



GUEST EDITORIAL

Treatment approaches for major depressive disorder with mixed features

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The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) has introduced changes in the classification and diagnosis of mood disorders, including the introduction of a "mixed features specifier" (1). The DSM-5's approach to the mixed features specifier is particularly relevant in the context of mood disorders such as major depressive disorder (MDD) and bipolar disorder (BD).

DSM-5 recognizes that individuals with major depressive episodes may experience features typically associated with hypomania or mania, even if they do not meet the threshold for a diagnosis of BD, thus occurring within the context of MDD. The presence of mixed features in major depressive episodes (MDE) in both BD and MDD implies the coexistence of depressive symptoms with multiple manic or hypomanic symptoms. This feature is particularly important in identifying individuals who may be at higher risk for BD or who have a more complex mood disorder presentation.

In patients with BD, DSM-5 allows the specifier to be applied not only to major depressive episodes but also to manic and hypomanic episodes. This recognition reflects the understanding that individuals with bipolar disorder may experience a mixture of depressive and manic symptoms, adding complexity to the diagnostic picture.

Symptoms considered for the mixed features specifier include elevated or expansive mood, inflated self-esteem, increased talkativeness, racing thoughts, distractibility, increased goal-directed activity or psychomotor agitation, and engagement in activities with a high potential for painful consequences.

The inclusion of mixed features in the diagnostic criteria allows for a more comprehensive understanding of mood disorders, which may influence treatment decisions. Indeed, individuals with mixed features often require different treatment approaches than those with purely depressive or manic symptoms. DSM-5 recognizes that individuals may not always meet the full criteria for a major depressive, manic, or hypomanic episode but may still exhibit subthreshold symptoms. The inclusion of the mixed features specifier acknowledges the importance of identifying and addressing these subthreshold symptoms.

Mixed features pose significant challenges in the treatment of both BD and MDD. Historically, however, they have been less studied in MDD because, prior to DSM-5, mixed features (in the context of what was called a mixed episode) were recognized only in patients with BD. In fact, diagnosing mixed features in patients with MDD was not possible. This editorial discusses the prevalence and clinical implications of mixed features in affective disorders, with special emphasis on mixed features in the context of MDD, aiming to encourage more research and attention to the need for tailored pharmacological interventions in MDD patients presenting with such features.

Prevalence and Clinical Implications

Mixed features are commonly observed in both BD and MDD, with reported prevalence rates ranging from 46.4% to 73.1% in BD patients and 7.6% to 48.7% in MDD patients (2). These features are associated

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with a more severe clinical course, including earlier onset, longer time to remission, decreased treatment response, increased relapse, and increased risk of suicide (2-4). Despite its clinical importance, there is a lack of specific pharmacological treatments approved for MDD with mixed features specifier (MFS).

Proposed Treatment Approach

My clinical and research group advocates a targeted approach to the treatment of MDD patients with concomitant mixed features and/or symptoms of 'activation'. Our conceptualization of 'activation' aligns, in part, with symptoms commonly associated with mixed features, encompassing psychomotor agitation, irritability, impulse dyscontrol, restlessness, heightened suicide risk, racing thoughts, increased energy, reduced need for sleep, or severe insomnia. We believe that when a patient with depression displays one or more of these 'activation' and/or mixed symptoms, these manifestations should be the primary focal point of any initial pharmacological intervention. Consequently, clinicians are advised to prescribe a mood stabilizer such as lithium or valproate (for non-pregnant or non-childbearing-age patients) and/or a 'calming' antipsychotic like quetiapine before considering the use of antidepressants.

It is noteworthy that the use of mood stabilizers lacks approval for any phase of major depressive disorder (MDD). Even antipsychotics (including aripiprazole, brexpiprazole, cariprazine, and quetiapine in the United States, and quetiapine in the European Union) are indicated in MDD only as adjunctive treatments for patients with an inadequate response to antidepressant monotherapy. A comprehensive review by Shim et al. (2018) (2) revealed a predominant focus on antipsychotic drugs such as lurasidone and ziprasidone in studies of MDD with mixed features, with favorable outcomes observed for lurasidone. Despite a weaker level of evidence for ziprasidone, other antipsychotics, which we find more 'calming' and efficacious in MDD with activation and/or mixed features, lack sufficient study in MDD patient samples but are recognized for their efficacy in mixed bipolar episodes (5).

Once the activation symptoms have subsided, the introduction of an antidepressant is usually appropriate. Preferences typically lean toward highly selective serotonin transporter antidepressants like citalopram, as they are less likely to elevate

norepinephrine or dopamine levels. Alternatively, antidepressants effective for insomnia and psychomotor activation, such as trazodone (6), may be prescribed.

In our clinical practice, several other strategies are employed: lithium is preferentially prescribed for patients considered at suicide risk; intravenous valproate, particularly when combined with oral or parenteral trazodone or benzodiazepines, is favored for non-pregnant patients with mild or moderate agitation. Quetiapine, or a non-sedating antipsychotic combined with a benzodiazepine, is preferred for patients experiencing agitation and insomnia. In a double-blind, randomized, placebo-controlled trial involving patients with major depressive disorder and subthreshold manic symptoms, lurasidone (40-60 mg/day) proved effective and well-tolerated. Notably, during the trial, lorazepam, temazepam, or zolpidem (or their equivalents) were permitted for anxiety or insomnia as needed during screening and weeks 1-3. Anticholinergic agents, propranolol, or amantadine were also allowed as needed for movement disorders (7). Intramuscular promazine or intramuscular/intravenous lorazepam is preferred for patients with severe agitation.

Over the years, our clinical observations consistently indicate that patients with MDD and mixed features benefit from initial treatment with a mood stabilizer and/or an antipsychotic, even if their symptoms do not reach the threshold for mixed features specifier (MFS). Although many of the medications mentioned lack official approval for MDD or MDD with mixed features, their mechanisms of action suggest efficacy in addressing mood disturbances (8).

However, uncertainty lingers regarding whether MDD patients who have never met the threshold for bipolar disorder should continue maintenance treatment with a mood stabilizer and/or an antipsychotic, as the balance between risks and benefits has not been adequately studied in this patient cohort. Consequently, we usually consider discontinuing these medications during the maintenance phase on an individual basis. The approach varies based on specific symptoms during the acute phase, the choice of mood stabilizer/antipsychotic, and the risk/benefit ratio for each patient. For example, in patients with bipolar disorder, suicidal acts are more frequent in the first year after discontinuation than before the start of lithium treatment (9). Therefore, discontinuation of lithium is

rarely considered in patients with significant suicide risk, including those with MDD. Even for patients experiencing significant side effects, there is a preference for considering the continuation of a minimal lithium dose (e.g., 150 mg) rather than complete cessation, as this may still reduce the risk of a rebound of suicidal acts based on our clinical experience.

More schematically, the proposed strategies include:

1. Initial treatment with antimanic agents:

Patients should be initially treated with antimanic agents such as mood stabilizers (e.g., lithium or valproate) and/or sedating antipsychotics (e.g., quetiapine).

2. Consideration of antidepressant therapy:

Adjunctive antidepressant treatments, especially those that do not increase norepinephrine or dopamine levels (e.g., trazodone or citalopram), should be considered once agitation symptoms are controlled.

Focus on Activation Symptoms

We suggest focusing on symptoms of "activation," including psychomotor agitation, irritability, restlessness, impulse dyscontrol, high suicide risk, racing thoughts, increased energy, severe insomnia, or decreased need for sleep. These symptoms should be the primary target of initial pharmacologic intervention.

Choice of Medications

The use of mood stabilizers and antipsychotics in MDD has not been formally approved, but our clinical experience supports their efficacy in treating mood disorders (8). We prefer highly selective serotonin transporter antidepressants, such as citalopram, or those effective for insomnia and psychomotor activation, such as trazodone.

Tailored Approaches for Specific Symptoms

We tailor our treatment approach based on specific symptoms in the acute phase, the choice of mood stabilizer/antipsychotic, and the risk-benefit ratio for each patient.

Discontinuation of Antimanic Agents

Once the acute episode has resolved, and considering that MDD patients with mixed features did not meet the full criteria for BD, discontinuation of antimanic agents should be considered, with careful consideration of individual patient factors.

Clinical Observations, Future Research and Conclusion

Recognizing the limited evidence for the proposed strategies, we emphasize the importance of future research to evaluate the appropriateness of these clinical interventions scientifically. We encourage collaboration among researchers to conduct well-designed, prospective, randomized trials for a more evidence-based approach to the treatment of MDD with mixed features.

This editorial proposes a nuanced approach to the treatment of MDD with mixed features, emphasizing individualized pharmacological interventions targeting activation symptoms. While acknowledging current gaps in clinical evidence, we call for concerted research efforts to validate and refine these strategies to improve patient outcomes.

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