Indian Journal of Clinical Psychiatry
An Official Journal of **Association of Clinical Psychiatry**
(Indian Psychiatric Society- Uttar Pradesh State Branch (IPS-UPSB))

REVIEW ARTICLE

Mixed Affective Disorder: An Update

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Abstract

This review article has attempted to summarise the findings discussed in a book titled 'Mixed Affective States: Beyond Current Boundaries' published by the 'Psychiatric Clinics of North America' (PCNA) in its March 2020 edition. In the beginning, we will discuss the development of a comparatively new concept of 'mixed affective states' since the beginning of the last century. A discussion on the nosology of mixed affective disorder will be followed as per ICD-10, DSM-V and ICD-11 draft. Next, we will discuss the various clinical presentations of mixed affective disorders and the possible, probable and established aetiology of mixed affective states. Finally, we will discuss the available treatment options of mixed affective states, both, its pharmacological as well as non-pharmacological management.

ARTICLE INFO

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Dates:
Received: 01-01-2022
Accepted: 17-03-2022
Published: 26-04-2022

Keywords:
Clinical presentation, Mixed affective state, Neurobiology of mixed state, Treatment strategies of mixed states.

How to Cite:
Aich TK, Khan AH, Agrawal PK. Mixed Affective Disorder: An Update. Indian Journal of Clinical Psychiatry. 2022;2(1): 4-8.

Introduction: Development of the Concept of Mixed Affective Disorder

Importance of the concept of 'mixed affective disorder' can be gauzed by the fact that the 'Psychiatric Clinics of North America' (PCNA) dedicated one entire issue on the subject, edited by Gabriele Saini and Alan C Swann recently[1]. Present review is an attempt to give a bird's eye-view of the various issues discussed in this book, in relation to mixed affective states.

Mixed affective state has been mentioned in the literature for more than a century. It is an established fact that opposite symptoms of mood do coexist, as mentioned in available literature. Mixed affective states challenged our known knowledge regarding bipolar disorder. Mixed states are usually associated with severe course of illness and there are new ideas put forth about an affective episode. We have seen the changes in the definitions of mixed affective states over the decades, based on the various available scientific, clinical, and social parameters.[1]

Thus, there is a need to develop a broader concept of bipolar disorder. This newer concept somewhat resembles the Kraepelinian concept of 'manic-depressive illness'. Kraepelin emphasized the need to understand the life-time course of the disorder and the clinical characteristics of individual manic or depressive episodes. Kraepelin in his 8th edition text-book has mentioned about 6 subtypes of affective disorder: (i) "depressive or anxious mania, (ii) excited

depression, (iii) mania with poverty of thought, (iv) manic stupor, (v) depression with flight of ideas, and (vi) inhibited mania".[2]

Salvatore *et al.* (2002) in a paper mentioned following percentages in various sub-types of mixed manic-depressive insanity, as it was observed and mentioned by Weygandt in the past: (i) pure type of recurrent mania and depression (7.3%), (ii) circular type of manic and depressive illness (23.3%), (iii) circular illnesses with mixed states (33.3%), (iv) sustained periods of mixed episodes (14.7%), (v) agitated depression (8%), (vi) manic stupor (7.3%), and (vii) unproductive mania (6%).[3]

Nosology: What does ICD-10, DSM-V ICD-11 Draft says about Mixed Affective Disorder?

As per 'ICD-10 classification of mental and behavioural disorders and its clinical descriptions' of mixed affective states mentioned following diagnostic guidelines: Mixed mood (affective) episode has been described under the coding F38.00 and the bipolar affective disorder, with mixed current episode is coded as F31.6.[4]

It is described as "the patient has had at least one manic, hypomanic, or mixed affective episode in the past and currently exhibits either a mixture or a rapid alteration of manic, hypomanic, and depressive symptoms. A diagnosis of mixed bipolar affective disorder should be made only if the two sets of symptoms are both prominent for the greater part of the current episode of the illness, and if that episode has lasted for at least 2 weeks".[4]

In DSM-V mixed features are mentioned as a symptom specifier in depressive disorders. It mentioned that "at least 3 among a set of 7 manic/hypomanic symptoms are present nearly every day during the majority of days of a major depressive episode. These mixed symptoms are observable by others and represent a change from the person's usual behaviour".[5] Same symptom specifier criteria are also applied for Bipolar-I disorder.[5]

In the ICD-11 draft bipolar disorder is coded as 6A6, which is further divided into 'type-I and type-II disorder'. "Further sub-divisions are further proposed as the Bipolar type-I disorder, current episode mixed, without psychotic symptoms (6A60.9) and the Bipolar type-I disorder, current episode mixed, with psychotic symptoms (6A60.A) and the Bipolar type-I disorder, currently in partial remission, most recent episode mixed (6A60.D)".[6]

Though we have seen the changes, that took place in the different editions of ICDs and DSMs, present-day diagnostic criteria in these two classificatory systems still does not have the adequate clinical usefulness. Premorbid characteristics like temperament, personality, and emotional reactivity, which are of potential clinical importance, are understudied till date in patients with mixed states and yet to be included in the current classificatory systems.[7]

Mixed Affective States: Clinical Presentations

Mixed affective states are not merely an admixture of symptoms of depression and mania. It reflects the presence of both depressive as well as manic symptoms. Irrespective of polarity of illness psychomotor activation is considered to be the core feature of mixed affective state. Most important clinical presentation that follows in a mixed state is the presence of dysphoria (irritability/hostility). Initial conceptual models of mixed state, that fit the clinically useful available empirical data were provided by Kraepelin and Koukopoulos.[8]

Barroilhet and Ghaemi (2000) in their review article on the "psychopathology of mixed states" discussed in detail about available multiple factor analytical studies on pure and mixed mania, pure and mixed depression. They also discussed about various clinical and conceptual models of mixed states, presented by various authors in the past.[8]

Even in most studies of 'pure mania' patients, there was reported underlying depressive symptoms. Similarly, symptoms of depressed mood, presence of guilt and suicidal behaviour may be seen in 13-30% of pure manic patients.[8] In a factor analytic study on 50 manic patients, Shah *et al.* (2017) revealed the presence of dysphoric mania in addition to other manic factors like pure mania, hostile mania and delirious mania.[9]

A consistent and independent factor that has been present across most studies is dysphoria (irritability/hostility). "Subtypes of pure and mixed

mania that has been reported in various cluster studies are euphoric, dysphoric, depressive, and psychotic manic states".[8] Similarly, contrary to the common belief, symptoms of mania are frequently seen in depressive illness, both in unipolar depression (38–47% patients) as well as in bipolar depression (68% patients). The main underlying manic factors were noted as psychomotor activation and dysphoria.[8]

"Agitated 'unipolar depression' is a clinical entity characterised by excitement together with depressed mood during the same episode".[10] Symptoms of agitated depression include presence of dysphoric mood, psychic and/or motor agitation, labile emotion, racing thoughts, and talkativeness, etc. Identifying mixed features in depressive episodes are important, as mixed states usually lead to state of worse course of illness and poor treatment outcome.[11]

There is increasing recognition of mixed features in depressive, manic as well as in hypomanic phases in bipolar affective disorders. Mixed clinical presentation is usually associated with increased suicide risk. "Mixed states of agitated depression and dysphoric mania are associated with much higher rates of suicidal behaviour than when such factors are not present".[12]

A special challenge for the clinicians is identifying a mixed state in early-onset bipolar affective disorder. Bipolar disorder patients in paediatric and adolescent age-group have severe symptoms, and a severer course of illness.[13]

Perinatal mixed affective state is another challenge for the psychiatrists and other mental health professional to handle and manage. Least studied and least understood affective disorder is the mixed affective state that is seen during the perinatal period. Perinatal period is the most vulnerable period in a woman for the emergence of mood episodes. Lifetime prevalence rate of mixed episodes is higher in women than men. In clinical practice agitated depression is more commonly seen in such women.[14]

Mixed affective states and various addictive disorders are frequently seen to be co-occurring together. Co-occurring substance abuse and/or dependence in mixed affective states modifies its various clinical presentations. Comorbid addictive disorders in mixed affective states are usually associated with poorer clinical outcome, treatment resistance, frequent recurrence of illness and hospitalizations. There is increase susceptibility to rapid-cycling of illness, high-cost of healthcare expenditure, and high suicide risk.[15] "Increased impulsivity and affective instability seem to be the common clinical symptoms of bipolar disorder and addictive disorders, being involved in the onset of both diseases and correlating with detrimental outcome".[15]

Aetiology of Mixed Affective States

While discussing about the neurobiology of mixed mania and mixed depression, we have to discuss the available knowledge and the role of multiple biological systems involved in the process; like circadian rhythms disturbances, and defect in the hypothalamic-pituitary-adrenal axis, monoamines, interleukins and other inflammatory mediators functioning. Mixed affective states show severe patho-physiologic processes when compared with their non-mixed states. "Biological alterations suggest that hyperactivation and hyperarousal are the core pathophysiologic mechanisms involved in both mixed mania and mixed depression".[16] Affective disorders and addictive disorders share same some of the above-mentioned neurobehavioral underpinnings, with some specific "impaired Response Inhibition and Salience Attribution (iRISA) networks".[15]

Various evidences are there that physical or psychological childhood trauma may lead to the development of mixed affective states in bipolar illnesses during adolescent years and early adulthood. Such traumas during childhood are likely related to emotional hyper-reactivity and, adolescents with bipolar disorder with mixed states reported to have higher levels of emotional hyper-reactivity.[17]

Is there a temporal correlation between the lifetime course of illness in a mixed affective state with that of sensitization due to childhood trauma? In clinical presentations of mixed state there is usually a range or dimension of symptoms ranging from a state of depression to mania. These symptoms may range from anxiety, impulsivity, hyperarousal to a

state of agitation. There may be frequent recurrence of illness with increase severity in expression of psychopathology, more stressful and traumatic life events and/or presence of co-morbid addictive disorder.[18]

Treatment of Mixed Affective States

Pharmacologic Treatment: Efficacy of second-generation of antipsychotic drugs (SGAs) and mood stabilising drugs has been established for the treatment of mixed affective illnesses. In acute phase of the illness, SGAs like olanzapine particularly showed encouraging results.[19] An effective treatment in the prevention of new episodes of mixed affective disorder is sodium valproate, especially in dysphoric mania. Lithium carbonate is still considered as the treatment of choice, to prevent the polarity of illness in a mixed affective episode.[19] We need a personalised management and treatment plan in cases of agitated unipolar depression. This includes use of mood stabilizers, atypical antipsychotics (SGAs) and benzodiazepines.[10]

When and how shall we use antidepressant drugs in case of treatment of mixed affective disorder? Antidepressants should only be used along with mood stabilizer drugs or along with a SGAs with associated mood stabilising properties.[19] Antidepressant drugs, if not combined with a mood stabilizer or a SGAs, can occasionally worsen agitation, worsen severity of mixed state, and/or potentially increase suicidal risk in such patients. Thus, using SGAs and mood-stabilizer in the treatment of mixed affective states reduces the associated suicidal risk, besides improving the mooed states in such patients.[12] Treatment of mixed affective states with comorbid addictive disorders are a challenging one, because we are yet to develop an ideal pharmaceutical drug with favourable response to deal with such complex clinical entity.[15]

Electroconvulsive therapy (ECT) is also considered as an important treatment option for patients of mixed affective disorder with severe psychopathology, especially, in drug-resistant patients.[20] Since the diagnostic criteria are still not adequately defined, patients with severe mixed affective disorder may get misdiagnosed and such patients may not get the necessary referral for the required ECT. As ECT is usually considered as the last resort treatment procedure, a delay in taking a decision to use ECT may lead to a state where the chances of recovery of our patients will decrease significantly.[20]

Whether psychotherapy has a role to play in the treatment and management of mixed affective disorder? We mainly have pharmacologic interventions as the available treatment guidelines for these patients. "In individuals with major depressive disorder, psychotherapy in conjunction with psychopharmacology has treatment effects almost twice as large as compared with single intervention".[21] While choosing a psychotherapy for the mixed affective state, we should incorporate modules which would aim to reduce the risk for suicide and would reduce the associated anxiety symptoms characteristics of mixed states. A psychotherapeutic treatment approach which includes a person-centered approach is the preferred approach over following a psychotherapy manual religiously.[21]

Conclusion

This review article attempted to summarise the findings discussed in a book titled "Mixed Affective States: Beyond Current Boundaries" published by the PCNA in its March 2020 edition.[1] In the beginning, we discussed the historical development of the concept of mixed affective states[2,3] and nosology of mixed affective disorder as per ICD-10, DSM-V and ICD-11.[4-7] Next we discussed the various clinical presentations of mixed affective disorders[8-15] and the possible, probable and established aetiology of mixed affective states.[16-18] Finally, we discussed the available treatment options of mixed affective state, both pharmacological as well as non-pharmacological management.[19-21]

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