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Diagnosing and Treating Major Depressive Episodes that Lie Along the Mood Disorders Spectrum: Focus on Depression with Mixed Features

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Review

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Diagnosing and treating major depressive episodes that lie along the mood disorders spectrum: focus on depression with mixed features

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Abstract

Growing evidence indicates that historical descriptions of mixed depression—broadly defined as major depressive episodes with subthreshold manic or hypomanic (hypo/manic) symptoms—are incredibly clinically relevant in this day-and-age. However, the first operational definition of mixed depression did not occur in the modern nomenclature until 2013 with publication of Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), and there has not been enough time to evaluate these criteria empirically. Thus, the most valid operational definition of a mixed depressive episode is still unknown, widely accepted treatment guidelines are not available, and no treatment has regulatory approval for mixed depression—whether associated with bipolar I disorder, bipolar II disorder, or major depressive disorder. This is despite seven drugs having regulatory indications for mixed episodes, defined as the co-occurrence of syndromal depression and syndromal mania, and now recognized as mania with mixed features by DSM-5. Indeed, we found only two randomized, placebo-controlled trials in patients with protocol defined mixed depression, one with ziprasidone and one with lurasidone. Both studies were positive, suggesting treatment with second-generation antipsychotics may be helpful for mixed depressive episodes associated with bipolar II or unipolar disorder. We found no randomized control trial of antidepressant monotherapy in mixed depression and many clinical reports that such treatment may worsen mixed depression Randomized, placebo-controlled trials of antidepressants, antipsychotics, and mood stabilizers—alone and in combination—in individuals with carefully defined mixed depression are needed before firm treatment guidelines can be produced.

Introduction

The term bipolar disorder is a misnomer as manic and depressive symptoms often co-occur, perhaps in an infinite number of combinations.[1-3] Often called mixed states, the Diagnostic and Statistical Manual, 5th Edition (DSM-5)[4] recognizes two broad types of these combinations: (1) mania or hypomania (hypo/mania) with depressive symptoms (called hypo/mania with mixed features or mixed hypo/mania) and (2) depression with subsyndromal hypo/manic symptoms (called depression with mixed features or mixed depression).[1-22] While both types of mixed states have been recognized since ancient times,[1] modern research has given far more attention to the diagnosis and treatment of mixed mania than to mixed depression.[14] Thus, while the DSM nomenclature has included descriptions of mixed episodes since 1980,[23] a description of mixed depression was not included until 2013 with the publication of DSM-5.[4] Moreover, DSM-5 specifies mixed episodes are forms of mania with mixed features and that mixed depression can occur in both bipolar and unipolar disorders. However, it is unclear whether mental health practitioners, drug companies that develop drugs for mood disorders, and regulatory agencies that evaluate drugs for treatment of mood disorders recognize mixed depression, including as defined by DSM-5, as a valid diagnostic entity. Indeed, though seven drugs (six second-generation antipsychotics and carbamazepine) have regulatory approval for treatment of mixed mania, no drug has regulatory approval for treatment of mixed depression.

DSM-5 provides diagnostic criteria for mixed depressive episodes associated with bipolar I, bipolar II, and major depressive disorders.[4] For all three diagnostic categories, depression with mixed features requires the presence of a syndromal major depressive episode and at least three of the following opposite polarity or nonoverlapping hypo/manic symptoms: elevated or expansive mood; inflated self-esteem or grandiosity; hyper-talkativeness or pressured speech; flight of ideas or racing thoughts; increase in energy or goal-directed activity; increased or excessive involvement in activities with a high potential for painful consequences; and decreased need for sleep. Moreover, at least three of these symptoms must be present nearly every day

during the most recent 2 weeks of the major depressive episode. The DSM-5 hypo/manic symptoms irritability, distractibility, and psychomotor agitation do not count towards a diagnosis of mixed depression. Of note, DSM-5 specifies that major depressive episodes occurring with syndromal mania are manic episodes with mixed features (rather than mixed episodes as specified in earlier DSM criteria sets).[4,23]

Although inclusion of mixed depression in the DSM-5 is a major step forward in modern nosology, many have concerns with the validity of the definition.[12,13,24] Thus, can mixed depression exist with only two or even one hypo/manic symptom? Are there really specific opposite polarity or nonoverlapping hypo/manic symptoms, or are all hypo/manic symptoms, like all depressive symptoms, in fact nonspecific?[25] Can depression with irritability, distractibility, and/or psychomotor agitation be a type of mixed depression, at least in some instances? Mahli et al[26] have argued that irritability, distractibility, and psychomotor agitation, the three hypo/manic symptoms excluded from the DSM-5 mixed features specifier for depression, may actually be cardinal features of mixed states.

A related concern is that the DSM-5 mixed features specifier is a categorical nosology while mixed states might better be conceptualized with dimensional models.[3,17] Thus, rather than specifying which and how many hypo/manic symptoms must occur in a depressive syndrome to define mixed depression, a certain level of subthreshold manic symptomatology, perhaps determined with a mania rating scale, including those that assesses specific as well as nonspecific manic symptoms, might be more appropriate. Indeed, trying to differentiate between mixed depressive vs mixed hypo/manic states may sometimes be like differentiating between a particle and wave—it cannot be done with careful clinical observation, but may require assessment of response to an intervention (ie, administration of an antidepressant to see if symptoms improve, worsen, or stay the same).[27]

Yet another important question is whether mixed depression is a unique state characterized by intense psychological suffering and excitatory symptoms[12,28] or distressing hyper-arousal.[29] Thus, important symptoms include anguish, panic-level anxiety, severe or delusional guilt, hopelessness, and helplessness in combination with psychic or physical agitation, inner tension, mood lability, and psychomotor agitation. In a study of the Koukopoulos definition of mixed depression (which includes agitation, irritability, and mood lability) in 435 patients, the most common symptoms were mood lability or marked reactivity and psychic agitation or inner tension and the absence of psychomotor retardation.[13] In a study of 241 outpatients with major depression, the DSM-5 anxious distress and mixed features episode specifiers were partially overlapping, with psychic agitation or inner tension and feeling keyed up or on edge present in both conditions.[30] Indeed, some have argued that agitated depression may be, at least in some cases, a form of mixed depression.[8,31,32]

Although the most valid operational definition of mixed depression is unclear, mounting research indicates that mixed depression is real, common (occurring in up to one third to three quarters of individuals with prominent depressive symptoms), and associated with female gender as well as a number of markers of greater illness severity.[6,9,10,15] The latter include early age of onset, suicide attempts and rapid cycling, greater psychiatric comorbidity (ie, with substance abuse and attention deficit hyperactivity disorder), head trauma, lower educational status, and greater family history of bipolar disorder and suicide[9,28,33,34] (Regarding mixed states and suicidality, though mixed mania is more often associated with suicidality than pure mania, it is unclear if the same is true for mixed versus pure depression).[35,36] Moreover, preliminary data suggest mixed features may be associated with treatment resistance in both bipolar and unipolar disorders.[37] One important unresolved issue, however, is how best to classify mixed depression. Thus, while DSM-5 specifies that mixed depression can be associated with unipolar or bipolar disorders, it might also be possible that unipolar mixed depression sometimes, or even always, reflects a bipolar spectrum disorder. Indeed, while Kraepelin identified six different types of mixed states, he argued that they were all due to one illness—manic depressive insanity.[5]

There is very little empirical evidence regarding the treatment of mixed depression.[16-18,20] Thus, just as it is unknown whether mixed bipolar depression be treated similarly to mixed mania, it is unknown whether mixed unipolar depression be treated similarly to pure unipolar depression or to mixed bipolar depression. In this paper, we will review studies of the medical and psychological management of mixed depression, discuss the various definitions of mixed depression used in these studies, and suggest that individuals presenting with depression should be assessed for mixed features, including both specific and nonspecific hypo/manic symptoms. We posit that well-designed treatment studies should inform the optimal treatment of mixed depression, as well as how to best define it operationally.

Methods

We reviewed PubMed from its inception to September 1, 2020 with the terms randomized controlled trial and mixed depression. Of 2011 papers, 36 were potentially relevant to this review. Of these, only two papers described randomized, placebo-controlled trials in protocol-defined mixed depression. Seven papers were post-hoc analyses of these studies, five papers were post-hoc analyses of positive randomized, placebo-controlled trials of second-generation antipsychotics in bipolar depression, and one paper described a randomized, placebo-controlled of valproate in bipolar depression where mixed features was a secondary outcome. The remaining papers were reviews, meta-analyses, and descriptions of various treatments in bipolar depression, mixed mania, or unipolar depression. Because this search yielded so few relevant studies, we also did searches of the term depression with mixed features with those of various treatments with reported effectiveness in hypo/mania or depression. The latter included lithium, valproate, carbamazepine, lamotrigine, second-generation antipsychotic, thyroid hormone, ketamine/esketamine, electroconvulsive therapy (ECT), and psychotherapy.

Results

Randomized, placebo-controlled controlled trials in protocol-defined mixed depression

As noted, we located only two randomized, placebo-controlled trials of a medication in the treatment of individuals with protocol-defined mixed depression.[38,39] Both tested second-generation antipsychotics. In the first study, 73 patients with major depressive disorder (N = 19) or bipolar II disorder (N = 43) and mixed depression, defined as a major depressive episode with two or three DSM-IV manic symptoms, were randomized to receive ziprasidone (40-160 mg/day) or placebo for 6 weeks.[38] Thirty-seven patients were not receiving other psychotropic medications

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and 28 patients were receiving antidepressants; only four patients were receiving an antidepressant and a mood stabilizer. Ziprasidone (mean dose 129.7 mg/day) was superior to placebo for reducing depressive symptoms as measured with the Montgomery Åsberg Depression Rating Scale (MADRS). Efficacy for ziprasidone was more significant in bipolar II than in major depressive disorder patients. Study drug was well tolerated, with no notable increase in weight or extrapyramidal symptoms. In a post-hoc analysis of this study, the most common symptom presentation was the triad of flight of ideas, distractibility, and irritable mood.[40] Importantly, irritable mood was the major predictor of response to ziprasidone treatment. The diagnostic distinction between bipolar II and major depressive disorders did not predict treatment response.

In the second study, 209 patients with major depressive disorder defined by DSM-IV-R criteria[41] who presented with two or three protocol-defined manic symptoms on most days for at least 2 weeks before screening were randomized to receive 6 weeks of the atypical antipsychotic lurasidone 20 to 60 mg/day or matching placebo.[39] Protocol-defined manic symptoms were: elevated or expansive mood; inflated self-esteem or grandiosity; more talkative than usual or pressure to keep talking; flight of ideas or racing thoughts; increased energy; increased or excessive involvement in activities with a high potential for negative consequences; and decreased need for sleep. Thus, the definition of mixed depression in this study was broader than the DSM-5 definition of major depressive disorder with mixed features. Lurasidone significantly improved depressive symptoms (measured with the MADRS) and global illness severity as compared to placebo. Of note, the effect size for lurasidone vs placebo was lower for individuals with three manic symptoms than for those with only two.[39,42] Nonetheless, significant improvement in manic symptoms (assessed with the Young Mania Rating Scale Score [YMRS]) was also found. In an analysis of participants' symptoms at baseline, the most common core manic symptoms were increased talkativeness and flight of ideas (both present in 65% of patients) and decreased need for sleep (present in 40%).[43] Other common manic symptoms were irritability and distractibility. Post-hoc analyses of study data found that lurasidone also improved irritability[44] and anxiety symptoms[45] in this patient population without adversely affecting sexual function.[46] Additionally, lurasidone was associated with greater rates of response and remission[47] and was efficacious in post-menopausal women with major depressive disorder with mixed features.[48]

To the best of our knowledge, there have been no randomized controlled trials in individuals with bipolar I disorder and protocol-defined mixed depression. However, a randomized controlled trial of quetiapine in patients with bipolar II disorder and mixed hypomania found drug superior to placebo for depressive and overall symptoms, but not hypomanic symptoms.[49] In this study, mixed hypomania was defined as hypomania as a YMRS score > 12 and a MADRS score > 15. While it is presently unknown if medication responses of mixed hypomanic states are generalizable to mixed depressive states, one could argue that the border between mixed hypomania mixed depression is very blurred and possibly undetectable.

Post-hoc analyses of randomized, placebo-controlled trials of second-generation antipsychotics in bipolar depression

Post-hoc analyses of a number of positive randomized, placebo-controlled trials of second-generation antipsychotics in bipolar depression have explored response of depression with hypo/manic symptoms vs pure depression (ie, bipolar depression with no hypo/manic symptoms). These studies found that olanzapine (with and without fluoxetine),[50,51] lurasidone,[52] and cariprazine[53] were as effective in mixed depression as in pure depression. A similar analysis showed that lurasidone reduced mixed features in children with bipolar depression.[54] In a post-hoc analysis of a randomized, placebo-controlled trial of olanzapine/fluoxetine combination (OFC) in patients with bipolar I depression, response rates in mixed vs nonmixed patients were 43% vs 49% for OFC, 27% vs 40% for olanzapine alone, and 16% vs 27.5% for placebo.[51] Although response rate of mixed depression was not significantly different between OFC and olanzapine, a higher number of baseline hypo/manic symptoms predicted lower response to olanzapine and placebo but not to OFC. The authors concluded that OFC might be an efficacious treatment for bipolar I mixed depression.

Of note, mixed depression was operationalized in a variety of ways in these post-hoc analyses. Thus, definitions of mixed depression included syndromal depression with one, two, or three or more hypo/manic symptoms. Despite these variations in definitions, second-generation antipsychotics were as effective in mixed bipolar depression as in pure bipolar depression. However, post-hoc analyses have limitations—they are not substitutes for adequately designed prospective randomized controlled trials for determining the efficacy and safety of a treatment for a specific diagnostic category.

Mood stabilizers

Although we found no randomized controlled clinical trials of a mood stabilizer in the treatment of individuals with protocol-defined mixed depression, preliminary data suggest valproate and lithium might be helpful for mixed depression. In a randomized controlled trial in 19 acutely depressed bipolar patients randomized to valproate or placebo for 6 weeks, valproate-treated patients had significantly greater reductions in MADRS scores compared with placebo-treated patients.[55] Moreover, there was a significant correlation between MADRS and Mania Rating Scale scores in the valproate group but not in the placebo group. The authors concluded that valproate was efficacious in bipolar depression, and might be beneficial in mixed depression. A meta-analysis of lithium in bipolar depression suggested that positive antidepressant response was related to the presence of mixed features.[56] Of note, although carbamazepine has regulatory approval for treatment of mixed mania and lamotrigine for maintenance treatment of bipolar I disorder to delay the time to occurrence of mood (including depressive) episodes, we found no reports of either drug in mixed depression. Nonetheless, both agents have been recommended as potential treatments for mixed depression.[17]

Antidepressants

We were unable to locate a randomized controlled trial of a unimodal antidepressant given either as monotherapy or in combination with a second-generation antipsychotic or mood stabilizer in the treatment of individuals with protocol-defined mixed depression.[16,57,58] In a comparison of 335 participants with bipolar mixed depression (defined as a depressive episode accompanied by two or more manic symptoms) from the National Institute of Mental Health Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), participants receiving adjunctive antidepressants had significantly higher mania symptom severity at 3-month follow up than those not receiving antidepressants.[59] Probability of recovery at 3 months was lower among participants with higher

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severity of baseline depression. After controlling confounding factors, antidepressant use neither hastened nor prolonged time to recovery. In a post-hoc analysis of 279 depressed patients from 9 controlled antidepressant trials, selective serotonin reuptake inhibitors (SSRI) responders were found to be more "anxious-agitated" at baseline than norepinephrine reuptake (NRI) responders.[60] The authors concluded that that anxious-agitated depression might respond better to SSRIs than NRIs. Studies suggesting serotonin-norepinephrine reuptake inhibitors (SNRIs) may be more likely than SSRIs or bupropion to induce the switch process[61,62] have lead some authorities to argue that if an antidepressant is to be used in mixed depression, it should be an SSRI or bupropion rather than an SNRI (or tricyclic antidepressant).[57]

Indeed, numerous reports describe adverse reactions of individuals with mixed depression to treatment with unimodal antidepressants.[6,8,13,14] Authorities have generated different recommendations—with some saying antidepressants are appropriate first line treatments,[16] especially for unimodal mixed depression, while others suggest their use should be minimized or even avoided, especially for bipolar I mixed depression.[57,58] Consistent with the latter view, two post-hoc analyses found that the presence of mixed features during bipolar depression predicted hypo/manic switch with antidepressant treatment.[63,64]

Thyroid hormone

Growing data indicate that positive treatment response of bipolar disorder, especially bipolar depression, requires optimized thyroid function. In a study of 65 patients with bipolar I depression, lower free thyroxine index values and higher thyroid stimulating hormone (TSH) values were both significantly associated with slower response to treatment.[65] In a post-hoc analysis of two 18-month randomized, controlled trials of lithium vs lamotrigine monotherapy in bipolar I patients recovering from a manic or depressive episode, lithium-treated participants who required an intervention for a depressive episode had a significantly higher mean TSH level (4.4 micro IU/ml0) compared with lithium-treated participants who did not require such an intervention.[66] Of note, in both studies, the majority of patients had thyroid function values that were within normal limits, suggesting that adequate TSH levels in bipolar patients may be lower than deemed appropriate in non-mood disorder patients. In a randomized, placebo-controlled trial of levothyroxine vs triiodothyronine in 32 patients with lithium-resistant rapid-cycling bipolar disorder, levothyroxine recipients spent significantly less time in a depressed or mixed state and more time euthymic than triiodothyronine recepients.[67] Compared to placebo recipients, levothyroxine recipients had increased time euthymic and decreased time in a mixed state.

Although in need of more study, the findings of these studies suggest that adequate treatment of bipolar depression, including possibly mixed depression, requires optimized thyroid function. Although the definition of the latter is unclear, it might be important to determine the optimal thyroid function test profile for the individual mood disorder patient in terms of both mood and hypothyroidism symptoms (eg, cold intolerance, hair loss, hoarse voice, and difficulty swallowing).

Ketamine

Mounting evidence indicates that ketamine (given intravenously and possibly intra-nasally) is efficacious for both unipolar and bipolar depression, including treatment resistant cases.[68] Indeed, the ketamine isomer esketamine has regulatory approval for adjunctive treatment of individuals with treatment-resistant major depressive disorder.[69] While we found no randomized controlled trials of ketamine oresketamine in the treatment of protocol-defined mixed depression, preliminary data suggest ketamine might be effective for mixed features when defined as the occurrence of anxiety, irritability, and agitation. Among 201 community-based patients with treatment resistant major depressive or bipolar disorders receiving intravenous ketamine, the 113 patients with anxiety, irritability, and agitation had a significantly greater reduction in depressive symptoms, anxiety, irritability, and agitation as compared to the patients without these features.[70] Additionally, in a randomized controlled trial in 36 bipolar patients with anxious and non-anxious treatment-resistant depression, a single intravenous infusion of ketamine reduced depressive symptoms in both groups, as well as anxiety in the anxious group.[71]

Electroconvulsive therapy

Available data from randomized controlled trials suggest mania, including mixed mania, and bipolar depression respond well to ECT.[72-74] Although we were unable to locate any randomized controlled trials of ECT in the treatment of individuals with protocol-defined mixed depression, naturalistic data describe positive response of mixed state patients to ECT, although it is not always clear if patients had mixed mania or mixed depression.[75-77] However, in a recent description of 607 patients with bipolar depression treated with ECT, 72% of whom were responders, putative predictors of response included symptoms of mixed depression, including tension or agitation and hyperactivity.[78] The authors concluded that bipolar depressed patients with severe mixed features were highly responsive to ECT. Moreover, there are clinical descriptions of patients responding well to ECT, including some who initially have adverse responses to unimodal antidepressants.[6,8,13,14]

Psychotherapy

Growing data show that psychotherapy is efficacious for individuals with unipolar and bipolar depression, and authorities have suggested it might also be efficacious for mixed depression.[79] Thus, O'Brien et al[79] advocate taking a patient-centered approach with mixed state patients incorporating techniques from various evidence-based therapies, including interventions that target anxiety. Indeed, psychoeducation (both group and family) is highly effective for individuals with bipolar disorder. Specifically, psychoeducation has been shown to reduce relapse and psychiatric hospitalization, enhance medication compliance (and lithium levels), and reduce stigma.[80,81] Of note, an important component of psychoeducation is explaining to patients, usually when they are euthymic, about the occurrence of mixed states.

Conclusion

Mounting modern empirical evidence indicates that mixed depression, whether associated with major depressive disorder, bipolar II disorder, or bipolar I disorder, is an important and frequent clinical presentation that causes profound distress, is associated with greater illness severity, suicidality, and psychiatric comorbidity, and may be less responsive to treatment. Defined conceptually as prominent depressive symptoms accompanied by subthreshold hypo/manic symptoms, it is important to realize that the precise operational definition of mixed depression is as yet unclear. While

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DSM-5 requires the presence of syndromal depression with three or more specific or polar opposite hypo/manic symptoms, other data suggest mixed depression may be defined with fewer hypo/manic symptoms, including so-called nonspecific symptoms. Thus, it could be argued that any patient presenting with a major depressive syndrome or prominent depressive symptoms should be evaluated for co-occurring hypo/manic symptoms, including classic or polar opposite DSM-5 hypo/manic symptoms, as well nonspecific symptoms, such as irritability, mood lability, distractibility, psychomotor agitation, and anxiety.

There are no widely accepted guidelines for the treatment of mixed depression. Indeed, it is unclear if industry or regulatory agencies, including the United States Food and Drug Administration, recognize this common clinical presentation as a distinct entity that may have a unique treatment profile. It is thus not surprising that expert opinion on how to best treat mixed depression is inconsistent. While some authorities advise treatment with antidepressants, especially for unipolar mixed depression,[16] others recommend treatment with second-generation antipsychotics or mood stabilizers before antidepressants, especially for mixed bipolar I depression.[14,17,57] We found only two randomized placebo-controlled trials in protocol-defined mixed depression; both showed that second-generation antipsychotics were efficacious in unipolar (lurasidone and ziprasidone) and bipolar II (ziprasidone) mixed depression.[38,39] Moreover, all published post-hoc analyses of positive studies of second-generation antipsychotics in bipolar depression that we located showed that mixed patients responded just as well to these drugs as nonmixed patients, although there are limitations to using post-hoc analyses for clinical decision-making. We found no randomized, controlled trials of mood stabilizers or antidepressants in protocol defined mixed depression, although one secondary analysis suggested valproate was just as effective in mixed as in nonmixed depression.[55] Of note, we found a number of reports describing worsening of mixed depression when treated with antidepressants.[6,8,14,17]

There are several general principles when treating mixed depression. First, both specific and nonspecific hypo/manic symptoms should be assessed in any patient presenting with prominent depressive symptoms. Moreover, it is always possible that what appears to be a pure depression may actually be a mixed depression or transition into a mixed depression. Thus, both depressive and hypo/manic symptoms should be monitored in patients with mixed and pure depression on an ongoing basis. In particular, if a patient with pure depression worsens, including after antidepressant exposure, he or she should be evaluated for development of hypo/manic symptoms.

Several other considerations apply to all patients with mood disorders, but are extremely important for mixed depression patients. Comorbid psychiatric and medical conditions must be carefully assessed and determined. Thus, the presence of co-occurring anxiety, substance use, and eating disorders should be evaluated, and thyroid function, be determined. If any of the former are present, their management should be addressed; if the latter is abnormal, it should be optimized. Patients should be educated about good sleep hygiene, healthy eating habits, and benefits of physical activity on mood and energy. Psychotherapy, including psychoeducation about the occurrence of hypo/manic symptoms during depression, should be offered to the patient and, if appropriate, his or her family.

Summary

Although recognized since ancient times,[1] mixed depression was not included in the modern psychiatric nomenclature until 2013 with the publication of DSM-5.[4] Hence, empirical study of DSM-5 defined mixed depression is in its infancy. Widely accepted diagnostic and treatment guidelines for mixed depression are not yet available and no treatment has regulatory approval for mixed depression. Indeed, it is unclear if industry and regulatory agencies recognize mixed depression as a discrete diagnostic entity with special treatment requirements. Further randomized controlled trials of a wide range of treatments (antidepressants, mood stabilizers, second-generation antipsychotics, and psychotherapy—alone and in various combinations) in individuals with protocol-defined mixed depression are greatly needed. Such randomized controlled trials might not only help in identifying how best to treat mixed depression, but also how to best define it operationally. An optimized operational definition of mixed depression will, in turn, hopefully aid in prediction of prognosis and treatment response of individuals with this complex and distressing presentation.

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1. Patients experiencing a depressive episode in the context of which diagnosis should be evaluated for co-occurring hypo/maniac symptoms?
   A. Major depressive disorder
   B. Bipolar II disorder
   C. Bipolar I disorder
   D. All of the above

2. A 29-year-old patient with a mixed depressive episode is seeking treatment. Which type of pharmacotherapy has the strongest evidence of efficacy for treating mixed depression?
   A. Mood stabilizer
   B. Atypical antipsychotic
   C. Selective serotonin reuptake inhibitor
   D. Serotonin norepinephrine reuptake inhibitor

3. Which of the following agents has regulatory approval for treatment of mixed depression?
   A. Ziprasidone
   B. Lurasidone
   C. Olanzapine/fluoxetine combination
   D. No agents are approved for treatment of mixed depression

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