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Diagnostic and Therapeutic Considerations in Depressive Mixed State

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ABSTRACT

Although the definition of depressive mixed state, more commonly known as mixed depression, is still controversial, about one-third of major depressive episodes are held to contain mixed components. The most frequent manifestations of mixed depression are irritability, distractibility and psychomotor agitation, although these symptoms are not included in the mixed features during a major depressive episode according to the DSM-5 criteria, which is therefore unlikely to cover the full scope of mixed depression in real-world settings. Mixed depression often accompanies risky behavior including impulsive suicide attempts. The early detection and treatment of these unstable conditions is therefore necessary. Also, sufficiently sensitive and specific screening methods for depressive mixed state are needed to avoid both under- and over-diagnosis. Antidepressants should be avoided since these drugs often worsen irritability, agitation and impulsivity, and increase risky behavior. Instead, combination therapy with mood stabilizer(s) to prevent the relapse of the depressive mixed state and atypical antipsychotics for rapid stabilization in the acute phase should be considered. Because there is very little evidence for effective pharmacotherapy in mixed depression, the efficacy of various mood-stabilizing agents, either as monotherapy or in combination therapies, should be extensively examined in the future using quantitative assessments of the psychopathology of mixed depression in patients with confirmed diagnoses of mixed depression.

Keywords: mixed depression, irritability, distractibility, agitation, diagnosis, pharmacotherapy

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INTRODUCTION

Most depressive symptoms have been usually regarded as combinations of the symptoms of lowered mood, inhibited thought and decreased activity, which are commonly understood to be characteristic of "pure" depression. However, in the clinical setting, there are various combination of altered mood, thoughts and behavior in major depressive episodes [1]. In "mixed" depression, the patient's mood may be rather dysphoric, irritable, or even agitated. Similarly, thought processes may be rapid and crowded despite the dysfunctionality of the content, and the patient's behavior may appear restless, impulsive, or even risky [2]. In fact, such psychopathology, which may seem unusual for "pure" depression, is not at all uncommon in the clinical setting if clinicians are sufficiently cognizant of the existence of dynamic and externalized manifestations of "mixed" depression during a major depressive episode (Fig. 1).

The psychopathology of depressive mixed state has been regarded as an intrusion of soft bipolarity into a predominantly depressive symptomatology based on a cross-sectional nosology of the disorders. On the other hand, it may also be regarded as an asynchronous crossover of biphasic and independent cycles of mood, thoughts and behavior throughout the longitudinal course of the disorders. Since depressive mixed state

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often appears as a transient and unstable phenomenon, it is difficult for researchers to detect its essential pathophysiology and seek specific evidence for effective treatments. Nevertheless, it is highly recommended that clinicians rapidly identify such mixed psychopathologies and respond to them appropriate as quickly as possible in order to manage the risks to the patient.

This review therefore aims to comprehensively summarize previous findings associated with the epidemiology, symptomatology, diagnosis and treatment of depressive mixed state and to provide a better understanding of its psychopathology and present strategic approaches for the diagnosis and treatment of depressive mixed state.

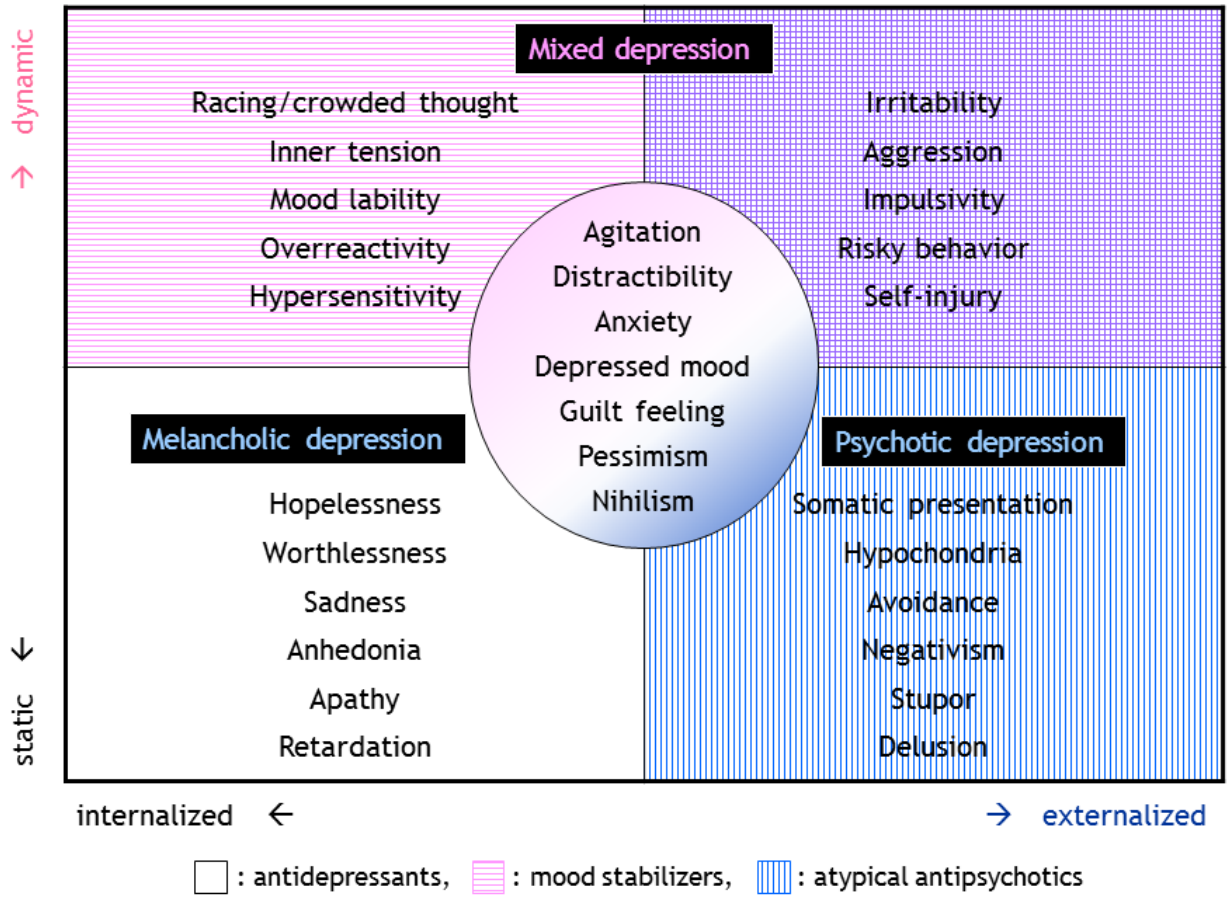

Fig. 1. Postulated depressive psychopathology structured by static/dynamic and internalized/externalized dimensions and matched treatment options. Mood stabilizers can be used for dynamic symptoms while atypical antipsychotics may be more suitable for externalized symptoms. Patients exhibiting both dynamic and externalized symptoms may need a differential diagnosis between depressive mixed state and borderline personality disorder.

EPIDEMIOLOGY OF DEPRESSIVE MIXED STATE

The prevalence of depressive mixed state differs among studies mainly due to differences in how it is defined by various criteria.

Depressive mixed state used to be very narrowly defined, according to the DSM-IV-TR, as “a mixed episode” of full manic and major depressive manifestations only for bipolar I disorder [3]. Results of the NIMH-funded Systematic Treatment Enhancement Program for Bipolar Disorder revealed that 14.8% of bipolar depressed patients exhibited full mixed episodes while 54.8% exhibited subsyndromal mania [4]. This finding suggests that most mixed states are expressed as a mild form with a few manic symptoms during a major depressive episode in bipolar patients. Therefore, there was concern that strict application of the criteria for mixed episode according to the DSM-IV-TR did not cover the full range of the mixed

states that are encountered during major depressive episodes in real-world settings.

Subsequently, the DSM-5 [5] proposed a "mixed features specifier" constituting three or more symptoms of the opposite pole during any mood episodes. It was initially expected that the new definition could encourage the wider use of mixed psychopathology diagnoses irrespective of the severity and polarity of mood episodes. However, the exclusion of irritability, distractibility and psychomotor agitation (overlapping symptoms in both manic and depressive episodes) from the manic/hypomanic symptoms by the DSM-5 (Table 1) may limit the diagnosis of major depressive episode with mixed features. The prevalence of mixed features in major depressive episodes remains unexpectedly low, ranging from only 3.2% [6] to 7.5% [7].

Although the concept of depressive mixed state is still a controversial issue, the definition of "mixed depression" by Benazzi [8-10] is a well-known practical criterion which covers a wide range of mild to moderate mixed states during major depressive episodes. It includes irritability, distractibility and psychomotor agitation as frequently observed manic/hypomanic symptoms for mixed depression [11], even though these were excluded from the DSM-5 criteria for mixed features due to nonspecific and overlapping symptoms in both manic and depressive episodes (Table 1). Benazzi defined mixed depression as a major depressive episode concurrent with three or more manic/hypomanic symptoms for one week or longer [8-10]. As a result, about one-third of major depressive episodes are supposed to contain mixed components [6], suggesting that a considerable number of patients with unipolar and bipolar depression have mixed depression. It has been also suggested that the presence of mixed depression can be regarded as a potent predictor of future bipolarity when making a differential diagnosis between major depressive disorder and bipolar disorders [12, 13], since previous studies have indicated that the prevalence of mixed depression is much higher in bipolar disorders (62.0-66.4%) than in major depressive disorder (12.8-32.5%) [6, 11].

Table 1. Hypomanic symptoms listed in Benazzi's criteria for mixed depression and DSM-5 criteria for mixed features (MFs) in major depressive episode (MDE)

	Mixed depression by Benazzi (≧ 3 symptoms)	MFs in MDE by DSM-5 (≧ 3 symptoms)
$1_{(a)}$. Elevated/expansive mood	○	○
$1_{(b)}$. Irritability	○	
2. Inflated self-esteem	○	○
3. Decreased need for sleep	○	○
4. Talkativeness	○	○
5. Flight of ideas/racing thoughts	○	○
6. Distractibility	○	
7. Increased energy/goal-oriented activity	○	○
8. Impulsive pleasurable activity with painful consequences	○	○
9. Psychomotor agitation	○	

* Hypomanic episode is defined as $1_{(a)}$ + ≧3 symptoms (2-8) or $1_{(b)}$ + ≧4 symptoms (2-8) for at least 4 days.

SYMPTOMATOLOGY OF DEPRESSIVE MIXED STATE

Nonspecific and overlapping symptoms in both manic/hypomanic and depressive episodes are predominant in depressive mixed state. Thus, among symptomatological manifestations of mixed depression, psychomotor agitation (16.1-53.5%), flight of ideas/racing thoughts (11.8-36.4%), irritability (32.6-35.9%) and distractibility (24.4-25.3%) were the most frequently observed symptoms [6, 7]. On the other hand, rather typical and non-overlapping manic/hypomanic symptoms, such as talkativeness (11.4-22.1%), risky activity (7.3-8.3%), decreased need for sleep (5.1%), inflated self-esteem (0.5-3.7%) and elevated mood (0.5%) were much less frequent in individuals with mixed depression [6, 7]. Therefore, the inclusion of irritability, distractibility and psychomotor agitation has been a topic of much discussion when considering the definition of real-world depressive mixed state and determining diagnosis sensitivity. Mainstream opinion currently holds that exploration using these nonspecific but core symptoms (irritability, distractibility and psychomotor agitation) as a probe for mixed psychopathology is more realistic for covering the full range of subjects with depressive mixed state.

Meanwhile, it has been noted that a considerable number of subjects with depressive mixed state have mild or even subthreshold manic/hypomanic symptoms. In an early study by Goldberg et al [4], the authors discovered that 54.0% of patients with bipolar I and II depressive syndromes had subsyndromal mania (only 1-3 manic symptoms, not fulfilling the DSM-IV criteria for a full mixed episode). Interestingly, these patients generally had more severe outcomes such as a younger onset of illness, more manic episodes, more rapid cycling and a higher suicide risk than patients with pure bipolar depression, despite their subthreshold mixed episodes. Malhi et al [2] also examined the symptomatology and severity of depressive mixed state (manic/hypomanic symptoms were assessed using 13 items of the Mood Disorders Questionnaire (MDQ) [14]) in patients with unipolar and bipolar depression. Although 7 symptoms or more out of the 13 items of the MDQ were originally regarded as the optimal cutoff for bipolar disorders [14], a considerable number of mood disorder patients with subsyndromal depressive mixed state had 2-6 symptoms of the MDQ [2]. The same authors also observed more frequent agitation and distractibility in patients with unipolar mixed depression and modest bipolar spectrum disorders (bipolar II disorder and bipolar disorder not otherwise specified) than in patients with non-mixed unipolar depression and bipolar I disorder [2]. These findings suggest that we should be alert to the presence of depressive mixed state among patients with unipolar and bipolar depression even though it may be mild or subthreshold when considering appropriate treatments and risk management.

Mixed psychopathology is more prevalent in patients with bipolar disorders than in patients with major depressive disorder [6, 11]. As the most prevalent 4 symptoms of mixed depression, distractibility (40.2-79.5%), flight of ideas/racing thoughts (58.7-77.7%), irritability (63.4-64.1%) and psychomotor agitation (37.4-59.8%) were very frequently observed in patients with bipolar disorders [6, 11]. Meanwhile, less distractibility (14.4-66%), flight of ideas/racing thoughts (20-56.4%), irritability (15.2-34.8%) and psychomotor agitation (17.8-48.8%) were seen in patients with major depressive disorder than in patients with bipolar disorders [6, 11]. Therefore, it is assumed that mixed psychopathology is basically a bipolarity-related manifestation of mood disorders.

Empirical or pragmatic criteria for mixed depression other than Benazzi's definition [8-10] include Sani et al.'s [15] proposed clinical definition of mixed depression (which is based on Koukopoulos's criteria for agitated depression [16]), i.e., a major depressive episode plus at least 3 out of the following 8 symptoms: 1) psychic agitation/inner tension, 2) racing or crowded thoughts, 3) irritability/unprovoked rage, 4) absence of retardation, 5) talkativeness, 6) dramatic description of suffering/frequent spells of weeping, 7) mood lability/marked reactivity and 8) early insomnia. Furthermore, in the Research-Based Diagnostic Criteria for mixed depression proposed by Perugi et al. [7], mixed depression was defined as a major depressive episode plus at least 3 out of the following 14 hypomanic symptoms for one week or longer: 1) irritable mood, 2) emotional/mood lability, 3) distractibility, 4) psychomotor agitation, 5) impulsivity, 6) aggression (verbal or physical), 7) racing thoughts, 8) more talkative/pressure to keep talking, 9) risky behavior, 10) hyperactivity, 11) increased energy, 12) euphoria, 13) grandiosity and 14) hypersexuality. These two criteria for mixed depression [7, 16] together with Benazzi's definition [8-10] share common prevalent symptoms of mixed depression (agitation, irritability, racing thoughts and distractibility/lability), and may better reflect the reality of the depressed mixed state that is usually observed in the clinical setting.

DIAGNOSTIC CONSIDERATIONS IN DEPRESSIVE MIXED STATE

It is clear that most depressive mixed states may be overlooked during major depressive episodes if the definition of mixed features in a major depressive episode presented in the DSM-5 [5], which excludes frequent symptoms like irritability, distractibility and psychomotor agitation as nonspecific overlapping symptoms, is used in the clinical setting [6]. However, the definition of mixed depression [8-10] may present another risk: the overdiagnosis of depressive mixed state. Therefore, it may be inferred that the definition of "mixed depression" according to Benazzi's criteria is realistic but too sensitive whereas the definition of "mixed features" according to the DSM-5 is specific but too ideal. Accordingly, sufficiently sensitive and specific screening methods for depressive mixed state will be needed to avoid both under- and overdiagnosis.

On the other hand, even if Benazzi's broader criteria for mixed depression are applied, there is still a considerable number of subjects with subthreshold mixed state [2, 4]. Therefore, given the clinical reality of depressive mixed state, we should be more alert to the detection of mild and nonspecific manifestations of mixed depression. The cutoff point of the criteria for mixed depression has been always a central problem. Koukopoulos's criteria for mixed depression ($\geq$ 3 out of 8 symptoms associated with mixed depression) showed fairly good specificity (86.3%) and sensitivity (76.4%) as well as a relatively high positive predictive value (86.0%) and negative predictive value (75.0%) when differentiating mixed depression from non-mixed depression [15]. However, such categorical criteria for mixed depression may essentially limit the sensitivity or specificity of the diagnosis and consequently result in false positives or false negatives. Therefore, a dimensional approach to comprehensively determine depressive psychopathology that is structured by static/dynamic and internalized/externalized dimensions (Fig. 1) may be useful for quantitative assessments of mixed psychopathology in the future.

Mixed depression has also been considered an important discriminator for bipolar diagnosis [12, 13]. However, in fact, the cutoff of $\geq$ 3 hypomanic symptoms according to Benazzi's criteria [8-10] is still too strict to cover the full range of bipolar subjects (sensitivity/specificity: 55.1%/87.2%) while a cutoff of $\geq$ 2 hypomanic symptoms improves sensitivity somewhat but worsens the specificity (88.5%/61.6%) [6]. Only from aspects of the sensitivity, mixed depression including subthreshold levels may be an excellent predictor for future bipolarity, although it needs to be kept in mind that there are many patients with unipolar depression who fulfill Benazzi's criteria for mixed depression. A better balance between sensitivity and specificity will be required in order to use mixed depression as an index for bipolarity.

THERAPEUTIC CONSIDERATIONS IN DEPRESSIVE MIXED STATE

Since mixed depression often accompanies risky behavior including impulsive suicide attempts [7, 17], early detection and urgent treatment of these unstable conditions is necessary. In fact, suicide attempters with major depressive episodes showed higher prevalence in any mixed symptoms according to the Research-Based Diagnostic Criteria (RBDC) [17]. Furthermore, there was a significant correlation between the number of lifetime suicide attempts and RBDC depressive mixed state. These findings suggest a close relationship between mixed depression and the risk of impulsive suicide attempts. It is therefore believed that patients with mixed depression need to be constantly and carefully evaluated for suicide risk and management, including inpatient therapy, depending on the severity and urgency.

Although there is unfortunately little reliable evidence or established guidelines on pharmacotherapy for mixed depression, there are three principles that are generally followed in drug therapies for mixed depression. First, antidepressants, especially as monotherapy, should be avoided in mixed depression since these drugs often worsen irritability, agitation and impulsivity, and increase risky behavior [16, 18]. Second, instead of antidepressants, mood stabilizers possessing predominantly antimanic properties, such as valproate, carbamazepine and lithium, should be primarily used in depressive mixed state, especially in relapse prevention as opposed to acute-phase therapy, whereas monotherapy with a predominantly antidepressive mood stabilizers such as lamotrigine are not generally recommended [19, 20]. Third, atypical antipsychotics, like olanzapine, quetiapine and aripiprazole, may be considered for the urgent stabilization of depressive mixed state, especially in acute-phase therapy [19-21]. Also, asenapine [22] and lurasidone [23] may also hold promise for the treatment of depressed mixed state.

There is no established rationale for the selection of mood stabilizers/atypical antipsychotics and in mono-

therapy/combination therapy in depressive mixed state. A symptomatological structure in depression based on the postulated model with static/dynamic and internalized/externalized dimensions may provide some useful information for the selection of pharmacotherapy, e.g., mood stabilizer(s) for dynamic but internalized symptoms and the combined use of mood stabilizer(s) and atypical antipsychotics for dynamic and externalized symptoms (Fig.1). However, because there is very little evidence for efficient and effective pharmacotherapy in depressive mixed state, the efficacy of monotherapy or combination therapy with various mood-stabilizing agents should be extensively examined in the future using quantitative assessments of the psychopathology of mixed depression in patients with confirmed diagnoses of mixed depression.

Although very little evidence has been obtained to date on the clinical implications of electroconvulsive therapy (ECT) in depressive mixed state, several ECT trials in severe and drug-resistant patients with bipolar mixed states have shown successful efficacy based on the treatment outcome in refractory mixed state [24, 25]. At the end of the ECT course, 41.6% responded to ECT, and 30.5% were in remission [25]. In particular, the subgroup with agitated-irritable mixed depression showed the highest remission rate after ECT than any of the other subgroups with psychotic-retarded mixed depression, psychotic-mixed mania and anxious-irritable-psychotic mixed mania [24]. ECT therefore shows promise as a treatment option for treatment-resistant cases with depressed mixed state.

CONCLUSIONS

The most frequent manifestations of depressive mixed state are irritability, distractibility and agitation, which are covered by Benazzi's definition of mixed depression but not by the DSM-5 criteria for mixed features. Therefore, use of the former criteria is more realistic for discovering mild and nonspecific mixed psychopathology with a greater level of sensitivity in the clinical setting. However, sufficiently sensitive and specific screening methods for depressive mixed state are still needed to avoid both under- and overdiagnosis of mixed depression.

Since mixed depression often accompanies risky behavior, including impulsive suicide attempts, early detection and treatment of these unstable conditions are necessary. Antidepressants should be avoided since these drugs often worsen irritability, agitation and impulsivity, and increase risky behavior. Instead, combination therapies with mood stabilizer(s) for relapse prevention in depressive mixed state and atypical neuroleptics for urgent stabilization in acute-phase therapy should be considered.

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CONFLICTS OF INTEREST

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