

Guidelines for the recognition and management of mixed depression

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A significant minority of people presenting with a major depressive episode (MDE) experience co-occurring subsyndromal hypo/manic symptoms. As this presentation may have important prognostic and treatment implications, the DSM–5 codified a new nosological entity, the “mixed features specifier,” referring to individuals meeting threshold criteria for an MDE and subthreshold symptoms of (hypo)mania or to individuals with syndromal mania and subthreshold depressive symptoms. The mixed features specifier adds to a growing list of monikers that have been put forward to describe phenotypes characterized by the admixture of depressive and hypomanic symptoms (e.g., mixed depression, depression with mixed features, or depressive mixed states [DMX]). Current treatment guidelines, regulatory approvals, as well the current evidentiary base provide insufficient decision support to practitioners who provide care to individuals presenting with an MDE with mixed features. In addition, all existing psychotropic agents evaluated in mixed patients have largely been confined to patient populations meeting the DSM–IV definition of “mixed states” wherein the co-occurrence of threshold-level mania and threshold-level MDE was required. Toward the aim of assisting clinicians providing care to adults with MDE and mixed features, we have assembled a panel of experts on mood disorders to develop these guidelines on the recognition and treatment of mixed depression, based on the few studies that have focused specifically on DMX as well as decades of cumulated clinical experience.

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Introduction

The recent addition of the mixed features specifier in the latest edition of the *Diagnostic and Statistical Manual* (DSM–5) codifies a new nosological entity characterized by subthreshold hypomanic or manic symptoms occurring during depressive episodes of either major

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depressive disorder (MDD) or bipolar I or bipolar II disorder.¹ The introduction of the DSM–5 mixed features specifier also reflects a growing consensus that mood disorders may be conceptualized along a spectrum ranging from pure unipolar depression, through an admixture of varying degrees and presentations of depressive and manic symptoms, to pure mania (Figure 1).^{2–6} Perhaps one of the greatest challenges in recognizing the existence of mixed depression or depressive mixed states (DMX) is the question of how to optimize treatment for patients with depression who exhibit concomitant subthreshold features of hypomania or mania. Although there are several guidelines available that provide recommendations for the treatment of unipolar depression, for bipolar depression, and for bipolar mania, there is currently only one treatment guideline that has provided decision support for individuals presenting with a major depressive episode with mixed features (i.e., the Florida Best Practice Psychotherapeutic Medication Guidelines for Adults [2015], available for download at http://www.medicicaidmentalhealth.org/_assets/file/Guidelines/Web_2015-Psychotherapeutic%20Medication%20Guidelines%20for%20Adults_Final_Approved1.pdf).^{7–19} In fact, any treatment guidelines developed prior to the release of the DSM–5 that mention “mixed states” are based on the previous DSM–IV diagnostic criteria that refer to co-occurring full-blown, threshold-level depression with full-blown, threshold-level mania (mixed mania) and simply lump mixed states together with bipolar mania in terms of treatment recommendations.²⁰

Since the release of the DSM–5 in 2013, it has been suggested that clinicians follow existing guidelines written for the treatment of MDD or bipolar disorder (BD) without any particular reference to individuals presenting with depressive episodes with mixed (DMX) features. However, not only is DMX different in its clinical presentation compared to an MDE, it is not pathognomonic of either MDD or BD. Toward the aim of filling the gaps between updated diagnostic criteria, the latest research findings, and optimal clinical practice, we have gathered together a panel of experts on mood disorders to develop a set of guidelines for the recognition and treatment of DMX.

The guideline recommendations throughout this article are made in reference to DSM–5 rather than DSM–IV descriptions and criteria. However, the diagnostic criteria warranting a DSM–5 major depressive episode (MDE) with mixed features diagnosis exclude “overlapping symptoms” of irritability, distractibility, insomnia, and psychomotor agitation as defining of the opposite polarity due to the presence of these symptoms in both mania and depression. The exclusion of

overlapping symptoms increases the specificity of the diagnosis at the expense of sensitivity and possibly face validity insofar as most individuals presenting with an MDE and mixed features do present with “overlapping symptoms.”^{21–31} The potential of DMX being misdiagnosed and treated as pure unipolar depression is far greater than if unipolar depression is misdiagnosed and mistreated as DMX).

Overview and Key Points

- Not all patients with depression (as part of bipolar disorder or major depressive disorder) should be prescribed an antidepressant.
- All patients who receive antidepressants for an MDE should be monitored for signs of abnormal behavioral activation or psychomotor acceleration.
- The use of antidepressants in MDE patients with mixed features may not alleviate depressive symptoms and may pose a potential hazard for exacerbating subthreshold mania symptoms that accompany depression.
- For an individual presenting with a depressive episode with mixed features, in addition to antidepressant medication, alternative psychotropic agents (e.g., lithium, anticonvulsant mood stabilizers, atypical antipsychotics) with demonstrated efficacy in treating depressive symptoms as part of MDE may be considered.
- You will not know if a depressed patient has (hypo)manic symptoms or a positive family history of bipolar disorder unless you ask! **Ask every patient. Every time.**

Assessment

DSM–5 diagnostic criteria for a major depressive episode¹ (consider an itemized depression screener such as the Quick Inventory Depressive Symptomatology–Self Report or Clinically Useful Depression Outcome Scale)

- **EITHER** depressed mood **OR** anhedonia/loss of interest **AND** four (or more) of the following symptoms:
 - Weight/appetite changes
 - Sleep disturbances
 - Psychomotor agitation or retardation
 - Fatigue
 - Worthlessness or guilt
 - Executive dysfunction
 - Suicidal ideation or thoughts of death
- May be part of unipolar depression, bipolar II depression, or bipolar I depression

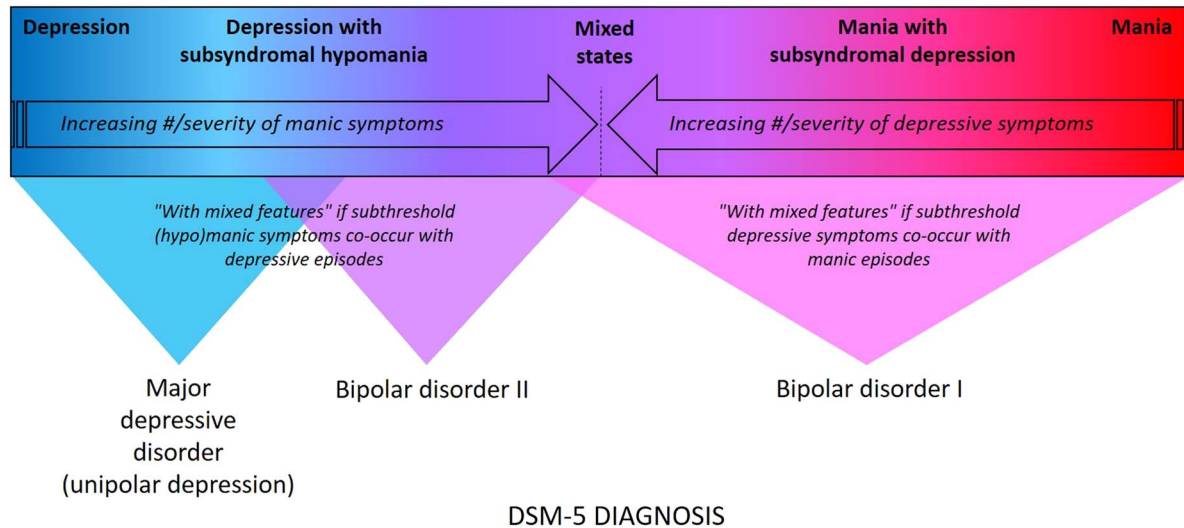


FIGURE 1. Mood disorders spectrum and DSM-5 diagnosis. Mood disorders can be conceptualized as existing along a spectrum that spans from pure unipolar depression with no intra- or inter-episode symptoms of (hypo)mania all the way to threshold level mania.

DSM-5 diagnostic criteria for the mixed features specifier¹

- Full criteria for a major depressive episode and at least three of the following (hypo)manic symptoms during the majority of days of the current or most recent depressive episode:
 - Elevated, expansive mood
 - Inflated self-esteem or grandiosity
 - More talkative than usual or pressure to keep talking
 - Flight of ideas or subjective experience that thoughts are racing
 - Increase in energy or goal-directed activity
 - Increased or excessive involvement in activities that have a high potential for painful consequences
 - Decreased need for sleep (to be contrasted with insomnia)
- May be part of unipolar depression, bipolar II depression, or bipolar I depression

- Anxiety
- Distractibility
- Psychomotor agitation
- Racing/crowded thoughts
- Initial and middle insomnia
- Indecisiveness
- Anger
- Increased talkativeness
- Emotional lability/tearfulness
- Inner tension
- Rumination
- Initial or middle insomnia
- Impulsivity
- Risky behaviors

- These alternative diagnostic criteria for DMX also stress how critical it is to assess the patient for any family history of bipolar spectrum disorders:³³⁻³⁵
 - **Always** inquire about family history of bipolar symptoms or **ANY** symptoms of (hypo)mania in patients presenting with a major depressive episode
 - Inquire about common bipolar comorbidities (e.g., migraine, anxiety disorders, substance abuse, obesity, binge eating, ADHD). Although these comorbidities are observed in both BD and MDD populations, data suggest that patients with BD (especially those with BDII and pediatric populations) are more likely to be affected^{17,36-39}

Non DSM-5 diagnostic criteria for mixed depression (overlapping symptoms)^{2,21-23,25,29}

- Controversy exists as to whether the symptoms of DMX are fully captured by the DSM-5 diagnostic criteria, as well as the extent to which DMX symptoms can be differentiated from comorbid disorders or other conditions, including borderline personality disorder, posttraumatic stress disorder, substance use disorders, and attention deficit hyperactivity disorder^{29,32}
- Alternative diagnostic criteria have been proposed and focus on the most common symptoms seen in patients with DMX, including:
 - Irritability

Differential Diagnosis

- The prognosis for depression with cooccurring subthreshold hypomania (DMX) is much worse than for pure unipolar depression or bipolar depression without mixed features^{26,40}

- A significant minority (about 13–20%) of individuals with unipolar DMX will eventually meet diagnostic criteria for bipolar I or bipolar II disorder
- In order to avoid treatments that could worsen symptoms of hypo/mania in MDE patients with mixed features (e.g., antidepressant monotherapy), to prevent the development of resistance to appropriate treatments, and to avert treatment-emergent affective switch (TEAS), it is essential that DMX be distinguished from pure unipolar depression as early as possible^{40–45}
- A key differential diagnostic issue is unipolar depression with borderline personality disorder versus DMX. Most of the correlates listed below are also correlates of unipolar depression with borderline personality disorder
- MDD with active substance use disorders could inflate rates of false-positive detection of hypo/mania symptoms and requires a careful longitudinal history⁴⁶
- DMX has been associated with:
 - Family history of bipolar spectrum disorders
 - Suicidality
 - Antidepressant-induced mania
 - Rapid cycling
 - Young age of onset
 - Long duration of illness
 - Poor prognosis
 - Severe depression
 - Antidepressant resistance
 - Females
 - Comorbid anxiety
 - Comorbid substance-use disorder (SUD)
 - Impulse control disorders
- There are several assessment tools available to aid in the recognition of subthreshold hypomanic symptoms, including:
 - Bipolar Depression Rating Scale (BDRS)⁴⁷
 - ⊙ Clinician-administered assessment of current symptoms
 - Hypomania Interview Guide (HIG)^{48,49}
 - ⊙ Clinician-administered assessment of current symptoms
 - Mini International Neuropsychiatric Interview (M.I.N.I.)⁵⁰
 - ⊙ Patient self-report assessing current (hypo) manic symptoms
 - Clinically Useful Depression Outcome Scale with DSM–5 Mixed (CUDOS–M)⁵¹
 - ⊙ Patient self-report assessing current (hypo) manic symptoms

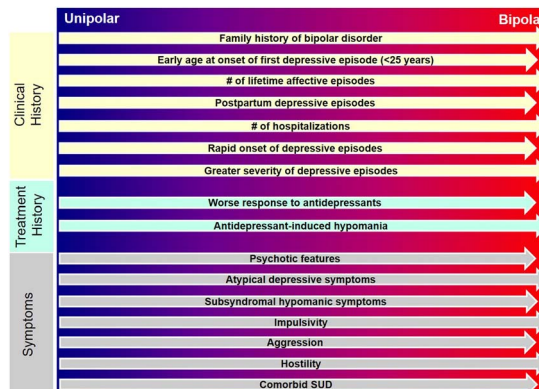


FIGURE 2. The probabilistic approach to differential diagnosis. Numerous factors, including early age at onset of first depressive episode, seasonality, antidepressant-induced (hypo)mania, and impulsivity, while not diagnostic of bipolar depression, are less common in pure unipolar depression compared to bipolar spectrum disorders. Moreover, the presence of psychotic features and extensive family history of psychopathology are additional probabilistic factors for BD. Patterns of comorbidity can also be evaluated as substance-use disorders, and several medical disorders (e.g., migraine and metabolic disturbances) are more common in BD when compared to MDD. Although the presence of any of these probabilistic qualities is not pathognomic, accumulation of these factors should alert clinicians to the possibility that their patient may lie along the bipolar spectrum, either with mixed depression or with bipolar depression.

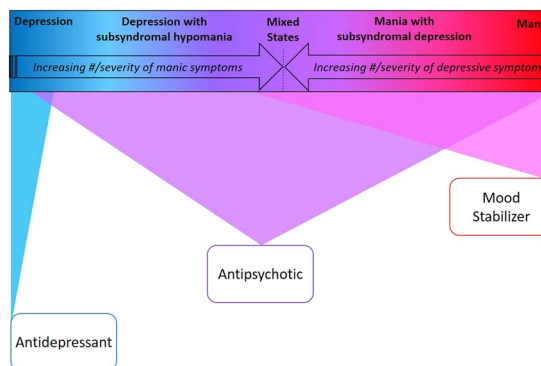


FIGURE 3. Bipolar spectrum-based first-line monotherapy treatment recommendations.

- Hypomania Checklist (HCL–32)^{33,52}
 - ⊙ Patient self-report that screens for lifetime (hypo)manic symptoms—this does not assess mixed episodes, and has not been suggested to do so
- Mood Disorder Questionnaire (MDQ)⁵³
 - ⊙ Patient self-report that screens for lifetime (hypo)manic symptoms
- Altman Mania Rating Scale⁵⁴
 - ⊙ Patient self-report assessing current (hypo) manic symptoms

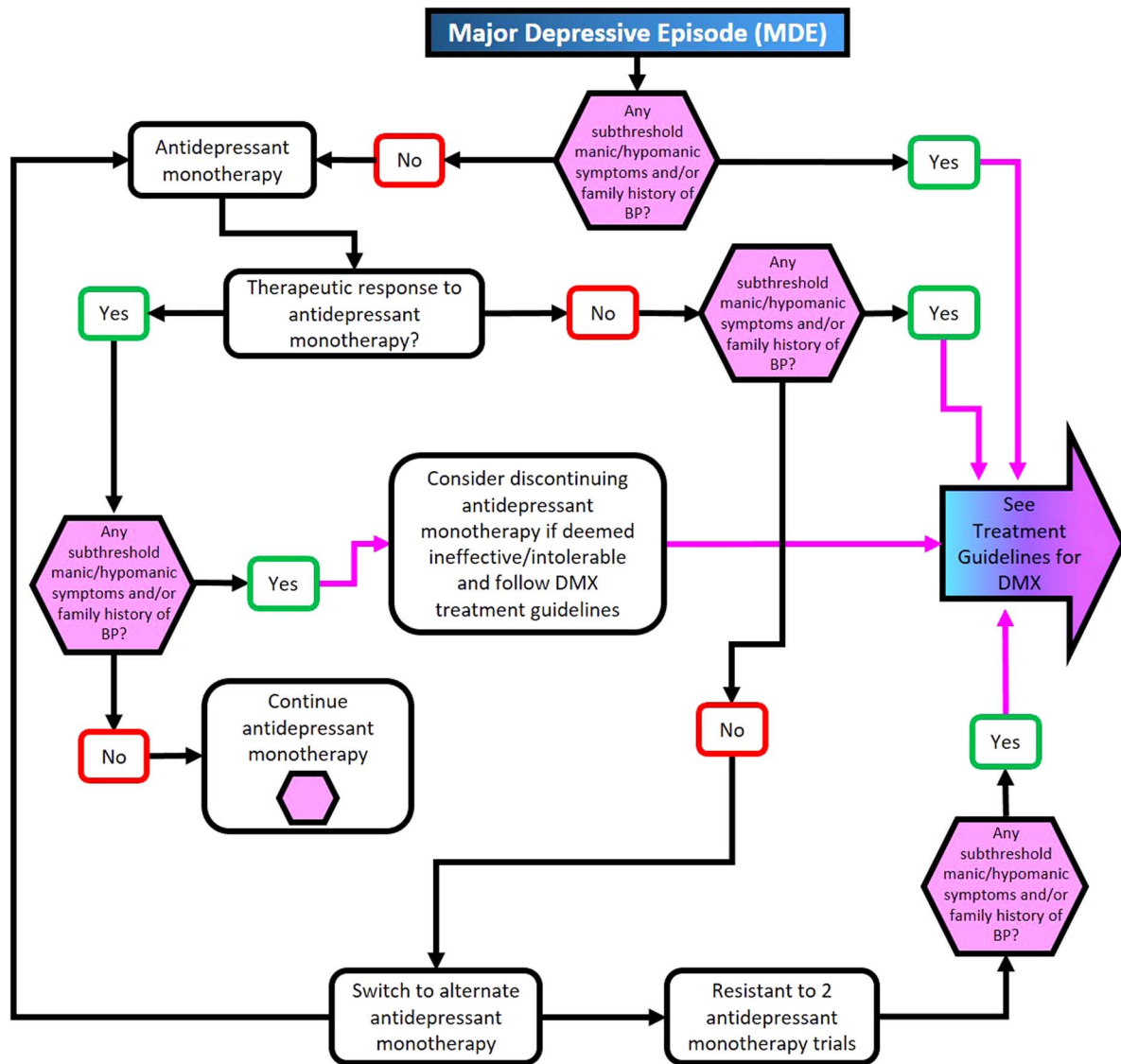
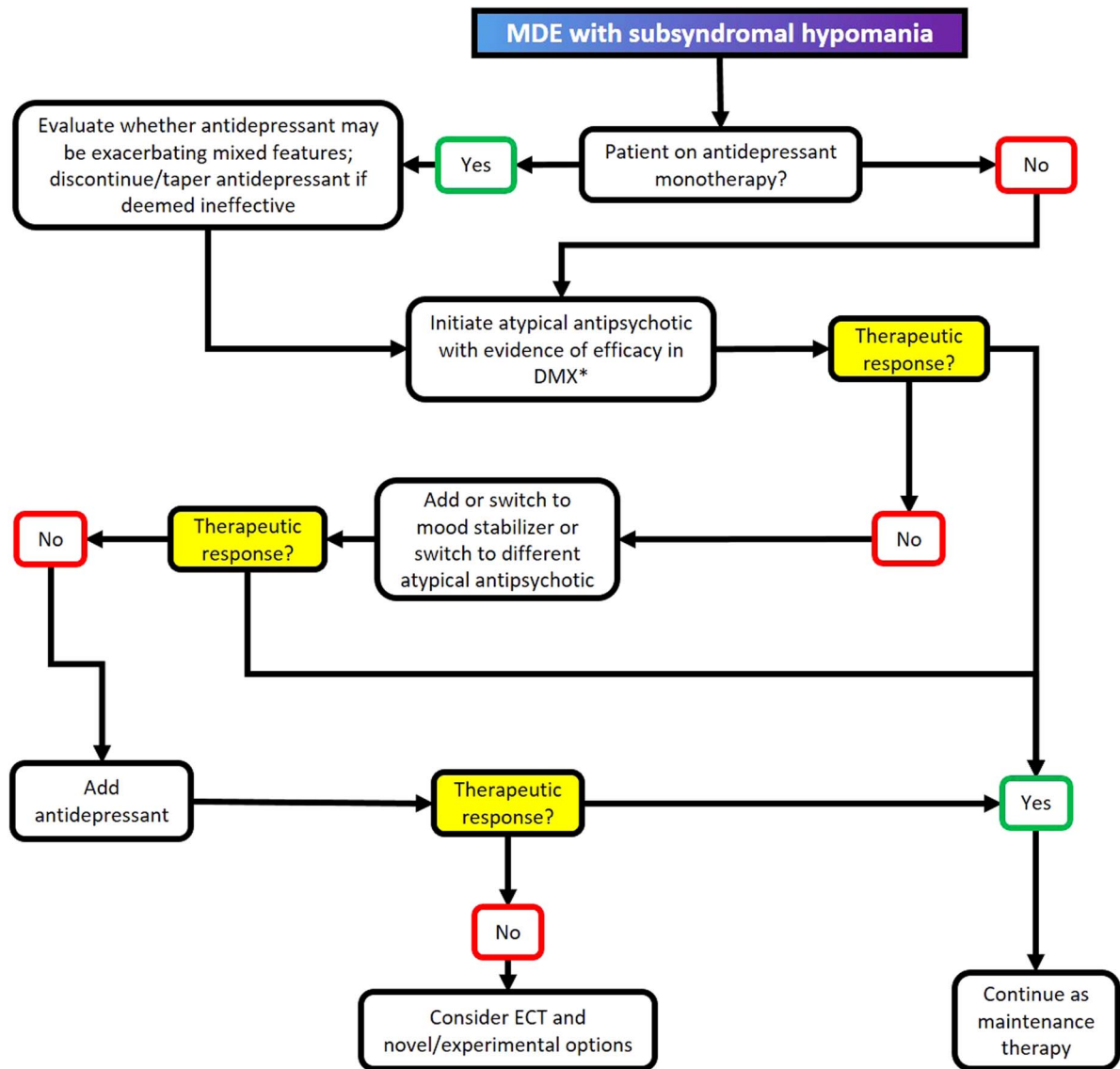


FIGURE 4. Treatment algorithm for major depressive episode without mixed features.

- Patient self-report that screens for “bipolar spectrum disorder” (which includes bipolar I and bipolar II), and the “probabilistic” approach may help to identify patients who are more likely to have a bipolar spectrum disorder rather than pure unipolar depression (Figure 2)
 - > The same factors that indicate bipolarity are also evident in patients with DMX
- Rule out comorbid conditions that phenotypically overlap with mixed features and/or secondary causes of (hypo)mania, but keep in mind that some secondary causes (e.g., substance use) could be more frequent among individuals with bipolar than unipolar disorder
 - > Drug and/or alcohol misuse
 - If comorbid, the mood state will generally precede and significantly outlast the state induced by intoxication or withdrawal, and a diagnosis of bipolar disorder can be made
 - > Certain medications
 - e.g., L-dopa and corticosteroids, stimulants
 - > Organic conditions
 - Most likely in older patients
 - > Caffeine use
 - > Infections (HIV, syphilis, other)
 - > Multiple sclerosis
 - > Traumatic brain injury (TBI), brain lesion(s) involving subcortical or cortical areas
 - > Thyroid disease
 - > Disruptive behavior disorders (CD, ODD)



*Asenapine, lurasidone, olanzapine, quetiapine, and ziprasidone have each shown some efficacy in treating DMX

FIGURE 5. Treatment algorithm for major depressive episode with mixed features (DMX).

- Cyclothymic temperament, novelty seeking, narcissistic and borderline personality disorders
- Agitated or anxious depression

⊙ It has been proposed that agitated depression (a major depressive episode with psychomotor agitation) is a form of mixed depression because it often occurs along with other symptoms of hypomania^{22,27,55}

Baseline Medical History and Laboratory Parameters^{11,56}

- Medical history
- Smoking history

- Cardiometabolic family history
- Waist circumference and/or BMI
- Blood pressure
- Complete blood count (CBC)
- Electrolytes, urea, and creatinine (EUC)
- Urine toxicology for substance use
- Fasting glucose
- Fasting lipid profile (TC, vLDL, LDL, HDL, TG)
- Liver enzymes
- Hepatitis A, B, C; syphilis testing in patients deemed at risk
- Estimated glomerular filtration rate
- Platelets
- Thyroid-stimulating hormone
- Serum bilirubin

Side Effect	Best choice	Worst choice
SEDATION	Aripiprazole	Quetiapine
SEDATION	Brexiprazole	Clozapine
SEDATION	Cariprazine	Olanzapine
SEDATION	Iloperidone	Asenapine
SEDATION	Lurasidone	Risperidone
SEDATION	Paliperidone	Ziprasidone
SEDATION	Risperidone	Asenapine
SEDATION	Ziprasidone	Paliperidone
SEDATION	Asenapine	Risperidone
SEDATION	Olanzapine	Quetiapine
WEIGHT GAIN	Aripiprazole	Olanzapine
WEIGHT GAIN	Brexiprazole	Clozapine
WEIGHT GAIN	Cariprazine	Asenapine
WEIGHT GAIN	Lurasidone	Iloperidone
WEIGHT GAIN	Ziprasidone	Paliperidone
WEIGHT GAIN	Asenapine	Risperidone
WEIGHT GAIN	Iloperidone	Asenapine
WEIGHT GAIN	Paliperidone	Risperidone
WEIGHT GAIN	Risperidone	Asenapine
WEIGHT GAIN	Asenapine	Iloperidone
EPS	Clozapine	Risperidone
EPS	Iloperidone	Paliperidone
EPS	Quetiapine	Ziprasidone
EPS	Aripiprazole	Olanzapine
EPS	Brexiprazole	Lurasidone
EPS	Cariprazine	Olanzapine
EPS	Asenapine	Lurasidone
EPS	Lurasidone	Olanzapine
EPS	Olanzapine	Ziprasidone
EPS	Ziprasidone	Paliperidone
EPS	Paliperidone	Risperidone
EPS	Risperidone	Risperidone

Patients on atypical antipsychotics should be regularly monitored for side effects, including BMI

FIGURE 6. Relative tolerability of atypical antipsychotics.

- Electrocardiogram (>40 years or if indicated)
- Prolactin (if relevant)
- Pregnancy test (if relevant)
- Contraceptive use (if relevant)

Treatment

Initial treatment

- Antidepressant monotherapy should probably **NOT** be utilized for patients with mixed depression of any type (unipolar, BP II, or BP I), given persisting doubts about the relative efficacy of standard antidepressants in treating bipolar disorders and their potential to destabilize mood^{7,8,11,12,25,32,57–68}
 - It is critical that patients presenting with a major depressive episode be assessed for the presence of any symptoms of (hypo)mania and family history of mood disorder, including bipolar disorder, before initiating treatment
 - Patients with mixed depression should be monitored regularly for the emergence or worsening of (hypo)mania and suicidality
 - Tricyclic antidepressants (TCAs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) may carry the highest risk of causing a treatment-emergent affective switch,^{11,17,30,62,63,69–73} while bupropion and some selective serotonin reuptake inhibitors (SSRIs) may have a lower risk of affective switch
 - There is some evidence for the adjunctive use of monoamine oxidase inhibitors in the treatment of bipolar depression^{74,75}
 - For symptomatic patients with mixed depression, antidepressant monotherapy should generally be tapered and discontinued. Clinicians should carefully assess whether mixed features may be exacerbated by antidepressant monotherapies; in

TABLE 1. Recommendations for acute pharmacological treatment of mixed depression^a

First-line	Monotherapy: lurasidone, asenapine, quetiapine, quetiapine XR, aripiprazole, ziprasidone
Second-line	Monotherapy: lamotrigine, valproate, lithium, cariprazine, olanzapine Lithium, lamotrigine, or valproate + atypical antipsychotic Lithium + valproate Lithium or valproate + lamotrigine Olanzapine + fluoxetine
Third-line	Monotherapy: carbamazepine Lithium + carbamazepine Lithium + pramipexole ECT Lithium or lamotrigine or valproate or atypical antipsychotic + bupropion Lithium or lamotrigine or valproate or atypical antipsychotic + SSRI Lithium or lamotrigine or valproate or atypical antipsychotic + MAOI Adjunctive modafinil, armodafinil, pramipexole Adjunctive folic acid, inositol, ketamine, N-acetyl cysteine, omega-3 fatty acids, ramelteon, or celecoxib
GENERALLY NOT recommended	Monotherapy: antidepressants Monotherapy: topiramate Carbamazepine + olanzapine or risperidone

such instances, consideration should be given either to augmentation with an atypical antipsychotic or antimanic mood stabilizer (e.g., lithium, divalproex, carbamazepine) or else tapering and discontinuing antidepressants altogether if deemed ineffective

- There are currently no psychotropic agents that are FDA- or EMA-approved for the treatment of depression with mixed features
- First-generation antipsychotics and sedatives (benzodiazepines, hypnotics) have been used successfully in the treatment of depressive mixed states
- Atypical antipsychotics (including asenapine,^{76,77} lurasidone,^{78,79} olanzapine,⁸⁰ quetiapine,⁸¹ and ziprasidone⁸²) are the only psychotropic agents that have been specifically tested (and shown some efficacy) for the treatment of depression with mixed features
 - Not all atypical antipsychotics have demonstrated efficacy in bipolar depression (e.g., Lombardo *et al.*, 2009⁸³). Caution is therefore warranted when extrapolating to DMX from outcome studies in frank bipolar disorder. Moreover, these studies did not enroll subjects according to the DSM–5 definition of mixed features
 - Cariprazine and aripiprazole have also both shown some efficacy in improving both manic and depressive symptoms^{84,85}
 - The efficacy of the atypical antipsychotics listed above is suggested largely based on post-hoc

TABLE 2. Dosing recommendations for pharmacotherapy of mixed depression

Medication (brand)	Dose ranges based on studies of bipolar disorder
Monotherapies	
Aripiprazole (Abilify®)	15–30 mg/d
Asenapine (Saphris®)	5–10 mg/d
Carbamazepine (Carbatrol®, Epitol®, Equetro®, Tegretol®)	600–1200 mg/d (serum level 4–15 mg/L)
Cariiprazine (Vraylar)	3–6 mg
Divalproex (Depakote®/Depakote® ER)	750 mg/60 mg/kg/d
Fluoxetine (Prozac®, Sarafem®)	20–80 mg/d
Lamotrigine (Lamictal®, generic)	50–200 mg/d
Lithium (Lithane®, Lithobid®, generic)	600–1200 mg/d (serum level 0.5–1.2 mEq/L)
Lurasidone	20–120 mg/d
Olanzapine (Zyprexa®)	5–20 mg/d
Quetiapine (Seroquel®)	300–600 mg/d
Valproate (Depacon®, generic)	Serum level 70–90 mg/L
Ziprasidone (Geodon®)	80–160 mg/d
Combination and augmentation treatments	
Olanzapine + fluoxetine (OFC) (Symbyax®)	6–12 mg olanzapine and 25–50 mg fluoxetine
Lamotrigine + lithium	Lamotrigine: up to 200 mg/d
Modafinil (Nuvigil®, Provigil®)/armodafinil + ongoing treatment	Modafinil: 100–200 mg/d Armodafinil: 150–250 mg/d
N-acetylcysteine + lithium or valproate	N-acetylcysteine: 2 g/d
SSRI/SNRI/bupropion + lithium or valproate	Various
Tranylcypromine (Parnate®, generic) or phenelzine (Nardil®, generic) + ongoing treatment	Tranylcypromine: up to 100 mg/d Phenelzine: up to 90 mg/d
Venlafaxine (Effexor®, generic) + lithium or valproate	Venlafaxine: up to 375 mg/d
L-thyroxine (Leventa®, Levothroid®, Levoxy®), Novothyrox®, Synthroid®, Thyrolar®, Tyrosint®, generic) + ongoing treatment	L-thyroxine: up to 450 mcg/d

analyses of mixed mania in BDI (i.e., DMX with severe manic symptoms)

- Dose ranges of the atypical antipsychotics suggested in Table 1 may be too strongly sedative for mild to moderate DMX
- No mood stabilizer (lithium and divalproex) is actually approved for use in depression of any kind (unipolar, mixed, bipolar),⁸⁶ except lamotrigine, which is approved for maintenance treatment in bipolar I disorder.^{9,11,14,71}
 - Lithium has traditionally been considered an effective antidepressant treatment augmentation strategy, and often very low doses of lithium can be effective for selected patients
 - Lithium is well-known for its anti-suicide, anti-aggression, anti-cycling, and antimanic effects. However, lithium also may yield less favorable effects as compared to divalproex in bipolar mixed states.⁸⁷ The efficacy of lithium in bipolar depression and especially mixed depression has not been adequately investigated

Patients failing to respond to monotherapy and continuing to experience subthreshold symptoms or relapses

- The treatment of DMX may require a combination of medications^{15,18,60,74,88}
 - Combinations with potential efficacy in DMX:
 - Atypical antipsychotic + mood stabilizer
 - Atypical antipsychotic + antidepressant
 - Olanzapine/fluoxetine combination in particular (caution in overweight or obese patients and those with metabolic dysregulation)
 - Mood stabilizer + antidepressant
 - If an antidepressant is prescribed for DMX, it should be used in conjunction with a mood-stabilizing agent (atypical antipsychotic or mood stabilizer); however, it is questionable whether adding an antidepressant to a mood stabilizer or atypical antipsychotic has therapeutic benefit in bipolar disorder patients.⁸⁹
 - (Hypo)manic symptoms, irritability, dysphoric mood, and insomnia can deteriorate or develop during antidepressant treatment even in conjunction with mood-stabilizing agents.^{89,90}
 - The role of antidepressants in long-term treatment is controversial and not established by controlled trials in DMX, but they may be used effectively in a small minority of patients in the long term,¹¹ particularly if there is a robust initial response or remission without signs of mood destabilization.⁹¹
 - The combination of olanzapine or risperidone with carbamazepine is not recommended due to potent pharmacokinetic induction of cytochrome P450 enzymes by carbamazepine.¹⁵
- The use of additional short-term medication (e.g., benzodiazepines) may be necessary when an acute stressor is imminent or present, early symptoms of relapse (especially insomnia) occur, or anxiety becomes prominent
- Addition of hypnotics for the treatment of insomnia unresponsive to mood disorder medications may be helpful/necessary
- Higher doses of the long-term treatments may also be effective, thus avoiding the need for additional medications
- Ensure adequate doses of medicines and that serum levels of lithium and valproate are within the therapeutic range
- Address use of alcohol or illicit psychoactive substances that can destabilize mood
- Address current stressors; consider psychosocial interventions in general, particularly those targeting lifestyle/daily rhythms, e.g., interpersonal social rhythm therapy (IPSRT)

TABLE 3. Notable side effects associated with mood stabilizers

Lithium	<ul style="list-style-type: none"> ■ Lithium toxicity; toxic levels are near therapeutic levels; signs of toxicity include tremor, ataxia, diarrhea, vomiting, sedation ■ Renal impairment (interstitial nephritis) ■ Nephrogenic diabetes insipidus ■ Arrhythmia, cardiovascular changes, sick sinus syndrome, bradycardia, hypotension ■ T-wave flattening and inversion ■ Dysarthria, delirium, memory problems ■ Nausea ■ Weight gain
Valproate	<ul style="list-style-type: none"> ■ Tachycardia or bradycardia ■ Rare hepatotoxicity with liver failure ■ Rare pancreatitis, sometimes fatal ■ Rare but serious skin condition known as “drug reaction with eosinophilia” (DRESS) ■ Sedation, dose-dependent tremor, dizziness ■ Abdominal pain, nausea, vomiting, diarrhea, reduced appetite, constipation, dyspepsia, weight gain ■ Ataxia, asthenia, headache
Carbamazepine	<ul style="list-style-type: none"> ■ Rare aplastic anemia, agranulocytosis (unusual bleeding or bruising, mouth sores, infections, fever, sore throat) ■ Rare severe dermatologic reactions (purpura, Stevens–Johnson syndrome) ■ Rare cardiac problems ■ Rare induction of psychosis or mania ■ SIADH (syndrome of inappropriate antidiuretic hormone secretion) with hyponatremia ■ Sedation, dizziness, unsteadiness, confusion ■ Nausea, vomiting, constipation, dry mouth ■ Blurred vision ■ Benign leukopenia (transient; in up to 10%) ■ Rash
Lamotrigine	<ul style="list-style-type: none"> ■ Rare serious rash (risk may be greater in pediatric patients but still rare) ■ Rare multi-organ failure associated with Stevens–Johnson syndrome, toxic epidermal necrolysis, or drug hypersensitivity syndrome ■ Rare blood dyscrasias ■ Rare aseptic meningitis ■ Benign rash (approximately 10%) ■ Dose-dependent: blurred or double vision, dizziness, ataxia ■ Sedation, headache, tremor, insomnia, poor coordination, fatigue ■ Nausea (dose-dependent), vomiting, dyspepsia, rhinitis

TABLE 4. Longitudinal monitoring according to treatment

Atypical antipsychotics	<ul style="list-style-type: none"> ■ Weight <ul style="list-style-type: none"> ◆ monthly for the first 3 months ◆ every 3 months ◆ as clinically indicated on an individual level ■ BP and fasting glucose <ul style="list-style-type: none"> ◆ every 3 months for the first year ◆ annually ◆ as clinically indicated on an individual level ■ Fasting lipid profile <ul style="list-style-type: none"> ◆ after 3 months ◆ annually ◆ as clinically indicated on an individual level ■ ECG and prolactin level <ul style="list-style-type: none"> ◆ as clinically indicated on an individual level
Lithium	<ul style="list-style-type: none"> ■ Serum levels <ul style="list-style-type: none"> ◆ two levels to establish therapeutic dose ◆ every 3–6 months ◆ following dosage changes ■ Electrolytes, urea, and creatinine (EUC) every 3–6 months ■ Calcium, TSH, and weight <ul style="list-style-type: none"> ◆ 6 months after initiating treatment ◆ annually
Valproate	<ul style="list-style-type: none"> ■ Serum levels <ul style="list-style-type: none"> ◆ two levels to establish therapeutic dose ◆ as clinically indicated ■ Weight, CBC, liver function, and menstrual history <ul style="list-style-type: none"> ◆ every 3 months for the first year ◆ annually ■ BP, fasting glucose, and lipid profile as clinically indicated ■ Bone density as clinically indicated
Carbamazepine	<ul style="list-style-type: none"> ■ Serum levels <ul style="list-style-type: none"> ◆ two levels (4 weeks apart) to establish therapeutic dose ◆ as clinically indicated ■ CBC, liver function, and EUC <ul style="list-style-type: none"> ◆ monthly for the first year ◆ annually ■ Monitor for rash, especially in first few months of treatment ■ Bone density as clinically indicated ■ Review contraceptive efficacy (where applicable)
Lamotrigine	<ul style="list-style-type: none"> ■ Monitor for rash, especially in first few months of treatment

- If the patient fails to respond to optimization of long-term treatment, consider augmentation or change of treatment^{9,11,12,17}
 - There are some limited data supporting the adjunctive use of L-thyroxine,^{92,93} N-acetyl-cysteine (NAC),^{94,95} omega-3 fatty acids,⁹⁶ ramelteon,⁹⁷

celecoxib,⁹⁸ modafinil,^{99,100} inositol,^{101,102} ketamine,^{103,104} and pramipexole¹⁰⁵ in the treatment of bipolar depression

- Consider electroconvulsive therapy (ECT) for patients with high suicidal risk, psychosis, severe depression during pregnancy, or life-threatening inanition. Consider simplifying preexisting polypharmacy, reducing drug-to-drug interactions; might lead to changes in seizure thresholds^{11,25}

- Transcranial magnetic stimulation (TMS) may also have some efficacy in treating mixed depression; however, this supposition is based on “off-label” data from preliminary trials in bipolar depression; attempt TMS only after other options have been tried⁷⁴

Maintenance treatment^{11,17,71,74,106}

- In an individual patient, if one of the recommended acute treatments led to prompt remission from the most recent mixed depressive episode, this may be considered evidence in favor of its long-term use as monotherapy
- The preferred strategy is for continuous rather than intermittent treatment with oral medication to prevent new episodes
- Without active acceptance of the need for long-term treatment, adherence may be poor; consider offering enhanced psychological and social support
- Consistent outpatient follow-up is necessary
- Long-term treatment is indefinite for the prevention of new episodes and to achieve adequate inter-episode control of residual or chronic mood symptoms
- Because of the high risk of relapse and the apparent progression to more frequent episodes, long-term treatment with appropriate medication is advocated from as early in the illness course as is acceptable to a patient and his or her family
- Remain vigilant to conversion to bipolar disorder of patients whose index episode is diagnosed as unipolar DMX
- In the absence of convincing evidence in favor of long-term treatment with antidepressants, the usual policy should be eventual discontinuation, although a small minority of patients have a robust initial antidepressant response and appear to do well on long-term combination treatment that includes an antidepressant⁸⁹

Safety monitoring⁵⁶

- Suicide is the main serious safety concern in this population, and an individualized approach is necessary depending on clinical variables, social support, and preexisting suicide risk factors
- Take all possible steps to protect and improve the physical health of patients in your care through active screening and treatment of risk factors or declared disease
- Higher morbidity and mortality have been reported in bipolar patients, even before treatment with psychotropic agents was initiated. It is of growing concern that many of the long-term treatments that appear to be required for mixed depression may add to the burden of physical disease
- In addition to baseline laboratory measurements, patients should be monitored continually for the

development of adverse events specific to the treatment(s) utilized

- The risk of tardive dyskinesia is significantly increased with the use of antipsychotics and should be monitored for regularly

Discontinuation of treatments^{9,11,15}

- Following discontinuation of medicines, the risk of relapse remains, even after years of sustained remission; accordingly, if considered, it should be accompanied by an informed assessment of the potential costs and dangers
- Discontinuation of any long-term medication should normally be tapered over at least two weeks and preferably longer. Early relapse to mania in bipolar disorder patients is a risk of abrupt lithium discontinuation. Clinical monitoring during treatment withdrawal is desirable
- When a patient has accepted treatment for several years and remains very well, he or she should be strongly advised to continue indefinitely, as the risk of relapse remains high

Children and adolescents^{12,16,17,34,43,56,61,70,107,108}

- The clinical features of childhood mood disorders often differ from those in adults
- Child and adolescent mood disorders are often comorbid with attention deficit and conduct disorders¹⁰⁹
- Mixed depression is especially common in children and adolescents^{40,110}
- The risk of antidepressant-induced suicidality may be highest in the pediatric population due to the presence of mixed features^{43,57,59,70,108}
 - Children and adolescents presenting with major depression should be screened and monitored for any (hypo)manic symptoms, suicidality, and family history of mood disorders
 - Antidepressant monotherapy should be avoided in children and adolescents until any presence of (hypo)mania or positive family history of bipolar spectrum disorder is ruled out
- With the exception of fluoxetine, the evidence for efficacy of antidepressants in treating major depressive disorder in the pediatric population is not robust¹¹¹
- Venlafaxine may have the highest risk of increasing suicidality in children and adolescents¹¹¹

Women of child-bearing potential^{11,17,56}

- The postpartum period is a time of very high risk of relapse or recurrence into severe illness in women with mood disorders. Vigilance and close monitoring

during the perinatal period is essential, and effective prophylactic treatment should be considered

- In pregnancy, there is a risk of teratogenicity from a number of medications used in all phases of treatment. Higher teratogenic risks appear to be associated with certain anticonvulsants (notably, valproate and carbamazepine). Lithium has also been associated with teratogenicity, although prospective studies suggest that the risk is lower than originally described. The lowest risks appear to be associated with the antipsychotics. However, risks for new compounds are usually unknown and always justify caution
- Many psychotropics can cause symptoms in neonates (including discontinuation effects from, e.g., antipsychotics, SSRIs). Neonates should be monitored for possible adverse effects following birth. Long-term effects on cognitive development have been reported with exposure to valproate in pregnancy
- However, optimization of maternal mental health remains a key determinant of pregnancy outcomes; thus, effective treatment of the mother must be carefully weighed against potential risks to the neonate¹¹²
- Discontinuation or switching medications risks destabilizing mood and precipitating relapse. Any risk putatively associated with the use of medications should be considered in the context of the relatively high age-related background risk for congenital malformations and spontaneous abortion in the general population
- If a mother takes medication and breastfeeds, the infant should be monitored for possible adverse effects
- Medications with a high risk in pregnancy such as valproate or carbamazepine should not be used routinely if there is a significant likelihood of pregnancy

Enhanced care^{9,11,12,25}

- Make use of evidence to address poor insight, the seriousness of the illness, reluctance to give up the experience of hypo(mania), the risk of relapse, and the benefit of therapeutic engagement
- While respecting patient preferences, education about the illness should emphasize the long-term need for medicines
- Help the patient, family members, and significant others recognize the signs and symptoms of mixed depressive episodes for early treatment; family psychoeducation may improve treatment outcomes
- Psychosocial interventions enhance care, which can increase adherence and reduce the risk of relapse
- A large and comprehensive program of psychoeducation may be superior to an equivalent time spent in nonspecific talking therapy

- Interpersonal and family therapy as well as cognitive behavioral therapy may be beneficial
- Group psychoeducation may also be more effective than cognitive behavioral therapy for some patients
- Internet-based psychosocial interventions may be helpful and hold promise, particularly with respect to accessibility
- A consistent long-term flexible alliance among the patient, the patient's family, and one effective clinician is the ideal arrangement for outpatient care in patients whose condition has been effectively stabilized. Patients' relatives should feel comfortable contacting the clinician to report escalations of symptoms or other emergencies
- Known tolerability of available medicines should guide prescribing:
 - Inform patients about possible side effects and monitor their possible emergence
 - Make side effect reduction a priority by lowering the dose, by employing different scheduling (e.g., prescribing all sedative medicines at bed time), or by using alternative formulations
 - Some patients with mixed depression may require or tolerate lower doses of mood-stabilizing drugs than those used for threshold-level mania

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