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CME Review Article

A Pragmatic Approach to the Diagnosis and Treatment of Mixed Features in Adults with Mood Disorders

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CME REVIEW ARTICLE

A pragmatic approach to the diagnosis and treatment of mixed features in adults with mood disorders

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Mixed features specifier (MFS) is a new nosological entity defined and operationalized in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), 5th Edition. The impetus to introduce the MFS and supplant mixed states was protean, including the lack of ecological validity, high rates of misdiagnosis, and guideline discordant treatment for mixed states. Mixed features specifier identifies a phenotype in psychiatry with greater illness burden, as evidenced by earlier age at onset, higher episode frequency and chronicity, psychiatric and medical comorbidity, suicidality, and suboptimal response to conventional antidepressants. Mixed features in psychiatry have historical, conceptual, and nosological relevance; MFS according to DSM-5, is inherently neo-Kraepelinian insofar as individuals with either Major Depressive Disorder (MDD) or Bipolar Disorder (BD) may be affected by MFS. Clinicians are encouraged to screen all patients presenting with a major depressive episode (or hypomanic episode) for MFS. Although "overlapping symptoms" were excluded from the diagnostic criteria (eg, agitation, anxiety, irritability, insomnia), clinicians are encouraged to probe for these nonspecific symptoms as a possible proxy of co-existing MFS. In addition to conventional antidepressants, second generation antipsychotics and/or conventional mood stabilizers (eg, lithium) may be considered as first-line therapies for individuals with a depressive episode as part of MDD or BD with mixed features.

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Key words: Bipolar disorder, bipolar spectrum, depression spectrum, major depressive disorder, mixed features, mixed states.

Introduction

Mixed features are commonly encountered in clinical practice and represent a primary therapeutic target.[1] Misdiagnosis in psychiatry, notably in mood disorders, continues to be a disquieting and modifiable deficiency.[2] Available evidence indicates that individuals exhibiting mixed features are highly likely to be misdiagnosed and, consequently, inappropriately treated. Individuals experiencing mixed features are differentially affected by the orthogonal aspects of suicidality (eg, suicidal ideation, suicide attempts), underscoring the urgency of accurate and timely diagnoses.[3]

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The *Diagnostic and Statistical Manual of Mental Disorders* (DSM), 5th Edition has introduced the new nosological entity, mixed features specifier (MFS).[4] The introduction of MFS supplants the previous diagnostic entity–mixed states–and conceptually is aligned with the dimensional approach as a framework for mood disorders. The authors of the DSM, Fifth Edition (DSM-5) have supported the decision to introduce MFS based on convergent and highly replicated findings across countries and continents that mixed features are "agnostic" and are not pathognomonic of bipolar disorder (BD).[5–9] The impetus to replace mixed states with MFS was based on recognition of the insufficient ecological validity of mixed states, the absence of a codifiable diagnostic entity for a major depressive episode (MDE) with MFS, the suboptimal detection and diagnosis rates in clinical practice, the risk of suicidality attendant to mixed features, and the high rate of inappropriate treatment for this phenotype.

The objective of this article is to provide a pragmatic approach to diagnosing mixed features along the mood disorder spectrum and to provide guidance on the safe

and appropriate treatment avenues for individuals presenting to clinical practice experiencing mixed features. The absence of a large, controlled, and replicated evidentiary base is a major limitation to decision support; notwithstanding, guiding principles, pragmatism, and the recent introduction of the Florida Best Practice Psychotherapeutic Medication Guidelines for adults with MDE and MFS provide important information for practitioners providing care for individuals with such phenomena.[10]

History

Mixed features in psychiatry have been described since antiquity with the writings of Hippocrates and Aretaeus of Cappadocia. Throughout the late eighteenth to the early twentieth century, the descriptive literature was augmented by many emissaries, including but not limited to Heinroth, Falret, Kahlbaum, Weygandt, and Kraepelin.[11] The dominant model of much of the twentieth century, prior to the introduction of DSM, First Edition (DSM-I) in 1952 up until DSM, Third Edition (DSM-III) in 1980, was the "Kraepelinian" model. The Kraepelinian model differentiated "manic depression" illness from "dementia praecox" on the basis of deterioration in function (ie, dementia). Kraepelin proposed that individuals with disorders other than dementia praecox could be categorized along 3 intersecting dimensions, ie, disturbance in mood, thought, and volition (MTV). Kraepelin proposed that if all aspects of MTV were elevated, the individual was manic. Conversely, when all aspects of MTV were reduced, the individual was in melancholic depression. Mixed states represented a calculus of various permutations of MTV. It was noteworthy that Kraepelin, and his student Weygandt, had noted that mixed patients represented the majority of patients seen in the inpatient units encountered at the time.[12]

The introduction of DSM-III in 1980 atomized the dimensional concept of manic depression into major depressive disorder (MDD) and BD. Subsequent iterations of the DSM [ie, Third Edition, Revised (DSM-III-R) in 1987, Fourth Edition (DSM-IV) in 1994, and Fourth Edition, Text Revision (DSM-IV-TR) in 2000] perpetuated the notion that hypomanic symptoms were prima facie evidence of BD. This consequence was expected, insofar as MDD was delimited to the appearance of 1 or more MDE(s) and no prior history of hypo/mania. The essential feature of hypo/manic symptoms is elevation of thought processes, mood, and activity. The notion that an adult with MDD could also be "elevated" seemed tacitly oxymoronic. Notwithstanding, detailed international phenomenological studies provided convergent and compelling evidence that many adults with "mood disorders" experience subsyndromal hypomanic symptoms, but never declare full hypomania or mania.

During the past 2 decades, it is amply documented that high rates of misdiagnosis occur in mood disorders. Toward the aim of timely and accurate diagnosis, it is critical that the diagnostic manual have optimal ecological validity (ie, the diagnostic criteria reflect the real-world presentation). In addition, most adults with a manic episode do not experience contemporaneous syndromal MDE, and many adults with either MDD or BD experience an MDE with subsyndromal hypomanic symptoms. In other words, most adults experiencing a "mixed state" were in fact experiencing a manic episode with mixed features, and conversely, many adults experiencing an MDE had mixed features, rather than a full blown depressive mixed state. Also accumulating were data indicating that many individuals with mixed features were receiving treatments that were discordant with both regulatory approvals and evidence-based treatment guidelines. The consequence was that many individuals had insufficient outcomes, and in some cases, intensification and/or engendering of psychopathology (eg, emergence of hypomanic symptoms). Moreover, concerns that "activation syndrome" associated with antidepressants may in some cases represent a forme fruste of BD, rather than an inherent statement of iatrogenic suicidality, provided further impetus to rethink the diagnostic criteria.[13]

Diagnoses

The diagnoses of MDD and BD in DSM-5 have not changed substantially from the previous iterations. Depressive disorders were disaggregated from the BDs, the latter of which were described in a separate and dedicated chapter. Essential to the diagnostic criteria of MDD is the occurrence of an MDE, while the diagnostic criteria of BD-I and BD-II require the presence of a manic and hypomanic episode, respectively. An important edit to the diagnostic criteria of a manic episode was the requirement for increase in activity or energy, along with disturbance in mood, as an essential criterion item.

The MFS was defined as the presence of 3 or more "opposite polarity symptoms" during an MDE or hypo/manic episode, respectively. The decision to have 3 symptoms as the minimum threshold was based on validation data indicating that a threshold of 3 or more hypomanic symptoms provided the greatest degree of differentiation between mood disorders.[14] Toward the aim of avoiding redundant and nonspecific symptom counting, the authors of the DSM-5 proposed that only non-overlapping symptoms could be included in the MFS criteria. For example, insomnia, indecision, distractibility, irritability, and agitation, all of which are encountered during both MDE and hypo/manic episode, could not be included in the MFS criteria. The DSM-5 authors took a specific approach at the expense of "sensitivity."

Clinical experience coheres with published evidence that many of the overlapping symptoms are some of the most commonly encountered features in individuals experiencing mixed phenomena (eg, agitation).[15] A valid indictment against the DSM-5 criteria is that the specific approach may result in a higher level of false negatives than would be acceptable. This indictment, however, needs to be countered with the valid concern of overdiagnosing (ie, false positives) mixed features.

Tacit to the DSM-5 conceptualization is the neo-Kraepelinian foundation. Clinicians no longer need to agonize whether hypomanic symptoms denote MDD or BD. Indeed, comprehensive clinical assessment and arrival at an accurate diagnosis is sine que non for appropriate treatment selection and sequencing. Notwithstanding, many individuals along the mood disorders spectrum are "orphaned" and are not discretely MDD or BD. The DSM-5 provides MFS as a codable diagnostic entity, which instantiates this common phenotype and provides rationale for its direct treatment. Results from the International Mood Disorders Collaborative Project (IMDCP) indicate that approximately 25% and 35% of adults with MDD and BD-I/II, respectively, presenting to a university-based mood disorders program with symptoms commensurate with an MDE meet the DSM-5 criteria for MFS.[16,17] It was additionally reported that this group was more likely to have greater illness burden, select comorbidities (eg, anxiety disorders), and greater functional impairment. Results from the IMDCP were replicated and extended by investigators from the Stanley Foundation Bipolar Network (SFBN), who reported that among adults with BD, subsyndromal hypomanic symptoms were common during an MDE (ie, up to 65%) and differentially affected women with BD.[17]

Clinicians are encouraged to probe for the presence, quantity, and severity of hypomanic symptoms in any patient presenting with symptoms of an MDE. Conversely, in any patient presenting with a hypomanic episode, the occurrence of subsyndromal MDE symptoms should be sought. A pragmatic approach would be to systematically ask patients about each of the items within the polythetical criteria lists for MDE and hypo/manic episodes, respectively. Semistructured diagnostic interviews (eg, M.I.N.I.) are standard approaches to reliably establishing a diagnosis in the research setting. Most busy practitioners, however, would be neither familiar with and/or have sufficient time availability for the incorporation of semistructured instruments in busy clinical practice. A recently published screening tool–the Clinically Useful Depression Outcome Scale (CUDOS)–has been published and has established sufficient psychometric properties for identifying DSM-5–defined MFS in an individual presenting with an MDE.[18]

Treatment

Notwithstanding the U.S. Food and Drug Administration (FDA) approval of an assortment of mechanistically dissimilar agents and modalities of treatment, no intervention is currently FDA-approved specifically for MFS. Moreover, MFS has not been rigorously studied with sufficient randomized, double-blind, placebo-controlled trials. Available evidence suggests that conventional antidepressants prescribed for an MDE with MFS provide a less reliable therapeutic outcome, higher rates of non-remission, and intolerability.[19] Prospective data evaluating the course of illness in individuals experiencing MFS indicate that MFS has a much more pernicious illness trajectory (eg, earlier age at onset, greater episode frequency, higher rates of comorbidity and suicidality). Prescription data indicate that a significant percentage of individuals experiencing an MDE with MFS are treated with antipsychotic agents (first- and second-generations), as well as traditional mood stabilizers (eg, lithium).[13,20]

A single placebo-controlled trial compared treatment outcomes in adults experiencing an MDE with subthreshold hypomanic symptoms as part of MDD or BD-II. The second-generation antipsychotic ziprasidone was the primary intervention in this study.[21] Results indicated that ziprasidone significantly reduced overall depressive symptoms without exacerbating, or engendering, hypomanic symptomatology. The only controlled trial that sought to determine whether a pharmacological agent was efficacious in individuals with MDD with MFS has recently been published.[22] More specifically, adults (age 18–75) experiencing a moderate to severe MDE [ie, Montgomery–Åsberg Depression Scale (MADRS) $\geq$ 26] exhibited significantly greater improvement with lurasidone when compared to placebo treatment during a 6-week study. Similar to the foregoing ziprasidone study, hypomanic symptom intensification or engendering was not observed.

In 2015, multiple stakeholders assembled and participated in an iterative process resulting in the Florida Best Practice Psychotherapeutic Medication Guidelines (FBPPMG) for Adults with mood disorders.[10] The FBPPMG is the first guideline to provide decision support for MDD with mixed features (RSM is a contributor FBPPMG). The need to balance evidence with pragmatism was a guiding principle throughout the process, and despite recognition of the paucity of sufficient evidence to inform the guideline, a consensus was arrived at as to what would be safe, well tolerated, and possibly effective. Critical to this guideline is the recommendation to consider either a second-generation antipsychotic (with low metabolic/tolerability concerns) or a mood stabilizing agent (eg, lithium) as a first-line treatment in individuals

presenting with MDD and MFS. Lithium can be conceptualized as an initial adjunctive therapy to a conventional antidepressive or as an alternative monotherapy to antidepressants. The use of antidepressants is not proscribed, but is considered with caution for iatrogenic intensification of symptomatology and/or emergence of suicidality.

A significant percentage of individuals with MDE and MFS also present with complaints of insomnia, cognitive impairment, anxiety, irritability, and agitation.[15] As mentioned earlier, the foregoing symptoms are not part of the formal definition of MFS, yet they are highly prevalent and distressing to patients, inviting the need for evaluation and direct treatment. Guiding principles are to manage contributing/aggravating factors (eg, abnormal social rhythms) and to rule out other concurrent conditions (eg, substance use disorders). Nonpharmacological interventions [eg, cognitive behavioral therapy-insomnia (CBT-i)] are recommended as possible first-line treatments for insomnia, as well as other cognitive/mindfulness-based approaches for anxiety, dysphoria, and affect dysregulation. Pharmacological approaches are often required to directly mitigate disturbances in irritability and agitation. Reasonable choices include atypical antipsychotics, mood stabilizing agents, and, in some cases, judicious use of benzodiazepine therapy. It is often the case that individuals with MFS are diagnosed (appropriately or inappropriately) with attention deficit hyperactivity disorder, reflecting the common occurrence of cognitive dysfunction (eg, distractibility). Guiding principles to managing cognitive dysfunction in mood disorders are reviewed elsewhere, but begin with prevention, including but not limited to, discontinuing offending agents (eg, benzodiazepines), management of comorbidity (eg, cannabis misuse, obesity), and prevention of episode frequency.[23] Psychostimulants, as well as agents with stimulant-like properties, may have a role in treating select individuals with mood disorders, but are not recommended for persons with MFS.[24]

Conclusion

Clinicians are encouraged to provide detailed inquiry for hypomanic symptoms in any patient presenting with an MDE. Although "overlapping" symptoms are not formally included in the MFS diagnostic criteria, it seems prudent that clinicians should be screening patients for the presence of overlapping symptoms (eg, anxiety, agitation, irritability), which are distressing to patients, commonly experienced, and are often insufficiently mitigated with conventional antidepressant therapy. Moreover, the presence of non-overlapping symptoms may provide a proxy and suggest the possible presence of specific criterion items.

Clinicians are reminded that the current state or history of hypo/mania identifies bipolar spectrum, while its absence does not permanently rule out the possibility that BD may be declared later. Results from the National Institute of Mental Health (NIMH) collaborative depression study indicate that approximately 20% of adults with MDE and subsyndromal hypomanic symptoms will later declare BD, underscoring the possibility of both a diagnostic conversion and the longitudinal stability of MDD with mixed features.[25] Clinicians are encouraged to include the Florida Best Practice Psychotherapeutic Medication Guidelines into their clinical practice. Antidepressants are to be considered as a first-line treatment approach for a MDE with or without MFS. Heightened vigilance for safety concerns (eg, suicidality) is warranted in patients with MDE and MFS receiving conventional antidepressants and as well anticipation of suboptimal therapeutic outcomes. Second generation antipsychotics that are without metabolic hazard and other tolerability concerns can be considered as adjunctive or alternative treatments to antidepressants, as can conventional mood stabilizers such as lithium. For highly malignant, treatment-resistant, and severe MDE with MFS, neuromodulatory approaches could be considered (eg, electroconvulsive therapy, transcranial magnetic stimulation).

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1. A 23-year-old patient with major depressive disorder presents with several symptoms that may indicate the presence of mixed features. Which of the following symptoms was NOT excluded from the DSM-5 mixed features specifier diagnostic criteria?
   A. Agitation
   B. Irritability
   C. Increased goal-directed activity
   D. Distractibility

2. Maria is a 31-year-old patient with bipolar disorder II. During major depressive episodes, this patient often experiences several symptoms of hypomania, including flight of ideas, increased risk-taking behavior, and increased talkativeness. According to data from the Stanley Foundation Bipolar Network, how many patients with bipolar disorder exhibit subsyndromal hypomanic symptoms during a major depressive episode?
   A. 5%
   B. 25%
   C. 45%
   D. 65%
   E. 85%

3. Thomas, a 28-year-old patient with major depressive disorder with mixed features, complains of significant irritability and agitation that are affecting his family and work. Which psychotropic treatment would be the most reasonable option for this patient?
   A. An antipsychotic such as lurasidone
   B. A mood stabilizer such as lithium
   C. An antidepressant such as duloxetine
   D. A and B only
   E. B and C only

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