Mixed Signals on Mixed Features: Clearing up Confusion in Patients with Major Depressive Disorder

Clinical Compendium

- Major Depressive Disorder (MDD) has a lifetime prevalence of 15-20%, with most patients experiencing moderate or severe symptoms.[1]
- Approximately 15-33% of patients with MDD have mixed features.[1-5]
- The term "mixed features" was introduced in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). This is a change in terminology from previous versions of the DSM. In the DSM-IV, "mixed episodes" could only be diagnosed in a patient with bipolar disorder, whereas the "mixed features" specifier can be applied to patients with bipolar or unipolar depression.[6]
- The DSM-5 specifies that at least THREE manic or hypomanic symptoms must be present nearly every day during the majority of days of a major depressive episode for a patient to be classified as having MDD with mixed features.[6] These symptoms include:
  - Elevated or expansive mood
  - Talkative, pressured speech
  - Increased energy or goal-directed activity
  - Decreased need for sleep
  - Grandiosity or elevated self-esteem
  - Flight of ideas or racing thoughts
  - Risky behaviors
- Patients with mixed features may respond poorly to antidepressants, generally have more severe and more frequent episodes of depression, and are at a greater risk for suicide, hospitalization, and functional disability than patients without mixed features.[6-11]
- Potential "red flags" for mixed features include symptoms of irritability, distractibility and agitation.[12,13]
- Screening tools such as the Mood Disorders Questionnaire (MDQ) and the Bipolar Depression Rating Scale (BDRS), which screen for manic/hypomanic symptoms, may aid clinicians in detecting mixed features in their patients with MDD.[3,14]
- Between 13-20% of patients with MDD with mixed features will go on to be diagnosed with bipolar disorder.[14] Therefore ongoing monitoring for the presence of manic/hypomanic symptoms is important. The Clinically Useful Depression Outcome Scale-Mixed (CUDOS-M) assesses for the presence of current hypomanic symptoms.[14,15]
- There is currently minimal evidence for treatment for MDD with mixed features. Due to the poor response to antidepressants, augmentation with a second-generation antipsychotic (SGA) or mood stabilizer such as lithium may be preferred.[16]
- Some experts recommend avoiding the use of antidepressants in favor of monotherapy with an SGA such as lurasidone, asenapine, quetiapine, aripiprazole or ziprasidone first-line.[14] Lurasidone and ziprasidone are specifically recommended in the Canadian Network for Mood and Anxiety Treatment (CANMAT) guidelines as they have been studied in placebo-controlled trials in patients with mixed features.[17]
- Another concern with using antidepressants in patients with mixed features is a "switch" to mania/hypomania. Tricyclic antidepressants (TCAs) and serotonin norepinephrine reuptake inhibitors (SNRIs) may carry the highest risk of exacerbating manic/hypomanic symptoms, while bupropion and selective serotonin reuptake inhibitors (SSRIs) may have a lower risk of affective switch.[14]

	CANMAT[17]	Expert Consensus Guidelines[14] (Stahl et al.)	Florida Medicaid 2019-2020[16]
First-line	Lurasidone	Lurasidone, asenapine, quetiapine, aripiprazole, ziprasidone	Antidepressant +/- SGA or mood stabilizer
Second-line	Ziprasidone	Lamotrigine, valproate, lithium, cariprazine, olanzapine or combination	Lurasidone +/- antidepressant
Third-line		Carbamazepine, antidepressant + (lithium, lamotrigine, valproate or SGA)	Alternate adjunctive SGA, lithium or lamotrigine, TCA, monoamine oxidase inhibitor (MAOI), first generation antipsychotic, electroconvulsive therapy, transcranial magnetic stimulation
Not recommended		Antidepressant monotherapy	

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