

DSM-5 Criteria: Major Depressive Disorder

Box 3.

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

Conduct comprehensive assessment and use measurement-based care. Refer to Principles of Practice on pages 6-10.

The therapeutic objectives of acute treatment are safety, response to therapy, patient psychoeducation, 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:

- Prior history of hypomania/mania*
- 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)

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

Level 1 Initial Treatment:

- ◆ Evidence-based psychotherapy [Cognitive-Behavioral Therapy (CBT), Interpersonal Psychotherapy (IPT), Behavioral Activation]

Note: Manualized-based psychotherapies are preferred (where available) as first-line treatment for major depressive disorder (MDD) of mild severity.

- ◆ Monotherapy 4-8 week 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 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.

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) ◇ An antidepressant (do not combine SSRI and SNRI) <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-adenosylmethionine) ◆ Tricyclic antidepressant (TCA) ◆ Monoamine oxidase inhibitor (MAOI) ◆ Electroconvulsive therapy (ECT) ◆ Transcranial magnetic stimulation (TMS)* <p><i>*Note: TMS only has Level 1 evidence for 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)] ◆ Intravenous ketamine (at specialized centers only and in accordance with best practices) <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

Conduct comprehensive assessment and use measurement-based care. Refer to Principles of Practice on pages 6-10.

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 options, 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

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.

- ◇ Bupropion (if tolerability concerns) or mirtazapine
- ◆ 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 different monotherapy SGA** or mood stabilizer*.
- ◆ Antidepressant monotherapy from different or same class
- ◆ Combine existing antidepressant with different SGA**.
- ◆ Combine SGA** or mood stabilizer with antidepressant.

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">◆ 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 major 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.

**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.



Florida Clozapine Hotline
available to give guidance:
1-727-562-6762
Rhemsath@aol.com

Treatment of Major Depressive Disorder with Psychotic Features

Conduct comprehensive assessment and use measurement-based care. Refer to Principles of Practice on pages 6-10.

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
- 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) + second generation antipsychotic (SGA)* ◆ Electroconvulsive therapy (ECT) (if patient welfare is an immediate concern) ◆ Cognitive-behavioral therapy (CBT) and interpersonal psychotherapy (IPT) are not recommended as 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)

Pharmacological Treatment of Major Depressive Disorder: 2017-2018 Update Summary

Roger S. McIntyre, M.D., FRCPC

Professor of Psychiatry and Pharmacology, University of Toronto

Head, Mood Disorders Psychopharmacology Unit (MDPU), University Health Network

Chairman and Executive Director, Brain and Cognition Discovery Foundation (BCDF)

Director, Depression and Bipolar Support Alliance (DBSA)

INTRODUCTION

Major depressive disorder (MDD) is one of the most common mental disorders throughout the United States and much of the developed and developing world. Evidence indicates that MDD is the leading cause of disability amongst young individuals (i.e., 18-24), and is a frequent cause of workplace impairment and absenteeism. In addition to being a highly disabling and distressing condition, MDD complicates many other psychiatric and medical conditions, adding to, and in some cases, multiplicatively, affecting overall morbidity and mortality.

Results from patient-reported outcome literature indicate that adults with MDD prioritize quality of life improvement, function, positive mental health, resiliency, and general well-being, over conventional symptomatic improvement. Notwithstanding the high prevalence and costs of MDD, many affected individuals are not accurately diagnosed and as a consequence are not receiving timely guideline-concordant treatment. Screening for MDD is highly recommended by the United States Preventative Services Taskforce, where resources to provide treatment are available. As the population of the United States and other developed nations ages, the association between MDD and age-related disorders (e.g., Alzheimer's disease, cardiovascular disease) is of increasing concern. The biomedical literature provides evidence suggesting that MDD is associated with premature aging processes in subpopulations of affected individuals. In accordance with this hypothesis, guideline-concordant treatment for MDD may forestall and prevent some age-related conditions. Finally, the adverse effect of MDD on the workforce is stark reminder that screening for, and attention given to, best practices in mood disorders extends beyond the ecosystem of the medical clinic and involves disparate settings including, but not limited to, education settings, the workplace, and the general community.

PRINCIPLES OF TREATMENT

Similar to the 2015 Florida Best Practice Guidelines, the **2017-2018 Florida Best Practice Psychotherapeutic Medication Guidelines for Adults** emphasize the importance of full functional recovery in MDD as the overarching therapeutic guideline. The possibility of achieving this foregoing objective is increased when individuals achieve symptomatic and syndromal remission, and attention is given to psychiatric and medical comorbidity, negative attitude towards treatment, as well as psychoeducation around the illness and its treatment (Zimmerman et al., 2017).

During the past ten years, extant evidence indicates that individuals with MDD and higher levels of pre-treatment function have higher response rates to conventional antidepressant treatment. The bidirectional association between symptoms and function in MDD raises a myriad of conceptual questions and hypotheses, as well as clinical implications. An axiomatic clinical implication derived

Pharmacological Treatment of Major Depressive Disorder: 2017-2018 Update Summary *(continued)*

from the foregoing observation is that augmenting patient function contemporaneously with symptom targeting in MDD provides a greater probability to therapeutic success and acceptability.

The integration of multimodality treatment with emphasis on positive mental health, resiliency, and human function invite the need for evidence-based psychosocial treatments combined with pharmacotherapy. The efficacy of antidepressants in improving symptoms in persons with MDD is well established, particularly for individuals with moderate-severe pre-treatment illness severity. It is recognized that drug-placebo differences in mild MDD are less replicated and/or compelling, suggesting psychosocial treatments as prioritized in many cases of MDD of mild severity.

The expert panel recognizes that there have been significant advances in computational psychiatry, machine learning, as well as data-driven approaches to predict (using big data) which antidepressant is appropriate. It is additionally recognized by the expert panel, that pharmacogenetics/pharmacogenomics testing has widespread availability, and in many jurisdictions, reimbursement, as well as clinician and patient acceptance. Notwithstanding, it is the opinion of the expert panel that compelling evidence supporting pharmacogenetics/pharmacogenomics testing as a robust method to guide treatment selection remains to be fully established (Rosenblat, Lee, and McIntyre, 2017).

MAJOR DEPRESSIVE DISORDER WITHOUT MIXED FEATURES

The expert panel did not make any substantive changes to the guidelines for MDD without mixed features. The expert panel recognizes that vortioxetine has received extensive study targeting cognition in MDD. Notwithstanding, vortioxetine, as well as many other first-line antidepressants, are considered as a first-line treatment option for most other symptoms in MDD.

MAJOR DEPRESSIVE DISORDER WITH MIXED FEATURES

The expert panel recognizes that approximately 25% of adults with MDD have mixed features (McIntyre et al., 2015). It is also recognized by the expert panel that mixed features is associated with healthcare service utilization, polypharmacy, and significant functional impairment (McIntyre et al., 2017). The expert panel recognizes that the United States Food and Drug Administration (FDA) has not approved any specific agent for MDD with mixed features. The preponderance of evidence, however, is that MDD with mixed features are less consistently responsive to conventional antidepressants, and may in some circumstances be more safely and effectively treated with mood stabilizing agents.

MAJOR DEPRESSIVE DISORDER WITH PSYCHOSIS

Major depressive disorder with psychotic features affects approximately 20% of adults with MDD, with higher percentages reported in younger and older populations. The best available evidence supports combining antidepressants with antipsychotics, or electroconvulsive therapy as the treatment of choice for MDD with psychosis. It is strongly recommended that MDD with psychosis not be treated with manualized-based psychotherapy as a stand alone modality of treatment.

Pharmacological Treatment of Major Depressive Disorder: 2017-2018 Update Summary *(continued)*

MAINTENANCE TREATMENT IN MAJOR DEPRESSIVE DISORDER

Evidence indicates that most individuals with MDD are at risk of recurrence, with each episode further increasing risk probability. The current recommendation for maintenance treatment is a minimum of 6-12 months upon completion of the acute phase pharmacotherapy. Individuals at higher risk for recurrence (e.g., residual symptoms, multiple episode frequency, comorbidity, ongoing psychosocial stressors) can remain on treatment for longer periods of time, individualized on a case-by-case basis. Most pharmacotherapeutic interventions have demonstrated acute and maintenance efficacy, while psychosocial treatments have distinct levels of evidence for each modality across phases of therapy. For example, cognitive-behavioral therapy has rigorous evidence supporting acute and recurrence prevention in MDD, while other psychosocial modalities have more rigorous evidence in relapse prevention than in acute phase treatment (e.g., mindfulness-based psychotherapy). It is also recommended by the expert panel that advocacy [e.g., Depression and Bipolar Support Alliance (DBSA)] can play a critical role in education support service access and illness/treatment literacy and should be considered an integral component of care for any person affected by MDD.

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