

# Treatment of Major Depressive Disorder

Conduct comprehensive assessment and use measurement-based care as found in the Principles of Practice (review pages 4-9).

The goals of acute treatment are safety, response to therapy, patient psychoeducation, and to begin the process of symptomatic, syndromal, and functional recovery.

Assess for:

- Prior history of hypomania/mania
- Psychiatric and medical comorbidities (e.g. substance use 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)

## Level 1 Initial Treatment:

- ◆ Discuss treatment options, including evidence-based psychotherapy [Cognitive-behavioral therapy (CBT), Interpersonal psychotherapy (IPT)]
- ◆ Monotherapy 4-8 week trial at adequate dose and evaluate:
  - ◇ Selective serotonin reuptake inhibitor (SSRI)\*, serotonin-norepinephrine reuptake inhibitor (SNRI), or vortioxetine (if cognitive complaints)
  - ◇ Bupropion (if tolerability concerns) or mirtazapine (if insomnia a focus of clinical concern)
- ◆ If partial response at 4 weeks may continue for another 2-4 weeks or go to Level 2
- ◆ If no response at 4 weeks go to Level 2

*\*consider propensity for drug-drug interactions, differential risk for teratogenicity*

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

- ◆ Evaluate adherence
- ◆ Dose optimization
- ◆ Switch to different monotherapy
  - ◇ Agent from different or same class (SSRI, SNRI, mirtazapine, bupropion)
- ◆ Combine existing monotherapy with:
  - ◇ Evidence-based psychotherapy (e.g. CBT, IPT)
  - ◇ Atypical antipsychotic FDA-approved for major depressive disorder (MDD) (i.e. aripiprazole, brexpiprazole)
  - ◇ An antidepressant (do not combine SSRI and SNRI)

## Treatment of Major Depressive Disorder *(continued)*

	<p><b>Level 3</b> If Levels 1 and 2 are ineffective and/or not well tolerated:</p> <ul style="list-style-type: none"><li>◆ Evaluate adherence</li><li>◆ Seek psychiatric consultation</li><li>◆ (SSRI or SNRI) + quetiapine (tolerability concerns)</li><li>◆ (SSRI or SNRI) + (lithium or T3)</li><li>◆ (SSRI or SNRI) + (L-methylfolate or S-adenosylmethionine)</li><li>◆ Tricyclic antidepressant (TCA)</li><li>◆ Monoamine oxidase inhibitor (MAOI)</li><li>◆ Electroconvulsive therapy (ECT)</li><li>◆ Transcranial magnetic stimulation (TMS)</li></ul>
	<p><b>Level 4</b> If Levels 1 – 3 are ineffective and/or not well tolerated:</p> <ul style="list-style-type: none"><li>◆ Re-evaluate diagnosis if patient has failed to respond to two or more treatments</li><li>◆ Monoamine oxidase inhibitor (MAOI) augmentation <b>(AVOID CONTRAINDICATED COMBINATIONS)</b></li><li>◆ L-methylfolate augmentation</li><li>◆ Triple drug combination (little evidence exists supporting or refuting this strategy)<ul style="list-style-type: none"><li>◇ (SSRI or SNRI) + mirtazapine + bupropion</li><li>◇ (SSRI or SNRI) + mirtazapine + lithium</li><li>◇ (SSRI or SNRI) + bupropion + second generation antipsychotic (SGA)</li></ul></li><li>◆ Other neuromodulatory approaches (e.g. vagus nerve stimulation)</li></ul>

# Treatment of Major Depressive Disorder with Mixed Features

Conduct comprehensive assessment and use measurement-based care as found in the Principles of Practice (review pages 4-9).

Mixed features are subsyndromal hypomanic features defined according to the DSM-5.

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)]
- ◆ Consider second generation antipsychotic (SGA) or mood stabilizer (e.g. lithium)
- ◆ Antidepressant monotherapy 4-8 week trial at adequate dose and evaluate (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):
  - ◇ Selective serotonin reuptake inhibitor (SSRI) (consider propensity for drug-drug interactions, differential risk for teratogenicity), serotonin-norepinephrine reuptake inhibitor (SNRI), or vortioxetine (if cognitive complaints)
  - ◇ Bupropion (if tolerability concerns) or mirtazapine (if insomnia a focus of clinical concern)
- ◆ For all Level 1 treatments, if partial response at 4 weeks, may continue for another 4 weeks or go to Level 2
- ◆ For all Level 1 treatments, if no response at 4 weeks, go to Level 2

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

- ◆ Reassess for hypomania/mania
- ◆ 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

## Level 3 If Levels 1 and 2 are ineffective and/or not well tolerated:

- ◆ Consider electroconvulsive therapy (ECT) or transcranial magnetic stimulation (TMS)
- ◆ Alternative antidepressants, including tricyclic antidepressant (TCA), monoamine oxidase inhibitor (MAOI), or first generation antipsychotic (FGA)

# Treatment of Major Depressive Disorder with Psychosis

Conduct comprehensive assessment and use measurement-based care as found in the Principles of Practice (review pages 4-9).

Assess for:

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

## Level 1 Initial Treatment:

- ◆ Selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) + second generation antipsychotic (SGA)\*
- ◆ Electroconvulsive therapy (ECT) (if patient welfare an immediate concern)
- ◆ Cognitive-behavioral therapy (CBT) and interpersonal psychotherapy (IPT) are not recommended as first-line modality

*\*Consider extrapyramidal symptoms (EPS) risk, weight gain, and metabolic concerns.*



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

- ◆ Alternative antidepressant + SGA combination
- ◆ ECT



## Level 3 If Levels 1 and 2 are ineffective and/or not well tolerated:

- ◆ 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: 2015 Update Summary

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## INTRODUCTION

The Global Burden of Disease study update (2013) is a reminder of the significant human capital costs and disability associated with Major Depressive Disorder (MDD).<sup>4</sup> There is increasing attention given to aspects of medical comorbidity, which differentially affect adults with MDD. The American Heart Association consensus statement (2015) identifies MDD as an independent Tier 2 risk factor for cardiovascular and atherosclerotic disease.<sup>8</sup> Misdiagnosis of MDD continues to be a modifiable deficiency, unnecessarily delaying the initiation of guideline-informed treatments, and warranting careful screening and diagnostic assessment. Measurement-based care has been unevenly adopted and implemented across healthcare settings. Evidence supporting improved health outcomes with the use of measurement-based care to evaluate symptoms, adverse events and function is compelling. There is growing interest in patient-reported outcomes in MDD, in light of the priority given by individuals with MDD to aspects of positive mental health, quality of life, and function as desired therapeutic objectives.

## MIXED FEATURES

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) provides definitions for nine specifiers as part of a Major Depressive Episode (MDE). The mixed features specifier is a new specifier in the DSM-5 and would apply to a depressive episode as part of MDD or Bipolar I/II Disorder. The impetus to include mixed features as a specifier and to replace mixed episodes was provided by replicated evidence indicating that a significant proportion (i.e., 20-40%) of individuals with MDD will experience subsyndromal hypomanic symptoms, but will not declare themselves as having Bipolar I/II Disorder. The longitudinal stability of MDEs with mixed features has been established with longitudinal, phenomenological studies. The impetus for identifying mixed features within individuals with MDD is the observation that a MDE with mixed features as part of MDD is associated with greater illness severity (e.g., symptom severity, functional impairment, and suicidality), as well as insufficient outcomes with conventional antidepressants.

As the DSM-5 mixed features specifier was recently introduced, there is insufficient controlled trial evidence to provide decision support for clinicians selecting and sequencing treatments for patients with such a clinical presentation. There is growing interest in the use of second generation antipsychotics (SGAs) as well as conventional mood stabilizing therapies (e.g., lithium) for individuals presenting with MDE with mixed features. However, to date, there is no U.S. Food and Drug Administration (FDA)-approved agent for MDD with mixed features and there is insufficient evidence to strongly prioritize SGAs, mood stabilizers, or to suggest that conventional antidepressants cannot be considered as first-line agents. Until further evidence becomes available, we have taken a pragmatic position that a conventional antidepressant should be considered as first-line therapy. We recognize that the foregoing recommendation is based on minimal evidence

## Pharmacological Treatment of Major Depressive Disorder: 2015 Update Summary *(continued)*

and assumptions that efficacy and tolerability are acceptable in this population. We are aware that the foregoing assumptions have not been affirmed, or refuted, with randomized controlled trials. Results from a largely descriptive body of literature suggest that conventional antidepressants may be less effective and/or poorly tolerated in MDD with mixed features. The guiding principle of pragmatism provided the rationale for us recommending either SGAs or mood stabilizing agents as possible considerations as first-line therapy for MDD with mixed features. We recognize the paucity of data supporting such a recommendation, albeit recently published controlled trials provide preliminary support. We believe it is prudent for clinicians to be vigilant for clinical presentations suggestive of mania or hypomania in the past history and/or during prospective follow-up in patients presenting with MDD and mixed features.

### NON-PSYCHOTIC MAJOR DEPRESSION

Lack of adherence to treatment continues to be a modifiable deficiency (and should be probed) is common across all complex brain disorders including, but not limited to, MDD. Consequently, evaluation for adherence to treatment should be a routine part of assessment and treatment monitoring. The introduction of levomilnacipran and vortioxetine represent mechanistically different antidepressant options. There remains an absence of compelling evidence that any single antidepressant or class is superior in efficacy to another. The genericization of antidepressants has resulted in the availability of a greater number of generic selective serotonin reuptake inhibitor (SSRI) and serotonin–norepinephrine reuptake inhibitor (SNRI) agents. Empirical evidence does not yet provide sufficient and unequivocal data as to whether switching medication versus combining medication is consistently the preferred therapeutic avenue in individual's insufficient response to an optimized index antidepressant.

Since the publication of the fifth edition of the Florida Best Practice Psychotherapeutic Medication Guidelines for Adults in 2013, brexpiprazole represents an additional FDA-approved agent for augmentation in adults with MDD. For individuals with milder pre-treatment severity levels, manualized-based psychotherapy is reasonable as a first-line treatment option. Notwithstanding decades of research, it is not compelling that pre-treatment phenomenological characteristics, specifically atypical, anxious and/or melancholic features, reliably and robustly predict antidepressant outcomes. Individuals with psychotic depression will require the combination, however, of an antidepressant and antipsychotic, while the seasonal onset specifier introduces the option of light therapy.<sup>9</sup>

During the past five years, a significant increase in the number of biomedical publications has appeared reporting on cognitive dysfunction in adults with MDD. Cognitive dysfunction in MDD is prevalent, pervasive, persistent, and a principle mediator of psychosocial impairment and workplace disability. Moreover, it has been determined that in subpopulations in individuals with MDD, cognitive performance decreases as a function of number of episodes, underscoring the number of progressive neurodegenerative disorders associated with MDD. It needs to be unequivocally stated that cognitive dysfunction in MDD is a core dimension of the illness and is detectable with both objective/subjective measures in individuals who are "in remission". It is additionally observed that, for many individuals with depression, cognitive dysfunction may

## Pharmacological Treatment of Major Depressive Disorder: 2015 Update Summary *(continued)*

be a consequence of illness severity (e.g., psychosis) as well as psychiatric (e.g., anxiety disorders and substance use disorders) or medical (e.g., obesity, diabetes mellitus, and thyroid dysfunction) comorbidity. The foregoing are opportunities for pre-emption, prevention, and treatment of cognitive problems. Moreover, in some cases, cognitive dysfunction may be an iatrogenic artefact not infrequently observed with treatments often prescribed for psychiatric (e.g., benzodiazepines and antipsychotics) and medical disorders (e.g., steroids).<sup>10</sup> Available evidence also indicates that there may be differences between antidepressants in their ability to improve measures of cognitive function.<sup>11</sup> The foregoing set of observations, as well as synthesis of existing data, provides a clarion call for evaluation and measurement of cognitive function and careful attention to this dimension of illness in patient assessment, management, and treatment selection.

### PSYCHOTIC DEPRESSION

The combination of antidepressant and antipsychotic therapy or electroconvulsive therapy (ECT) remains a strong, first-line recommendation in individuals with MDD and psychotic features. There remains, however, a paucity of data as to the duration of combination treatment in the case of antidepressant-antipsychotic co-therapy. Moreover, it is uncertain as to whether any one agent within a co-therapy regimen should be discontinued during maintenance treatment, and if both agents are discontinued, the temporality of discontinuation. In the absence of such data, it is our opinion that the combination treatment should continue without interruption with periodic assessment. The presence of psychotic symptoms in adults with MDD should provide additional impetus for screening for bipolar disorder.

### TREATMENT-RESISTANT DEPRESSION

Various definitions for treatment-resistant depression (TRD) have been proposed. The most often employed definition of TRD has been failure with adequate trials of at least two antidepressants from different categories. A significant percentage of individuals with treatment-resistant depression are pseudo-resistant (i.e., insufficient dose/duration of therapy). Compelling evidence exists for neuromodulatory approaches. Within the neuromodulatory category, the most compelling evidence is for ECT. However, repeated transcranial magnetic stimulation (rTMS), magnetic seizure therapy, and transcranial direct-current stimulation are often more acceptable to many patients. Results for deep brain stimulation (DBS) are mixed.

Principles of disease management are strongly recommended to improve health outcomes in treatment-resistant depression. For example, patient self-management entails defining therapeutic endpoints, treating to target, and treatment selection informed by decision support contained in these guidelines. Integrated, longitudinal, and accountable care are all considered critical aspects of managing individuals with MDD. There is inconsistent data with heterogeneous outcomes reported with anti-inflammatory agents, antioxidants, and nutraceuticals. Evidence for disparate formulations of ketamine, including S-ketamine, provides evidence of efficacy for both depression and suicidality measures in treatment-resistant populations.