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Review

Exploring treatment strategies for mood stabilization in patients with major depressive disorder and mixed features

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SUMMARY

We discuss strategies for mood stabilization in patients with major depressive disorder (MDD) and mixed features, challenging traditional paradigms and calling for a reevaluation of current diagnostic classifications. The DSM-5 "mixed features specifier" applies to several mood disorders, including MDD. In patients with MDD, this specifier blurs the traditional distinctions between depression and mania by introducing criteria that include symptoms such as elevated, expansive mood, inflated self-esteem, increased talkativeness, flight of ideas, increased energy, involvement in activities with potentially painful consequences, and decreased need for sleep. According to the DSM, when 3 of the above 7 symptoms are present during a major depressive episode, the episode may be characterized by the specifier "with mixed features". Despite the relatively high prevalence of mixed features in patients with MDD, no specific pharmacological treatments have been approved for these cases. We propose a treatment approach that includes: 1) initiating treatment with an antimanic agent (e.g., a mood stabilizer or a new-generation antipsychotic); 2) considering adjunctive low-dose serotonergic antidepressants; and then 3) considering discontinuation of the antimanic agent once the acute episode has resolved. We emphasize the lack of adequate studies of maintenance treatment with mood stabilizers and antipsychotics in patients with MDD and mixed features and the need for further research to improve our mood stabilization strategies for these patients.

Key words: mixed, depression, depressive, treatment, bipolar, disorder

Introduction

The contemporary framework for classifying and diagnosing psychiatric disorders traces its roots to Emil Kraepelin's differentiation between dementia praecox (schizophrenia) and manic-depressive insanity (bipolar and unipolar disorders). Over time, both the International Classification of Diseases (ICD) and the Diagnostic and Statistical Manual of Mental Disorders (DSM) have included distinct sections for psychotic disorders and mood disorders and have separated between bipolar and unipolar (major depressive) disorder. However, this traditional dichotomy has been criticized [1-3], and genetic, neurobiological, and pharmacological data suggest that the boundaries between certain forms of bipolar disorder and schizophrenia, and between other forms of bipolar disorder and major depressive disorder (MDD), may be more blurred than originally thought [1-6]. The conceptual boundaries between bipolar and unipolar disorders have been repeatedly challenged as theoretical studies have underscored the limitations of categorically diagnosing these disorders, while epidemiologic and genetic studies further highlighted the complexity of these diseases and urged a reevaluation of traditional classifications [3,4,7-9].

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5, American Psychiatric Association, 2022) [10] introduced a mood episode specifier called the "mixed features specifier" that applies to several mood disorders, including major depressive disorder (MDD), bipolar disorder, and persistent depressive disorder.

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The criteria for this specifier include the presence of both depressive and manic symptoms and apply not only to patients with bipolar disorder but also to patients with MDD, blurring the traditional distinctions between unipolar and bipolar mood disorders.

Mixed features specifier criteria

Mixed features are highly prevalent in patients with bipolar (BD) and unipolar (MDD) disorders, with reported occurrences in depressive episodes ranging from 46.4% to 73.1% in individuals with BD and from 7.6% to 48.7% in individuals with MDD [11].

DSM-5 provides criteria for major depressive, manic, and hypomanic episodes with mixed features. Mixed features are common in both bipolar disorder and major depressive disorder, with significant implications for the clinical course and outcomes of affected individuals.

For major depressive episodes (MDE) with mixed features, the criteria for the mixed features specifier are met when a patient with a major depressive episode also reports 3 of the following symptoms:

1. elevated, expansive mood;
2. inflated self-esteem or grandiosity;
3. more talkativeness than usual or pressure to talk more;
4. flight of ideas or subjective feeling that thoughts are racing;
5. increased energy or goal directed activity;
6. increased or excessive involvement in activities with a high potential for painful consequences;
7. decreased need for sleep.

Clinical implications

Mood stabilization has been a central focus of mental health research and treatment, which has traditionally relied on pharmacological interventions such as mood stabilizers, atypical antipsychotics, and adjunctive antidepressants.

The presence of mixed features is associated with a more severe clinical course, characterized by earlier onset, longer time to remission, inadequate response to treatment, increased recurrence, and increased risk of suicide, compared with affective episodes without mixed features [11-13].

Proposed treatment approach

In our view, the treatment of patients with major depressive disorder and mixed features, or any "activation" symptom, requires a nuanced approach:

1. Initiate treatment with an antimanic agent: Use a mood stabilizer and/or antipsychotic to stabilize mood and manage symptoms [14].
4. Consider the use of a benzodiazepine in the presence of anxiety and insomnia [15].
2. If symptoms of anxiety or depression are predominant, consider adjunctive treatment with a low dose of a serotonergic antidepressant: Administer antidepressants at doses that do not increase norepinephrine or dopamine levels to avoid worsening symptoms. Some antidepressants (e.g., citalopram) have a low affinity for the norepinephrine and dopamine transporter and therefore do not increase these neurotransmitters at high doses. Other antidepressants (e.g., venlafaxine or sertraline) increase norepinephrine or dopamine when used at high doses, and therefore should be used at low doses until symptoms of restlessness, activation, and severe anxiety have subsided [14,16].
3. Consider discontinuing the antimanic agent once the acute episode has resolved, evaluate the need for continued treatment, and possibly discontinue [14].

Our definition of "activation" includes symptoms such as psychomotor agitation, irritability, restlessness, impulse dyscontrol, high suicide risk, racing thoughts, increased energy, severe insomnia, or reduced need for sleep. We argue that if these symptoms are present, they should be the primary focus of pharmacologic intervention [14]. Therefore, the prescription of a mood stabilizer and/or sedating antipsychotic (e.g., quetiapine) is recommended prior to the introduction of an antidepressant, and the judicious use of an antidepressant may be considered after the symptoms of activation have subsided [14].

Specific interventions based on symptomatology

1. Prescribe lithium to patients at risk for suicide [17].
2. Prefer valproate for nonpregnant patients with mild agitation [14].
3. Give preference to quetiapine or a non-sedating antipsychotic combined with a benzodiazepine for patients with agitation and insomnia [14].
4. Consider intramuscular promazine or intramuscular/intravenous lorazepam for severe agitation [14].

Although many of the above medications are not specifically approved for MDD or MDD with mixed features, their mechanism of action supports efficacy for mood disorders [18]. While patients with MDD and mixed features often benefit from initial treatment with a mood stabilizer and/or antipsychotic during the acute treatment phase, the decision to continue maintenance treatment in the long term requires individualized assessment due to the lack of adequate trials and the potential unbalance between the potential risks (side effects) and benefits (prevention of new episodes with mixed features). If

a discontinuation is considered, the decision should be based on issues such as the specific symptoms present during the acute phase, the medication being used, and the risk-benefit ratio for the patient [14]. Particular caution should be exercise when lithium is discontinued, given the risk of rebound symptoms such as suicidality [17,19]. In our practice, we rarely discontinue lithium in patients with a history of suicidal thoughts or suicidal acts. If a higher dose is not tolerated, we believe that even 150 mg/die are better than nothing.

Conclusions

The presence of mixed features in MDD warrants consideration of antimanic agents, mood stabilizers, and antipsychotics. Specific interventions can be chosen based on symptomatology, taking into account factors such as suicide risk, agitation, and insomnia. Once the acute episode has remitted, the possibility of discontinuing the mood stabilizer or antipsychotic should be considered. Further research is needed to scientifically validate the appropriateness of the clinical strategies described.

Conflict of interest statement

Alessandro Cuomo is /has been a consultant and/or a speaker and/or has received research grants from Angelini, Boheringer Ingelheim, Lundbeck, Janssen, Mylan, Otsuka, Pfizer, Recordati, Viatris.
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Authors' contributions

Both authors contributed to the conceptualization and drafting of this paper.

Ethical consideration

Not applicable.

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