

DSM-5 Criteria: Major Depressive Disorder

Box 4.

DSM-5 Diagnosis: Major Depressive Disorder

Major Depressive Episode:

- ◆ Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

Note: Do not include symptoms that are clearly attributable to another medical condition.

- ◇ Depressed most of the day, nearly every day as indicated by subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful)
 - ◇ Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by subjective account or observation)
 - ◇ Significant weight loss when not dieting or weight gain (e.g., change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day
 - ◇ Insomnia or hypersomnia nearly every day
 - ◇ Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
 - ◇ Fatigue or loss of energy nearly every day
 - ◇ Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
 - ◇ Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
 - ◇ Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
- ◆ The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
 - ◆ The episode is not attributable to the physiological effects of a substance or to another medical condition.

Note: The above criteria represent a major depressive episode.

- ◆ The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.
- ◆ There has never been a manic episode or a hypomanic episode.

Note: This exclusion does not apply if all of the manic-like or hypomanic-like episodes are substance-induced or are attributable to the physiological effects of another medical condition.

Treatment of Major Depressive Disorder

Note: Treatment recommendations are based on levels of evidence and expert opinion. For a description of the criteria for each level, see page 4.

Conduct comprehensive assessment and use measurement-based care. Refer to Principles of Practice on pages 6–11.

The therapeutic objectives of acute treatment are to assure safety, measure response to therapy, provide psychoeducation to patient and circle of care, and to begin the process of symptomatic, syndromal, and functional recovery.

Strongly recommend psychiatric consultation prior to initiation of therapy + psychotherapeutic medication using a multi-disciplinary approach if treated by a non-psychiatrist.

Assess for:

- Current/Prior hypomania/mania, symptoms/episodes*
- Psychiatric and medical comorbidities (e.g., substance-related disorders, anxiety disorders, obesity, diabetes)
- Presence of specifiers, notably: psychosis, mixed features, suicidality
- Presence of cognitive dysfunction (e.g., memory complaints; difficulty with concentration, making decisions, and thinking clearly)
- Assess for recurrence vulnerability factors (e.g., symptom severity, age of onset, number of depressive episodes)
- Manual-based psychotherapy (e.g., CBT) or exercise therapy may be an appropriate treatment option for mild depression (e.g., PHQ-9 score 5 through 9).

**Note: Rule out the possibility of bipolar disorder in individuals presenting with depressive symptoms.*

Level 1 Initial Treatment:

- ◆ Antidepressant Monotherapy trial at adequate dose and evaluate*:
 - ◇ Selective serotonin reuptake inhibitor (SSRI)**, serotonin-norepinephrine reuptake inhibitor (SNRI), or vortioxetine
 - ◇ Bupropion or mirtazapine
- ◆ If partial response at 2 to 4 weeks, may continue for another 2 to 4 weeks or go to Level 2.
- ◆ If no response at 4 weeks, ensure dose optimization and go to Level 2.




Notes:

**Medication response is more pronounced in moderate to severe depression.*

***Consider propensity for drug-drug interactions and differential risk for teratogenicity.*

Initiate combination therapy for individuals with recurrent depression, persistent depressive disorder, and history of trauma. Be vigilant of emergence of hypomanic symptoms.

Treatment of Major Depressive Disorder (continued)

	<p>Level 2 If Level 1 is ineffective and/or not well tolerated:</p> <ul style="list-style-type: none"> ◆ Evaluate adherence ◆ Ensure dose optimization of medication used in Level 1. ◆ Switch to different monotherapy agent from different or same class (SSRI, SNRI, bupropion, or mirtazapine). ◆ Combine existing monotherapy with: <ul style="list-style-type: none"> ◇ Evidence-based psychotherapy (e.g., CBT, IPT) ◇ Second-generation antipsychotic FDA-approved for augmentation therapy for major depressive disorder (MDD) (i.e., aripiprazole or brexpiprazole; quetiapine is level 3 due to tolerability concerns) ◇ Intranasal esketamine or intravenous racemic ketamine. In the case of intranasal esketamine, co-administration with a separate antidepressant. ◇ An antidepressant (avoid SSRI and SSRI/SNRI combinations) <p><i>Note: FDA-approved adjunctive agents for MDD are select atypical antipsychotics. Preliminary evidence evaluating comparative effectiveness of adjunctive antidepressant versus adjunctive atypical antipsychotic medications indicates superior efficacy for adjunctive antipsychotics and superior tolerability for adjunctive antidepressants.</i></p>
	<p>Level 3 If Levels 1 and 2 are ineffective and/or not well tolerated:</p> <ul style="list-style-type: none"> ◆ Evaluate adherence ◆ Seek psychiatric consultation ◆ (SSRI or SNRI) + quetiapine (tolerability concerns) ◆ (SSRI or SNRI) + (lithium or T3) ◆ (SSRI or SNRI) + (L-Methylfolate or S-adenosylomethionine) ◆ Tricyclic antidepressant (TCA) ◆ Monoamine oxidase inhibitor (MAOI) ◆ Electroconvulsive therapy (ECT) ◆ Transcranial magnetic stimulation (TMS)* <p><i>*Note: Most evidence for TMS is in the acute treatment.</i></p>
	<p>Level 4 If Levels 1 – 3 are ineffective and/or not well tolerated:</p> <ul style="list-style-type: none"> ◆ Re-evaluate diagnosis if patient has failed to respond to 2 or more treatments ◆ Monoamine oxidase inhibitor (MAOI) augmentation (AVOID CONTRAINDICATED COMBINATIONS) ◆ L-methylfolate augmentation ◆ Triple drug combination (little evidence exists supporting or refuting this strategy) <ul style="list-style-type: none"> ◇ (SSRI or SNRI) + mirtazapine + bupropion ◇ (SSRI or SNRI) + mirtazapine + lithium* ◇ (SSRI or SNRI) + bupropion + second generation antipsychotic (SGA) ◆ Other neuromodulatory approaches [e.g., vagus nerve stimulation (VNS)] <p><i>*Note: Caution should be used when prescribing lithium due to increased risk to the fetus with use during pregnancy (i.e., Ebstein's anomaly).</i></p>

Treatment of Major Depressive Disorder with Mixed Features

Note: Treatment recommendations are based on levels of evidence and expert opinion. For a description of the criteria for each level, see page 4.

Conduct comprehensive assessment and use measurement-based care. Refer to Principles of Practice on pages 6–11.

Mixed features are subsyndromal hypomanic features defined according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).

Strongly recommend psychiatric consultation prior to initiation of therapy + psychotherapeutic medication using a multi-disciplinary approach if treated by a non-psychiatrist.

Assess for:

- Prior history of hypomania/mania
- Psychiatric and medical comorbidities (e.g., substance use disorders, anxiety disorders, obesity, diabetes)

Level 1 Initial Treatment:

- ◆ Minimal evidence for treating major depressive disorder (MDD) with mixed features specifier
- ◆ Discuss treatment option, including evidence-based psychotherapy [Cognitive Behavioral Therapy (CBT), Interpersonal Psychotherapy (IPT), Behavioral Activation]
- ◆ Consider FDA-approved second generation antipsychotic (SGA)** for augmentation in MDD or mood stabilizer (e.g., lithium*)
- ◆ Antidepressant monotherapy 4 to 8 week trial at adequate dose and evaluate
 - ◇ Selective serotonin reuptake inhibitor (SSRI), serotonin-norepinephrine reuptake inhibitor (SNRI), or vortioxetine
 - ◇ Bupropion (if tolerability concerns) or mirtazapine

Note: Antidepressant monotherapy in MDD with subsyndromal hypomania may be associated with a higher rate of suboptimal therapeutic outcomes when compared to MDD without subsyndromal hypomania.


- ◆ For all Level 1 treatments, if partial response at 4 weeks, may continue for another 2 to 4 weeks or go to Level 2.
- ◆ For all Level 1 treatments, if no response at 4 weeks, ensure dose optimization and go to Level 2.



Level 2 If Level 1 is ineffective and/or not well tolerated:

- ◆ Reassess for hypomania/mania
- ◆ Ensure dose optimization of medication used in Level 1
- ◆ Switch to lurasidone monotherapy or adjunct

Treatment of Major Depressive Disorder with Mixed Features (continued)

	<p>Level 3 If Levels 1 and 2 are ineffective and/or not well tolerated:</p> <ul style="list-style-type: none">◆ Alternative adjunctive SGA or lithium or lamotrigine◆ Consider electroconvulsive therapy (ECT) or transcranial magnetic stimulation (TMS)◆ Alternative antidepressants, including tricyclic antidepressant (TCA), monoamine oxidase inhibitor (MAOI), or first generation antipsychotic (FGA)**
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Notes:

*Caution should be used when prescribing lithium, lamotrigine, divalproex or carbamazepine to women of reproductive age due to increased risks to the fetus with use during pregnancy, including neural tube and other birth defects. Please see Florida Best Practice Recommendations for Women of Reproductive Age with Serious Mental Illness and Comorbid Substance Use Disorders and online guideline on the Pharmacological Treatment of Mood Disorders During Pregnancy available at floridamedicaidmentalhealth.org.

**Side-effect concerns with these agents include weight gain, metabolic syndrome, and extrapyramidal symptoms (EPS). Side-effects warrant vigilance and close monitoring on the part of the clinician.

Treatment of Major Depressive Disorder with Psychotic Features

Note: Treatment recommendations are based on levels of evidence and expert opinion. For a description of the criteria for each level, see page 4.



Conduct comprehensive assessment and use measurement-based care. Refer to Principles of Practice on pages 6–11.

Psychotic features are the presence of delusions and/or hallucinations as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Psychotic features may be mood-congruent, where the content of all delusions and/or hallucinations are consistent with typical depressive themes of personal inadequacy, guilt, disease, death, nihilism, or deserved punishment, or mood-incongruent, where the content of the delusions and/or hallucinations either does not involve these typical depressive themes or is a mixture of mood-congruent and mood-incongruent themes.

Strongly recommend psychiatric consultation prior to initiation of therapy + psychotherapeutic medication using a multi-disciplinary approach if treated by a non-psychiatrist.

Assess for:

- Prior history of hypomania/mania
- If MDD with psychosis presents post-partum, evaluate for bipolar disorder.
- Psychiatric and medical comorbidities (e.g., substance use disorders, anxiety disorders, obesity, diabetes)

<p>Level 1 Initial Treatment:</p> <ul style="list-style-type: none"> ◆ Treatment with Level 1 antidepressant for major depressive disorder without psychotic features. Selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) or vortioxetine + second generation antipsychotic (SGA)* ◆ Electroconvulsive therapy (ECT) (if patient safety is an immediate concern) ◆ Cognitive-behavioral therapy (CBT) and interpersonal psychotherapy (IPT) are not recommended as a first-line modality. <p><i>*Consider extrapyramidal symptoms (EPS) risk and metabolic concerns, including weight gain.</i></p>
<p> Level 2 If Level 1 is ineffective and/or not well tolerated:</p> <ul style="list-style-type: none"> ◆ Alternative antidepressant + SGA combination ◆ ECT
<p> Level 3 If Levels 1 and 2 are ineffective and/or not well tolerated:</p> <ul style="list-style-type: none"> ◆ Re-evaluate diagnosis ◆ Other antidepressant combinations with SGA ◆ Other antidepressant combinations with first generation antipsychotic (FGA) ◆ ECT (if not attempted earlier)

Summary for Treatment of Major Depressive Disorder

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INTRODUCTION

Convergent evidence from international studies indicates that Major Depressive Disorder (MDD) is one of the most common mental disorders affecting adult populations. Within the broader category of “non-communicable” chronic diseases (i.e., NCDs), MDD is associated with relatively higher rates of disability (e.g., impairment in role function) when compared to most other NCDs (e.g., diabetes mellitus) and is also associated with premature mortality of up to 10 years of potential years of life lost. In addition to being a highly disabling disorder, MDD is also a risk factor for several other NCDs (e.g., cardiovascular disease) and has been demonstrated to complicate health outcomes from conditions ranging from cardiovascular disease and diabetes to obesity.

Emerging evidence indicates that, in some cases, MDD exhibits a neuroprogressive process as evidenced by changes in brain structure, volume, and connectivity as a function of illness duration and episode frequency. This observation provides the basis for pressing the point strongly that screening for MDD should be paramount in clinical care settings that are likely to be utilized by individuals with MDD (e.g., primary care). The DSM-5 Field Trials sought to determine the inter-observer agreement of the MDD phenotype. These trials reported a somewhat underwhelming kappa correlation coefficient of 0.28. Translationally, the foregoing finding comports with other lines of evidence that a large percentage of adults with MDD are either not diagnosed accurately and/or are receiving the diagnosis many years after observable characteristics of the illness appear.

Along with individual risk and aspects of heritability that are well-described in MDD, there is growing interest in the role of social determinants in both predisposing and in some cases, offering resiliency to MDD. For example, poverty and exposure to physical and sexual trauma are not only common in the life narrative of individuals with MDD, but are identified as accounting for substantial variability in the risk for MDD. Moreover, protective factors including but not limited to, social connectedness, spirituality, and meaningful interpersonal relationships have all been identified as buffering individuals against the effects of chronic uncontrollable stress. The national and global interest in loneliness involves many aspects that interdigitate with risk and resiliency for depression but the current state of the art is such that we are uncertain whether the so-called “loneliness epidemic” represents a discrete phenomenon entirely or to some extent intersects with the phenotype of MDD.

The criteria items for a depressive episode, the essential feature of MDD, are well-known to clinicians. Emerging evidence now indicates that select symptoms and domains disproportionately account for adverse patient reported outcomes (PROs) (e.g., decreased quality of life, poor functioning, life satisfaction and vitality). A consistent finding amongst patient surveys is that patients assign greater priority, relative to clinicians, to achieving optimal PROs as a therapeutic objective of antidepressant treatment. This observation further underscores of defining the therapeutic objectives in treating MDD collaboratively with affected individuals.

Summary for Treatment of Major Depressive Disorder (*continued*)

PRINCIPLES OF TREATMENT

Similar to the **2017-2018 Florida Best Practice Psychotherapeutic Medication Guidelines for Adults**, the emphasis for the 2019-2020 guidelines is the emphasis on full functional recovery and integration as a priority therapeutic objective in MDD. Towards this overarching and patient-desired aim, it is essential that clinicians consider self-rating instruments when screening for MDD. It is also essential that once the clinical diagnosis of MDD has been established that therapeutic objectives include full symptom mitigation and consensually agreed upon therapeutic objectives in collaboration with patients. Available evidence also indicates that individuals with MDD who function at a higher level, despite being depressed, are more likely to respond and remit with antidepressant therapy. Along with underscoring the complex interrelationship between symptoms and function in MDD, the improved symptomatic outcomes in higher functioning adults with MDD provides the impetus for simultaneously targeting symptoms and functioning in patients with MDD.

Along with careful attention to the presence of depressive symptoms, the relatively high rates of medical and mental disorder comorbidity in the MDD population provides the basis for careful attention to preventing and, when present, treating comorbidity in MDD populations. Commonly encountered comorbidities (e.g., anxiety disorder, substance use disorders, attention deficit hyperactivity disorder, eating disorders), as well as medical disorders (e.g., cardiovascular disease, obesity, diabetes mellitus) should be part of routine assessment of any adult with MDD. Moreover, as with all patients, assessing for imminent risk of suicide is critical. Unfortunately, psychiatry is unable to predict suicide in ways that are robust, evidence-based and clinically applicable. The hope is that the future, perhaps through artificial intelligence machine-learning, we position clinicians to better predict lethal self-harm.

For many individuals presenting with depression of mild severity, manual-based psychotherapy may be a preferred option. Moreover, exercise therapy has also demonstrated symptom mitigating effects in individuals with depressive episodes of milder severity. For others presenting with depression of moderate to severe depressive episodes as part of MDD, pharmacotherapy should certainly be considered. In many cases, manual-based psychotherapy can also be an alternative and/or adjunctive treatment. The current evidence base indicates that for adults with treatment-resistant MDD, manual-based psychotherapy is most effective when combined with pharmacotherapy. Moreover, combination pharmacotherapy-manual based psychotherapy approaches are recommended for persons with persistent depressive disorder, MDD with select comorbidities (e.g., obsessive compulsive disorder) and situations where patients report histories of childhood trauma and/or manifest maladaptive personality traits.

An important new entry and FDA-approved treatment for MDD in 2019 is the approval of intranasal esketamine. Intranasal esketamine is approved for adults with treatment-resistant MDD (TRD), i.e., insufficient outcome with at least 2 conventional antidepressant approaches. Consensus amongst the panel was that before a patient is identified as having TRD, it is essential to assure that they have had optimal antidepressant trials including duration and dose optimization. The committee also agreed that dose optimization for any antidepressant should occur within 2–4 weeks of initiation in keeping with “response trajectory” studies which provide replicated evidence that early

Summary for Treatment of Major Depressive Disorder (continued)

improvement in mood symptoms (i.e., within 2–4 weeks) has modest positive predictive value that the index agent and dose are sufficient. What is more compelling is that the lack of clinically significant improvement within 2–4 weeks (i.e., greater than or equal to 20% improvement in mood symptoms) has powerful negative predictive value (i.e., approaching 85%–90%) that the index agent and dose are insufficient, providing impetus for dose optimization at 2–4 weeks. Intranasal esketamine is approved as an adjunct to a recently initiated antidepressant; although evidence suggests that disparate ketamine formulations may mitigate suicidal ideation, it remains unclear whether ketamine formulations are capable of reducing suicide. What also remains unclear is which formulation of ketamine and/or route of delivery is superior with respect to PROs and patient acceptability. It is also strongly recommended that ketamine only be delivered in treatment centers capable of offering multidisciplinary care to patients with treatment-resistant MDD.

In addition to ketamine, intravenous brexanolone was approved for post-partum depression in 2019 by the U.S. FDA. Clinicians are encouraged to consider all treatment options for post-partum depression noting that brexanolone was the first treatment specifically developed for post-partum depression. Clinicians are also encouraged to carefully screen for the possibility of bipolar disorder in any clinical presentation of depressive symptoms, notably in individuals presenting with new onset depressive symptoms during reproductive life events (e.g., post-partum period).

Insufficient response to antidepressant medication, alone or in combination with manual-based psychotherapy, would provide the basis for recommending neurostimulation. The panel was of the view that the current state of science would support superior overall efficacy for electroconvulsive therapy (ECT) when compared to repetitive transcranial magnetic stimulation (rTMS). Notwithstanding, there are likely advantages in patient acceptability and perhaps tolerability in some cases with rTMS when compared to ECT.

MAJOR DEPRESSIVE DISORDER WITHOUT MIXED FEATURES

The DSM-5 introduced mixed features specifier in the manual published in 2013. Mixed features refers to subthreshold hypomanic symptoms occurring during a depressive episode in an individual with MDD. The panel was of the view that the hazards posed by mixed features (e.g., a more complex illness presentation, higher rates of comorbidity, suicidality) as well as diminished response to conventional antidepressants warrants assessment as to the presence or absence of mixed features. In an adult who is presenting MDD without mixed features, clinicians are encouraged to select and sequence treatments according to the **2019–2020 Florida Best Practice Psychotherapeutic Medication Guidelines for Adults**.

MAJOR DEPRESSIVE DISORDER WITH MIXED FEATURES

For patients presenting with MDD and mixed features, the panel was of the view that it is important to consider the possibility that the identified patient may possibly have bipolar disorder. Longitudinal studies indicate that the majority of individuals with MDD and mixed features exhibit phenotypic stability across time (i.e., they retain the diagnosis of MDD). Notwithstanding, the relative risk for bipolar disorder in adults with MDD and mixed features is increased relative to the general population. Conventional antidepressants can and should be considered with careful attention for any amplification and/or new onset hypomanic symptoms. Symptom intensification

Summary for Treatment of Major Depressive Disorder (continued)

manifests in many ways including, but not limited to, anxiety, agitation, irritability, dysphoria and sleep disruption. Preliminary evidence suggests that for some adults with MDD with mixed features, second-generation antipsychotics may not only be efficacious but may also be better tolerated in this particular population. As per the Florida Best Practice Psychotherapeutic Medication Guidelines for Adults, the panel agreed that despite the lack of rigorous evidence, other agents with mood stabilizing properties (e.g., lithium, lamotrigine) may also be considered in MDD with mixed features as an adjunct to antidepressants or perhaps in some cases, as a treatment alternative.

MAJOR DEPRESSIVE DISORDER WITH PSYCHOSIS

There was no substantive change in the panel's recommendation in treatment for MDD with psychosis. MDD with psychosis affects at least 20% of individuals with MDD. Results from a recently completed randomized control trial provide results that comport with clinical impression that the combination of a conventional antidepressant and antipsychotic is the preferred, acute, and recurrence-prevention treatment option when compared to conventional antidepressant monotherapy. Indeed, electroconvulsive therapy is an alternative treatment option for MDD with psychosis; antidepressant monotherapy as well as manual-based psychotherapy as stand-alone treatment are not recommended.

MAINTENANCE TREATMENT IN MAJOR DEPRESSIVE DISORDER

Evidence indicates that the majority of individuals with MDD are at risk of recurrence. Furthermore, episode frequency is a powerful predictor of future episodes. Delineating which patients should be considered for longer-term therapy is informed by identifying recurrence vulnerability factors (e.g., number of prior episodes, residual symptoms, cognitive symptoms, comorbidity, stressors). Clinicians are encouraged to consider long-term tolerability and safety concerns (e.g., weight gain, glucose homeostatic disturbances) when selecting antidepressants acutely. Evidence also indicates that manual-based psychotherapy as well as mindfulness-based psychotherapeutic approaches can be helpful adjunctive and/or alternative treatment strategies during the maintenance treatment of MDD in individuals who have acutely responded to antidepressant monotherapy. The overarching therapeutic objective of maintenance treatment in MDD is to assist patients in full functional recovery in achieving consensually agreed upon PROs.

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