipolar” depression is characterized by a depressed and anxious mood with inner, psychic agitation, whereas motor agitation may or may not be present. Some investigators have conceptualized this disorder as a mixed affective state, laying on the bipolar disorder spectrum, but controversies still persist. The diagnosis of agitated “unipolar” depression has important prognostic and therapeutic implications, with many clinicians reporting difficulties to adequately diagnose and treat it.

Mixed Features in Depression: The Unmet Needs of Diagnostic and Statistical Manual of Mental Disorders Fifth Edition

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Isabella Pacchiarotti, Giorgio D. Kotzalidis, Andrea Murru, Lorenzo Mazzarini, Chiara Rapinesi, Marc Valentí, Gerard Anmella, Susana Gomes-da-Costa, Anna Gimenez, Cristian Llach, Giulio Perugi, Eduard Vieta, and Norma Verdolini

The Diagnostic and Statistical Manual of Mental Disorders Fifth Edition introduced the specifier “with mixed features” including 3 or more nonoverlapping typical manic symptoms during a major depressive episode in bipolar disorder type I or II or unipolar major depressive disorder. Excluding overlapping excitatory symptoms, which are frequently observed in mixed depression, leaves many patients with mixed depression undiagnosed. As a consequence, alternative diagnostic criteria have been proposed, claiming for the inclusion in the rubric of mixed features the following symptoms: psychomotor agitation, mood lability, and aggressiveness. A deeper diagnostic reconsideration of mixed features in depression should be provided by the new nosologic classification systems.

Clinical Contexts, Complications, and Challenges**The Ring of Fire: Childhood Trauma, Emotional Reactivity, and Mixed States in Mood Disorders**

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Delfina Janiri, Georgios D. Kotzalidis, Lavinia De Chiara, Alexia Emilia Koukopoulos, Monica Aas, and Gabriele Sani

Childhood trauma (CT) is strongly associated with bipolar disorder, possibly through emotional hyperreactivity (EH). Mixed symptoms/states (MSs) are associated with increased illness severity. The authors tested through a systematic review the association between CT and MSs. The authors systematically looked for studies exploring associations between MSs and CT, CT and EH, and EH and MSs. Most literature agrees that MSs are associated with CT; the latter was found to be associated to EH, which is in turn associated with MSs. The literature supports an association between CT and later development of MSs, possibly mediated through EH.

Suicidal Behavior Associated with Mixed Features in Major Mood Disorders

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Leonardo Tondo, Gustavo H. Vazquez, and Ross J. Baldessarini

Mixed features of the opposite nominal mood-polarity are increasingly recognized in both depressive and [hypo]manic phases of major affective

disorders. They are associated with major increases of risk of suicidal behaviors. The authors reviewed the association of suicidal behavior with mixed features in both major depressive and bipolar disorders, as well as potentially relevant adverse effects of antidepressant treatment and use of alternative treatments aimed at minimizing agitation and suicidal risk.

Mixed States in Early-Onset Bipolar Disorder

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Kirti Saxena, Sherin Kurian, Johanna Saxena, Adam Goldberg, Eugenia Chen, and Alessio Simonetti

Pediatric bipolar disorder (PBD) is a severe and chronic illness. The occurrence of mixed symptoms might add further risk of recurrence of treatment resistance and suicidality. Early recognition and treatment of mixed symptoms might prevent illness progression and development of suicide attempts. This article provides an update on the epidemiology, clinical profile, and treatment of youth with PBD with mixed states. Mixed states in PBD are characterized by higher rates of suicide and more chronic symptoms, and are associated with younger age of onset and greater comorbidity. A careful assessment for mixed states using standardized criteria is essential.

Perinatal Mixed Affective State: Wherefore Art Thou?

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Alexia Emilia Koukopoulos, Gloria Angeletti, Gabriele Sani, Delfina Janiri, Giovanni Manfredi, Georgios D. Kotzalidis, and Lavinia De Chiara

Mixed states in patients with a perinatal mood episode is seldom encountered. Lack of appropriate assessment tools could be partly responsible for this observation. The authors conducted a selective review of studies dealing with the reporting of mixed symptoms in women during the perinatal period with the intention to quantify the phenomenon. In many instances of reported postpartum depression, either a first onset or an onset in the context of bipolar disorder, mixed states were identifiable. However, the strict application of the Diagnostic and Statistical Manual of Mental Disorders, 5th edition, mixed features specifier to these episodes risks misdiagnosis.

Mixed States in Patients with Substance and Behavioral Addictions

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Marco Di Nicola, Maria Pepe, Marco Modica, Pierluigi Lanzotti, Isabella Panacione, Lorenzo Moccia, and Luigi Janiri

Mixed affective states occur in approximately 40% of patients with mood disorders and are burdened with a significant rate of comorbidities, including addictive disorders (AD). The co-occurrence of mixed features and AD represents a challenge for clinicians because the reciprocal, negative influence of these conditions leads to a worse course of illness, treatment resistance, unfavorable outcome, and higher suicide risk. This article discusses clinical presentation, possible common pathogenetic pathways, and treatment options. Further investigations are required to clarify the determinants and the implications of this co-occurrence, and to detect suitable approaches in clinical management.

Mechanisms

The Neurobiology of Mixed States

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Alessio Simonetti, Marijn Lijffijt, and Alan C. Swann

Interest in the coexistence of manic and depressive symptoms fostered hypotheses on neurobiological underpinnings of mixed states. Neurobiological properties of mixed states, however, have not been comprehensively described. The authors searched databases for articles on neurobiological markers related to mixed states. Results showed that mixed states are characterized by elevated central and peripheral monoamine levels, greater alterations in hypothalamic-pituitary-adrenal axis, increased inflammation, and greater circadian rhythms dysfunction than nonmixed forms. Furthermore, the magnitude of pathophysiologic alterations in mixed states exceeds those associated with nonmixed mania or depression and suggest that hyperactivation and hyperarousal are core features of mixed states.

Temporal Structure of Mixed States: Does Sensitization Link Life Course to Episodes?

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Alan C. Swann, Marijn Lijffijt, and Alessio Simonetti

Susceptibility to combined depressive and manic syndromes correlates strongly with arousal-related symptoms including impulsivity, anxiety and agitation. This relationship to a driven, "mixed" activation-depression state, generated by a life-long process, was described in classical times. Course of illness in mixed states includes increased episode frequency, duration, earlier onset, and association with addiction- and trauma/stress-related disorders. Mixed episodes have catecholamine and hypothalamic-pituitary-adrenocortical activity increased beyond nonmixed states of similar symptom severity. These properties resemble behavioral sensitization, where salient, survival-related stimuli (traumatic or rewarding) can generate persistently exaggerated responses with disrupted arousal and reward, with potential for suicide and other severe consequences.

Treatment

Pharmacologic Treatment of Mixed States

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Maurizio Pompili, Gustavo H. Vazquez, Alberto Forte, Debbi Ann Morrisette, and Stephen M. Stahl

Despite the relatively high prevalence of mixed symptoms and features among patients with mood disorders, the current literature supporting the specific efficacy of second-generation antipsychotics and mood stabilizers for the treatment of mixed symptoms is limited. Several studies have demonstrated that acute affective episodes with mixed symptoms or features tend to respond unsatisfactorily to treatments that are usually more effective for the management of other affective phases. There is clearly a need for clinical trials in order to determine the more adequate pharmacologic option for the treatment of individuals suffering from affective episodes with mixed features.

The Role of Electroconvulsive Therapy in the Treatment of Severe Bipolar Mixed State

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Giulio Perugi, Pierpaolo Medda, Margherita Barbuti, Martina Novi, and Beniamino Tripodi

Electroconvulsive therapy (ECT) results effective in two-thirds of the patients with severe and drug-resistant mixed states. The episode duration is the main predictor of nonresponse. This practice may increase the risk of mood destabilization and chronic complications and may decrease the chance of recovery in many patients. Compared with the burden of neurologic and metabolic side effects associated with long-term use of complex pharmacologic regimens, ECT should be considered a safe option with a very low incidence of severe adverse events and a long-term nondestabilizing effect.

Psychotherapy for Mixed Depression and Mixed Mania

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Brittany O'Brien, Delphine Lee, Alan C. Swann, Sanjay J. Mathew, and Marijn Lijffijt

Treatment guidelines for mixed states of depression or (hypo)mania focus almost exclusively on psychopharmacologic intervention without tapping into the benefits of psychotherapy. The authors highlight the complex clinical picture and illness course of mixed states, and discuss the benefit of taking a patient-centered approach to treatment incorporating techniques from a variety of evidence-based psychotherapies. A careful assessment of suicide risk as well as interventions designed specifically for anxiety are also recommended.