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CME Objective
After studying this article, you should be able to:

- Make guideline-concordant treatment decisions that are informed by recent evidence and stakeholder input for patients with major depressive disorder

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Florida Best Practice Psychotherapeutic Medication Guidelines for Adults With Major Depressive Disorder

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ABSTRACT

Objective: Herein we provide the 2015 update for the Florida Best Practice Psychotherapeutic Medication Guidelines (FPG) for major depressive disorder (MDD). The FPG represent evidence-based decision support for practitioners providing care to adults with MDD.

Participants: The consensus meeting included representatives from the Florida Agency for Health Care Administration (FAHCA), advocacy members, academic experts in MDD, and multidisciplinary mental health clinicians, as well as health policy experts. The FAHCA provided funding support for the FPG.

Evidence: Evidence was limited to results from adequately powered, randomized, double-blind, placebo-controlled trials; in addition, pooled-, meta-, and network-analyses were included. Recommendations were based on consensus arrived at by the multistakeholder Florida Expert Panel. Articles selected were identified on the electronic search engine PubMed with the dates 2010 to present. The search terms were *major depressive disorder*, *psychopharmacology*, *antidepressants*, *psychotherapy*, *neuromodulation*, *complementary alternative medicines*, *pooled-analysis*, *meta-analysis*, and *network-analysis*. Bibliographies of the identified articles were manually searched for additional citations not identified in the original search.

Consensus Process: A consensus meeting comprising all representatives took place on September 25–26, 2015, in Tampa, Florida. Guiding principles (eg, emphasis on the most rigorous evidence for efficacy, safety, and tolerability) were discussed, defined, and operationalized prior to review of extant data. As MDD often pursues a recurrent and chronic course, principles of practice, measurement-based care, and comprehensive assessment and management of overall physical and mental health were emphasized. Evidence supporting pretreatment major depressive episode specifiers (eg, mixed features, anxious distress) and the role of pharmacogenomics (and other biological-behavioral markers) in informing treatment selection were comprehensively discussed. Algorithmic priority was assigned to agents with relatively greater therapeutic index (ie, efficacy) and minimal propensity for safety and tolerability disadvantages.

Conclusions: The updated 2015 FPG provide concise, pragmatic, evidence-based decision support for treatment selection and sequencing for adults with MDD. Principles of practice include measurement-based care, priority to both psychiatric and medical comorbidity, identification of *DSM-5*–defined specifiers (eg, mixed features), suicide risk assessment, and evaluation of cognitive symptoms. The FPG have purposefully aimed to minimize emphasis on "expert opinion" and instead differentially emphasized extant evidence for pharmacologic treatments.

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Clinical Points

- An updated guideline informing decisions in the treatment of major depressive disorder in adults has not been available in the United States since 2010, despite the introduction of the *DSM-5* (2013) and several antidepressants and adjunctive agents.
- The Florida Best Practice Psychotherapeutic Medication Guidelines provide up-to-date decision support for the safe and effective treatment of adults with major depressive disorder, with particular consideration given to chronic disease management, measurement-based care, attention to psychiatric and medical comorbidity, and newer nosologic entities (eg, mixed features).

Major depressive disorder (MDD) is a common and often severe disorder associated with high rates of nonrecovery, limited treatment response, recurrence, and chronic subsyndromal or syndromal symptomatology.[1] Results from patient-reported outcome studies indicate that despite achieving "symptomatic remission," most individuals affected by MDD report decreased quality of life and impaired psychosocial and workplace function. It is amply documented that MDD is a leading cause of human disability globally and significantly debases human capital.[2,3]

In addition to the enduring disability associated with MDD, compelling evidence also indicates that MDD is highly associated with psychiatric and medical comorbidity.[4] For example, the American Heart Association consensus statement (2015)[5] identified MDD as an independent tier II risk factor for cardiovascular and atherosclerotic disease in young populations. Notwithstanding the public health priority of MDD, as well as the increasing public, academic, and policy attention given to MDD, misdiagnosis or delayed diagnosis and failure to incorporate appropriate measurement-based care are significant modifiable deficiencies in current practice. Moreover, guideline-discordant care is frequently reported in MDD, unnecessarily contributing to failure to achieve patient- and society-defined treatment outcomes in MDD.[6,7]

The American Psychiatric Association (APA) Practice Guideline for the Treatment of Patients with Major Depressive Disorder, Third Edition (https://www.guideline.gov/summaries/summary/24158/Practice-guideline-for-the-treatment-of-patients-with-major-depressive-disorder-third-edition), was last updated in October 2010. The APA Practice Guideline is similar to most other international MDD guidelines insofar as it is a conflation of both evidence- and expert opinion–based recommendations.[8–11] Expert opinion is informed by extensive and comprehensive experience in the assessment, diagnosis, treatment, and management of individuals with MDD. In addition, mood-disorder experts are familiar with scientific, clinical, and therapeutic developments in their subspecialty. Notwithstanding, expert opinion neither replaces nor supersedes extant empirical evidence. Moreover, expert opinion is susceptible to systematic biases, and the patient population often served by experts in the field is not necessarily representative of most individuals with MDD.

Conversely, MDD guidelines derived exclusively from randomized controlled pharmacologic trials also have significant limitations. For example, the majority of large, high-quality studies evaluating pharmacologic agents in MDD are sponsored by industry wherein the principal aim is to seek regulatory approval and/or marketing authorization by establishing efficacy superiority of an agent (with acceptable safety and tolerability risk) compared to placebo. The foregoing studies provide substantial attention to internal validity; consequently, the majority of individuals with mood disorders seen in "real-world" clinical settings are not necessarily eligible for registration trials.[12] This limitation in ecological validity is a consequence of the differential emphasis placed on enhancing assay sensitivity in registration trials rather than on generalizability (ie, "external validity").

Consequently, practicing clinicians often utilize decision support derived from MDD populations with clinical characteristics (eg, substance use disorders, suicidal ideation) divergent from patients that they encounter. Moreover, there is a paucity of adequately powered, head-to-head comparator trials addressing critical questions posed by patients, families, health care providers, and other stakeholders as to the preferred agent for a specific patient. This gap in comparative effectiveness evidence impedes the ability to accurately adjudicate important therapeutic differences between available agents. An additional concern that is raised when interpreting extant trial data is the unavailability of negative study findings.[13]

A further limitation is that most clinical studies evaluating pharmacologic treatments for mood disorders do not have multiple-year follow-up. Consequently, there is insufficient data informing relapse-and-recurrence prevention[14] and possible effects on illness trajectory. A major limitation of clinical research in psychiatry, broadly, has been the disproportionate emphasis on symptomatic improvement with relatively less information regarding patient-reported outcomes such as quality of life and general and workplace functioning. Individuals affected by mood disorders are often seeking treatments that not only reduce their distress but also are capable of improving their overall function, self-regard, and general adaptation; unfortunately, extant research provides insufficient decision support across these critical domains.[15] Mindful of the foregoing set of limitations, the guiding principle of the Florida Best Practice Psychotherapeutic Medication Guidelines (FPG) for the treatment of MDD was to adhere to the most rigorous of evidence (with limitations noted) with a pragmatic understanding that such data may not necessarily align entirely with each encountered patient.

Most treatment guidelines for MDD are written almost exclusively by experts and academics, often without any contribution from multiple stakeholders who utilize or reimburse for the treatments. For example, relatively few treatment guidelines in MDD are the result of an iterative process involving payers (ie, public, private), advocacy groups (eg, patients, families), experts in public policy,

practitioners in community settings, and academics and experts. Implementation theory would posit that adoption of, and concordance with, guideline-based recommendations is optimized when all stakeholders are participants in the iterative process. A barrier to implementation of treatment guidelines broadly is the perception by stakeholders that recommendations are often overinclusive, lack sufficient specificity, and are not aligned with efforts to personalize treatments for busy clinical practice. In contradistinction to the APA Practice Guideline, as well as other guidelines in MDD (eg, Canadian Network for Mood and Anxiety Treatments [CANMAT][16]), the FPG purposefully included multiple stakeholders (eg, advocacy, public health policy experts) throughout the iterative and decision-making process.

Cognizant of the foregoing limitations in the consensus-based process previously mentioned, the overarching principle shaping the FPG was to optimize stakeholder input (eg, expert opinion, payer involvement, clinician preferences). Consequently, the FPG participants aimed to develop a set of algorithms that comport with, and reflect, the most rigorous evidence available in the published biomedical literature. Moreover, the FPG were informed by the aim to offer succinct, unambiguous, and specific recommendations.

The rationale for the Florida Medicaid Drug Therapy Management Program for Behavioral Health (MDTMP) has been described in detail elsewhere.[17] Briefly, the Florida legislature authorized the development of the MDTMP, of which the aim was "to improve the quality and efficiency of the prescribing of mental health drugs, and to improve the health outcomes of Medicaid beneficiaries with a mental illness."[17(p921)] The members of the MDTMP, as well as the authors of the FPG for MDD herein, were highly familiar with the existing treatment guidelines for MDD across the United States, European Union, Asia, Australia, Canada, and elsewhere.[9–11,16,18] A further impetus for creating the FPG was the absence of an updated US-based MDD treatment guideline and the introduction of many mechanistically dissimilar agents for the treatment of MDD. The FPG, in contradistinction to most other guidelines, are updated biannually, providing opportunity for timely modification of treatment recommendations, informed by the most recent available evidence. The overarching goal of the FPG is to support mental health care providers (notably primary care providers) in making treatment decisions that are safe and evidence based and that maximize benefit and minimize harm to patients.

CONSENSUS PROCESS

The current iteration of the FPG for MDD reflects a biennial revision of existing FPG inaugurated in 2012, last updated in 2013 (http://media.mycme.com/documents/168/florida_best_practice_psychoth_41790.pdf). The 2015 group of stakeholders is referred to as the Florida Expert Panel and comprises nationally and internationally recognized experts in mood disorders, Florida psychiatrists in private practice or working at community mental health centers, academics, pharmacists, medical directors at managed care organizations, and obstetrician-gynecologists (the names of the meeting attendees and meeting presentations are available on the program website at www.medicaidmentalhealth.org).

The 2015 Florida Expert Panel met in Tampa, Florida, on September 25–26, 2015, to review and update the adult MDD guidelines, last completed in 2013. (The FPG for adults with bipolar disorder were last published in 2015.) The Florida Expert Panel discussed treatment evidence in the context of prior data published since the previous FPG and reached a consensus about whether to revise and adopt a particular set of guideline recommendations. The aim was to produce a final FPG representing a comprehensive, up-to-date, succinct synthesis of the extant literature, with differential emphasis given to the highest level of clinical evidence (eg, randomized controlled trials; systematic reviews as well as pooled-, meta-, and network-analyses) and expert consensus on the strength of the evidence.[19]

The FPG for MDD begin with general principles of practice (Table 1). Also, the FPG for MDD are organized hierarchically based on the strength of the scientific evidence for efficacy, safety, and tolerability regarding any treatment option. Level 1 treatments have compelling evidence of efficacy, as well as safety and tolerability, and are given preference over treatments with lower levels of evidence or relatively inferior safety and tolerability. The levels of evidence have been codified as follows:

- Level 1 describes initial treatment recommendations for which there is established efficacy and relative safety (based on replicated, large randomized controlled trials).
- Level 2 is based on 2 considerations: first, if drugs with established efficacy have safety concerns that should limit their use compared to level 1 agents; second, if drugs from level 1 are ineffective or not well tolerated. Compared to level 1, the data on treatment efficacy in level 2 are less robust (based on smaller randomized controlled trials, smaller effect sizes, etc) or the data on comparative safety concerns are more robust and suggest safety concerns for level 2 treatments.
- Level 3 is considered if levels 1 and 2 are ineffective or not well tolerated. Treatments at this level have limited efficacy data or more tolerability limitations than levels 1 and 2.
- Level 4 is considered if levels 1 through 3 are ineffective or not well tolerated; however, the treatments are not as well empirically supported at this time and are listed because of expert opinion or use in clinical practice.

Hierarchical levels of evidence are not a tacit statement of their algorithmic sequence. Instead, as with all guidelines for medical disorders, the FPG for MDD take into account individual patient characteristics such as prior response

Table 1. Principles of Practice[a]

Comprehensive assessment
Careful, differential diagnostic evaluation
Risk for suicide and violence
Co-occurring disorders and physical comorbidities
Substance abuse disorders, including tobacco use
Potential bipolar disorder must be assessed in patients presenting with depression
Serious mental health conditions are chronic in nature; therefore, a long-term management plan is essential
Use measurement-based care to measure symptoms, side effects, and adherence
Select maintenance medications that have a low relative risk of weight gain and metabolic syndrome
Monitor physical health and medication side effects (see Program publication, "A Summary for Monitoring Physical Health and Side-Effects of Psychiatric Medications in the Severely Mentally Ill Population," available at www.medicaidmentalhealth.org)
Integrate care of psychiatrists and primary care providers
Collaborative/shared treatment decision-making with patients and family/caregivers
Perform a psychosocial assessment
Assess social support system (housing, family, other caregivers)
Evaluate threats to continuity of care (access to medication, adherence, etc)
Give patients tools/support for recovery and self-management
Adjunctive psychosocial treatments (as indicated)
Individual and family psychoeducation
Cognitive-behavioral therapy
Interpersonal psychotherapy
Interpersonal and social rhythm therapy
Family-focused therapy
Group psychoeducation (especially for bipolar disorder)
Social skills training (especially in schizophrenia)
Cognitive remediation/rehabilitation (to improve attention, memory, or executive function)
Measurement-based care
Questionnaires and rating scales are useful tools for diagnostic assessment and evaluation of treatment outcomes, and such instruments can be helpful in providing supplemental information to clinical judgment. The integration of measurement scales into routine clinical practice is suggested for each of the conditions covered in this document. Clinicians should use rating scales to assess symptom severity during the initial evaluation/treatment, when medication changes are implemented, and when the patient reports a change in symptoms.
Treatment targets need to be precisely defined.
Effectiveness and safety/tolerability of the medication treatment must be systematically assessed by methodical use of appropriate rating scales and side-effect assessment protocols.
Internet links to the following scales are available on the program website (www.medicaidmentalhealth.org)
Beck Depression Inventory
Brief Psychiatric Rating Scale
Clinical Global Impressions Scale
Clinician-Rated Dimensions of Psychosis Symptom Severity
Hamilton Depression Rating Scale
Montgomery-Asberg Depression Rating Scale
Patient Health Questionnaire
Positive and Negative Syndrome Scale
Quick Inventory of Depression Symptomatology
Young Mania Rating Scale

[a]Note on pharmacogenomic testing—limited data exist examining whether patient care that integrates pharmacogenomic test information results in better or safer treatment.

to treatment, patient preferences, and other aspects of care (eg, comorbidity) when selecting and sequencing treatments throughout the algorithm.

Safety is a particular focus of the FPG. Safety (as distinguished from tolerability) became a concern directly affecting recommendations in the 2014 FPG for the treatment of bipolar disorder (described therein). For example, olanzapine-fluoxetine, a US Food and Drug Administration (FDA)–approved agent for treatment-resistant depression is a level 2 recommendation. In contradistinction, aripiprazole and brexpiprazole, agents also with high-quality studies, are given priority on the basis of clinically significant weight gain and metabolic hazards associated with olanzapine. The previously published FPG for adults with bipolar disorder[17] list olanzapine-fluoxetine, an FDA-approved agent for the treatment of bipolar I depression, as a level 2A recommendation.

Although a large number of first-line treatment options are available for adults with MDD, the evidentiary base informing treatment steps after failure of the first-line treatment, and beyond, is considerably less robust. Moreover, despite minimal evidence supporting the notion that pretreatment phenomenology sufficiently informs treatment selection, specific principles and treatments would be recommended if supported by the evidence. Similar to the previous FPG for bipolar disorder, the guidelines for MDD herein provide decision support and education.

The *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*) defines and provides operational criteria for up to 9 specifiers as part of a major depressive episode (MDE). The consensus among the Florida Expert Panel was that there were insufficient data supporting the notion that specifiers significantly influence treatment selection.[16,18,20,21] Exceptions, however, were noted for the psychotic (mood congruent, mood incongruent) and mixed features specifiers. The consensus was that there was unequivocal evidence of illness validators, as well as response characteristics, for adults with MDD and psychosis that warrant a separate treatment algorithm when compared to MDD without psychosis.

It was also a consensus that MDD with mixed features exhibited differential illness validators, a more complex illness presentation, higher risk for suicidality, and insufficient outcome with conventional antidepressants when compared to MDD without mixed features. The foregoing consensus provided the impetus and rationale for the *DSM-5* taskforce to introduce the mixed features specifier during an MDE as part of MDD. The Florida Expert Panel recognized that the evidentiary base supporting treatment options for MDD with mixed features specifier was minimal and largely comprised predominantly descriptive and uncontrolled studies, with only 1 well-controlled trial[22] that we are aware of to date. Nonetheless, the differential illness trajectory (eg, increased probability of subsequent hypomanic or manic episodes) and the relatively higher probability of symptom intensification, destabilization, and unmasking of bipolar disorder warranted particular attention to the mixed features specifier. Consequently, the FPG for MDD were divided into 3 subsections: MDD without mixed features specifier and nonpsychotic, MDD with mixed features and nonpsychotic, and MDD with psychosis.

Guiding principles common to each of the 3 foregoing MDD algorithms are to assess and monitor for the presence or history of hypomania or mania, to assess and treat psychiatric and medical comorbidity, and to evaluate for the presence of psychosis, mixed features, and suicidality. Measurement-based care for assessing symptoms, side effects, and adherence is strongly recommended and has been demonstrated to significantly improve health outcome.[23] Several measurement tools are available for evaluating the presence and severity of depressive symptoms (eg, Patient Health Questionnaire-9, Quick Inventory of Depressive Symptomatology–Self-Report). Safety monitoring should include ongoing surveillance of anthropometrics, metabolic parameters, and, where indicated, electrocardiographic monitoring. Clinicians are encouraged to specifically probe for and monitor tolerability concerns commonly associated with antidepressants, eg, sexual dysfunction, gastrointestinal, and insomnia. Adherence should be evaluated at each visit by probing the percentage of days that individuals have been discordant with recommended treatment.

An additional principle of practice is integration of primary and specialist health care as part of a collaborative working relationship with patients and families.[24] During the initial assessment, and during the provision of ongoing care, psychosocial assessment, determination of social support systems, potential threats to continuity of (or access to) care, and the provision of tools and supplementary materials to foster self-management are encouraged. It is recognized by the Florida Expert Panel that the level of evidence supporting adjunctive exercise (ie, aerobic or resistance) as well as other lifestyle and health behavior modifications (eg, dietary modification, sleep hygiene/behavior, smoking cessation) as singular modalities of therapy does not comport with level 1 evidence.[25,26] Notwithstanding, the health benefits afforded by the foregoing, as well as their beneficial effects on general well-being, health, and quality of life, warrant discussion and, in many cases, specific recommendations at patients' first treatment visit as part of a comprehensive management plan.

The Florida Expert Panel recognized that cognitive symptoms are common during an MDE. During the past several years, a compelling body of literature[27,28] has indicated that cognitive symptoms in MDD are prevalent and often persistent despite resolution of mood and neurovegetative symptoms. It is further noted that cognitive symptoms in MDD are a principal mediator of psychosocial impairment and workplace disability.[29–32] The Florida Expert Panel recognized that a gold standard (eg, comprehensive, multidimensional, brief) neurocognitive measure capable of screening for cognitive symptoms as well as detecting change across time with intervention is not readily available.[27] Moreover, evidence supporting the premise that screening for cognitive dysfunction in MDD moderates health outcomes is not available. Nonetheless, the Florida Expert Panel concluded that particular emphasis should be given to cognitive symptoms in MDD as part of the overall assessment.

GUIDELINES

Major Depressive Disorder

Timely and accurate diagnoses, as well as consensually agreed upon, objective, and measurable therapeutic objectives that aim for symptomatic, syndromal, and functional recovery, are emphasized.[33]

Level 1 (initial treatment). Available evidence would support either manual-based psychotherapy (eg, cognitive-behavioral therapy, interpersonal therapy) or monotherapy with a conventional antidepressant for mild to moderate depressive episodes (Table 2). Evidence for superior efficacy of either modality as first-line treatment is not available.[34,35] The Florida Expert Panel recognizes that drug-placebo differences in antidepressant efficacy are greater in individuals with higher baseline levels of depressive symptoms. There remains an absence of compelling evidence that any single antidepressant or class is superior in efficacy to another.[35]

It is also recognized that higher baseline depression severity would proscribe manual-based psychotherapy as first-line treatment. Pragmatically, individuals with more severe pretreatment depression are often unable to sufficiently engage psychosocial interventions (eg, cognitive-behavioral therapy), warranting initial treatment with antidepressant therapy (a relatively new psychosocial treatment, cognitive remediation therapy, which specifically targets cognitive dysfunction, has demonstrated preliminary evidence[36] of improvement in cognitive functions in adults with MDD). Moreover, individuals with psychotic features should not be offered manual-based psychotherapy as a primary treatment option.[37,38] In addition, a pragmatic recommendation is that individuals with severe, nonpsychotic MDD who are not able to actively participate in psychosocial treatments should not be offered manual-based psychotherapy as a first-line and exclusive modality of treatment. The Florida Expert Panel also recognized that most conventional antidepressants have not been sufficiently studied with respect to their ability to provide independent, clinically relevant benefit on measures of cognition. Similar to comments earlier regarding the absence of head-to-head studies evaluating efficacy on conventional depression outcomes, there is minimal evidence directly comparing the relative benefits of antidepressants on measures of cognition.

Available evidence indicates that partial therapeutic improvement after 2–4 weeks warrants dose optimization or inclusion of level 2 treatment recommendations. The foregoing recommendation is supported by replicated evidence[39,40] that insufficient symptomatic outcome (ie, defined specifically as less than 20% reduction in scores on depression rating scales) after approximately 2–4 weeks of antidepressant therapy has robust negative prediction of nonresponse after 8 weeks. It is also highly recommended to consider propensity for drug-drug interactions and teratogenicity throughout the algorithm.

Level 2 (if level 1 is ineffective or not well tolerated; has high-quality evidence and established safety). Nonadherence is recognized as a principal detractor to achieving

Table 2. Consensus Guidelines for Treatment of Major Depressive Disorder

Conduct comprehensive assessment and use measurement-based care as found in the Principles of Practice (review "Consensus Process" section and Table 1).

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 or mania
- Psychiatric and medical comorbidities (eg, substance use disorders, anxiety disorders, obesity, diabetes)
- Presence of specifiers—notably, psychosis, mixed features, suicidality
- Presence of cognitive dysfunction (eg, 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- 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 (if insomnia a focus of clinical concern) are also Level 1 treatments
- If partial response, defined as ≥ 20% reduction in total depressive symptom severity at 2–4 weeks, may continue for another 2–4 weeks and then reassess
- If suboptimal response, defined as < 20% reduction in total depressive symptom severity at 2–4 weeks, then go to Level 2

**Note: consider propensity for drug-drug interaction, differential risk for teratogenicity.*

Level 2—If Level 1 is ineffective 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 (eg, CBT, IPT)
  - Atypical antipsychotic FDA-approved for major depressive disorder (MDD) (ie, aripiprazole, brexpiprazole)
  - An antidepressant (do not combine SSRI and SNRI)
  - Adjunctive aerobic exercise (manual-based)

Level 3—If Levels 1 and 2 are ineffective or not well tolerated
- Evaluate adherence
- Seek psychiatric consultation
- (SSRI or SNRI) + quetiapine (tolerability concerns)
- (SSRI or SNRI) + (lithium or T_3)
- (SSRI or SNRI) + (L-methylfolate or *S*-adenosylmethionine)
- Tricyclic antidepressant
- Monoamine oxidase inhibitor (MAOI)
- Electroconvulsive therapy
- Transcranial magnetic stimulation

Level 4—If Levels 1–3 are ineffective or not well tolerated
- Reevaluate diagnosis if patient has failed to respond to 2 or more treatments
  - MAOI augmentation **(AVOID CONTRAINDICATED COMBINATIONS)**
- L-methylfolate augmentation
- Triple drug combination (little evidence exists supporting or refuting this strategy)
  - (SSRI or SNRI) + mirtazapine + bupropion
  - (SSRI or SNRI) + mirtazapine + lithium
  - (SSRI or SNRI) + bupropion + second-generation antipsychotic
- Other neuromodulatory approaches (eg, vagus nerve stimulation)

Abbreviation: FDA = US Food and Drug Administration.

therapeutic success and should be systematically assessed. At level 2, full-dose optimization should be realized with the index agent. Level 2 decisions include either switching to a different antidepressant monotherapy or combining manual-based psychotherapy or an FDA-approved second-generation antipsychotic (SGA) for MDD (ie, aripiprazole or brexpiprazole).[41,42] Available evidence[43,44] indicates that if beneficial effects with SGAs are not observed after 1–2 weeks, dose optimization of the SGA should be considered. Meta-analytic data[45,46] indicate that SGA efficacy may be greater as a function of the number of previously failed antidepressants. The Florida Expert Panel recognizes that although combination antidepressant prescription is commonplace, the evidence base supporting the benefit of combined antidepressants that are either prescribed sequentially or coadministered at the initiation of therapy is insufficient. The evidence,[47,48] however, strongly suggests that the use of multiple antidepressants concurrently is associated with higher risks of adverse events. In addition, available evidence[25,26] and results of meta-analyses would also support the adjunctive inclusion of exercise-based therapy at this level.

Level 3 (if levels 1 and 2 are ineffective or not well tolerated). The Florida Expert Panel was of the view that the guiding principles of adherence and dose optimization should be revisited and considered for psychiatric consultation at this level. US Food and Drug Administration–approved SGAs for MDD with higher propensity for weight gain or metabolic dysregulation (eg, olanzapine) are recommended at this level. Tricyclic antidepressants (TCAs), monoamine oxidase inhibitor (MAOI), electroconvulsive therapy (ECT), and repetitive transcranial magnetic stimulation (rTMS) are recommended as level 3 treatments.[49–51] In addition, coadministration of lithium, triiodothyronine (T_3), L-methylfolate, or *S*-adenosylmethionine (SAMe) are recommended at this level, although the data supporting their use are much less robust than for the treatments listed above in this level. A point of emphasis is that the evidence for ECT and TMS is far superior to the evidence supporting lithium, T_3, L-methylfolate, or SAMe in MDD. The rationale for including the foregoing agents at this level with neuromodulatory (eg, rTMS) options is largely in response to relative lack of access to neuromodulatory treatments and limited patient acceptability of some modalities of neuromodulation (eg, ECT).

Level 4 (if levels 1–3 are ineffective or not well tolerated). The combination of level 1–3 treatments should be considered while avoiding contraindicated combinations (eg, combination of MAOI and SSRI). Triple pharmacologic therapy, as well as other neuromodulatory approaches (eg, vagus nerve stimulation), are recommended at this level.

It is well established that at least half of individuals with MDD are susceptible to relapse and recurrence of clinically significant depressive symptoms after recovery from the index episode. Individuals with recurrence vulnerability factors would be candidates for continuation or maintenance therapy. For any individual with ongoing subsyndromal symptoms, a

history of illness multiple recurrence, or a need for multiple-level treatments to achieve symptomatic, syndromal, and functional recovery, indefinite treatment may be warranted. It is also recognized that recurrence prevention in an individual responding acutely to pharmacotherapy may be achieved by the sequential administration of manual-based psychotherapies.[52,53] For now, however, the most robust body of evidence would support continuation or maintenance of pharmacotherapeutic regimens (and their respective doses) that resulted in remission during the acute phase.

The Florida Expert Panel also recognizes that disparate complementary alternative medicines (CAMs) and behavioral or psychosocial interventions are often utilized by individuals with MDD. The Florida Expert Panel concluded that insufficient evidence exists at this time for most CAMs as well as psychosocial interventions (eg, yoga therapy, music therapy) other than manualized, evidence-based psychotherapies. The Florida Expert Panel also recognized the growing interest in agents that target glutamatergic systems (eg, ketamine, rapastinel). The Florida Expert Panel concluded that there was insufficient evidence to recommend ketamine for the treatment of MDD. It should be recognized that ketamine remains an investigational approach and has significant safety and tolerability concerns.[54–57]

Major Depressive Disorder With Mixed Features

Mixed features (ie, subsyndromal hypomania) are common, affecting approximately 20%–40% of individuals during an MDE with no prior history of hypomanic or manic episodes.[58] Careful assessment for prior history of hypomania or mania, family history of bipolar disorder, and other probabilistic features of bipolar disorder is warranted in any individual with MDD with mixed features. The Florida Expert Panel recognizes the paucity of evidence supporting treatment strategies for MDD with mixed features. Consequently, the hierarchical levels of recommendation for treating MDD with mixed features are similar to those for MDD without mixed features (Table 3).

The Florida Expert Panel also recognizes that conventional antidepressants have not been systematically studied in patients with MDD and currently depressed with *DSM-5*–defined mixed features specifier. The available evidence[59,60] regarding antidepressants in adults with MDD and mixed features, albeit largely descriptive and uncontrolled, suggests that outcomes in MDD with mixed features may be less reliable when compared to outcomes in MDD without mixed features. Moreover, individuals with intradepressive episode subsyndromal hypomanic or manic symptoms may be at higher risk for antidepressant-induced mood destabilization; however, insufficient characterization of this risk with *DSM-5*–defined mixed features is a significant limitation.[8,61] Notwithstanding, the Florida Expert Panel concluded that available evidence does not warrant recommendations proscribing conventional antidepressants in MDD with mixed features. In addition, the hazards posed by antidepressants in susceptible individuals with bipolar spectrum disorders invited the need to specifically alert the possibility that, for some individuals, conventional antidepressants with MDD and mixed features specifier may not be a sufficient therapeutic selection. Given the limited available data on MDE with mixed features, the Florida Expert Panel took a pragmatic position that clinicians require decision support in individuals presenting with MDD and mixed features.

A single published study[62] with the SGA ziprasidone demonstrated clinically significant efficacy in mitigating depressive (and hypomanic) symptoms in a mixed population with MDD or bipolar II disorder experiencing an MDE with hypomanic symptoms. A recently published randomized controlled trial[22] compared lurasidone to placebo in the treatment of adults with *DSM-IV-TR*–defined MDD experiencing a depressive episode and presenting with

Table 3. Consensus Guidelines for Treatment of Major Depressive Disorder with Mixed Features

Conduct comprehensive assessment and use measurement-based care as found in the Principles of Practice (review "Consensus Process" section and Table 1)

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

Assess for:

- Prior history of hypomania or mania
- Psychiatric and medical comorbidities (eg, 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, interpersonal psychotherapy)
- Consider second-generation antipsychotic (SGA) or mood stabilizer (eg, lithium)
- Antidepressant monotherapy 4- to 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 (consider propensity for drug-drug interactions, differential risk for teratogenicity), serotonin-norepinephrine reuptake inhibitor, or vortioxetine
  - Bupropion (if tolerability concerns) or mirtazapine (if insomnia a focus of clinical concern)
- For all Level 1 treatments, if partial response, defined as ≥ 20% reduction in total depressive symptom severity at 2–4 weeks, may continue for another 4 weeks and then reassess
- For all Level 1 treatments, if suboptimal response, defined as < 20% reduction in total depressive symptom severity at 2–4 weeks, then go to Level 2

Level 2—If Level 1 is ineffective or not well tolerated

- Reassess for hypomania or 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
- Adjunctive aerobic exercise (manual-based)

Level 3—If Levels 1 and 2 are ineffective or not well tolerated

- Consider electroconvulsive therapy or transcranial magnetic stimulation
- Alternative antidepressants, including tricyclic antidepressant, monoamine oxidase inhibitor, or first-generation antipsychotic

2–3 hypomanic symptoms. Individuals meeting eligibility criteria were randomly assigned to double-blind treatment with monotherapy lurasidone 20–60 mg or placebo for up to 6 weeks. This first placebo-controlled trial in adults with MDD and subthreshold hypomanic symptoms noted a significant advantage at week 6 in total depression scores (effect size = 0.8) as well as across secondary measures (eg, Clinical Global Impressions-Severity of Illness scale, Hamilton Anxiety Rating Scale, and Sheehan Disability Scale scores). Individuals receiving lurasidone did not exhibit mood destabilization (ie, hypomanic symptom amplification), and instead overall hypomanic symptom severity (as measured by the Young Mania Rating Scale) was significantly reduced in lurasidone-treated individuals. The results of this study, however, cannot be generalized to MDD without the mixed features specifier.

Recognizing the limitations of the existing literature, as well as the need for decision support for this commonly encountered subgroup of patients, the Florida Expert Panel pragmatically concluded that SGAs and/or mood stabilizers (eg, lithium) could be considered as a level 1 or level 2 treatment in MDD with mixed features. The Florida Expert Panel would recommend a first-line agent recommended by the FPG for bipolar disorder in an individual with suspected bipolar spectrum illness.[17] The Florida Expert Panel would recommend a conventional antidepressant as a first-line agent in MDD with or without mixed features. For individuals with well-circumscribed mixed features as part of MDD, SGAs, and/or mood stabilizing options should be considered alongside conventional antidepressants. The expectation is that rigorous controlled trials will provide evidence supplanting the pragmatic and clinical recommendations that currently exist in the FPG algorithm for MDD with mixed features.

Major Depressive Disorder With Psychotic Features

It is recognized by the Florida Expert Panel that MDD with psychotic features (ie, mood congruent and mood incongruent) identifies a subgroup of individuals with a highly complex and severe illness presentation and suboptimal response to antidepressant monotherapy.[63] The risk for suicidality exists in every individual with MDD; it is noted, however, that persons with MDD with psychosis are at relatively higher risk of suicidality, inviting need for careful risk assessment.

Manual-based psychotherapy is not recommended as a first-line therapy for MDD with psychotic features. The combination of a first-line antidepressant with an SGA is a strongly supported recommendation (Table 4).[64] The Florida Expert Panel recognizes that there is insufficient comparative evidence of a conventional antidepressant as monotherapy to an SGA in psychotic depression. Risk for extrapyramidal side effects weight gain and metabolic abnormalities are critical considerations when selecting an SGA. Electroconvulsive therapy (ECT) is recommended as an initial treatment for MDD with psychotic features if patient welfare is an immediate concern. Second-level treatments to be considered for MDD with psychosis are an alternative antidepressant + SGA combination or ECT. Level 3 treatment recommendations are similar with consideration for alternative antidepressants.

Table 4. Consensus Guidelines for Treatment of Major Depressive Disorder with Psychosis

Conduct comprehensive assessment and use measurement-based care as found in the Principles of Practice (review "Consensus Process" section and Table 1).
Assess for: • Prior history of hypomania or mania • Psychiatric and medical comorbidities (eg, substance use disorders, anxiety disorders, obesity, diabetes)
Level 1—Initial treatment
• Selective serotonin reuptake inhibitor or serotonin-norepinephrine reuptake inhibitor + second-generation antipsychotic (SGA)* • Electroconvulsive therapy (ECT) (if patient welfare an immediate concern) • Cognitive-behavioral therapy and interpersonal psychotherapy are not recommended as first-line modalities **Note: Consider extrapyramidal symptoms risk, weight gain, and metabolic concerns.*
Level 2—If Level 1 is ineffective or not well tolerated
• Alternative antidepressant + SGA combination • ECT
Level 3—If Levels 1 and 2 are ineffective or not well tolerated
• Reevaluate diagnosis • Other antidepressant combinations with SGA • Other antidepressant combinations with first-generation antipsychotic • ECT (if not attempted earlier)

Evidence to inform recommendations regarding the optimal duration of combination antidepressant-antipsychotic (or ECT) is insufficient. It is also not known as to whether any 1 agent within a co-therapy regimen should be discontinued during maintenance treatment and, if both treatments are discontinued, the temporality of discontinuation. The Florida Expert Panel, however, concluded that co-therapy should continue uninterrupted with periodic assessment in MDD with psychosis.

CONCLUSION

The FPG 2015 for adults with MDD provide updated decision support for practitioners assessing and providing care for adults with MDD. The FPG 2015 integrate multiple stakeholder perspectives and are not created exclusively by academics and specialist experts. The FPG aim to be simple, succinct, evidence based, and pragmatic. A barrier to implementation for many practice guidelines across multiple medical areas has been the perception that they are impractical, over-inclusive, and nonrepresentative. In addition, it is widely known by patients' families, providers, payers, and other stakeholders that there are meaningful differences between features in tolerability and safety that would significantly impact the selection and sequencing of treatments in MDD. The FPG 2015 have endeavored to give significant consideration to both efficacy as well as tolerability and safety throughout the multiple level recommendations.

Treatment recommendations contained in the FPG 2015 herein are to be understood within the context of the principles of practice, which can be further reviewed at www.medicaidmentalhealth.org. Toward the aim of precision medicine in MDD, there has been tremendous interest in the role of pharmacogenomics informing treatment selection and improving health outcomes.[65,66] The Florida Expert Panel concluded that pharmacogenetic testing may be considered on an individual basis, particularly when treatment resistance or intolerability to medications frequently occur. The Florida Expert Panel also recognizes that a need exists for replicated, sufficiently powered randomized controlled trials in order to unequivocally establish that routine pharmacogenomics improves health outcomes and is cost-effective in the treatment of MDD.[67,68] The selection of antidepressant therapy for any particular individual will need to be informed by many factors, including, but not limited to, patient preference, safety and tolerability profiles, prior antidepressant utilization, potential for drug-drug interactions, cost and access, and comorbidities. It remains to be established whether any single antidepressant or class is unequivocally superior in subgroups of patients with MDD with any of the *DSM-5*–defined specifiers or symptomatic presentations (eg, insomnia, anxiety). Consequently, the decision to select antidepressants for such commonly encountered scenarios should be carried out on an individualized basis.

The overarching aim of the FPG 2015 is to improve health outcomes among individuals with MDD. By providing up-to-date decision support as well as concordance with principles of practice, it is believed that the probability of a satisfactory therapeutic outcome (defined by multiple stakeholders) in adults with MDD will increase. The FPG 2015 represent an update from the 2013 iteration of the FPG for adults with MDD. The FPG will continue to be updated biannually with additional planning to incorporate updates and edits on a regular ongoing basis.

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POSTTEST

To obtain credit, go to PSYCHIATRIST.COM **(Keyword: June) to take this Posttest and complete the Evaluation.** A nominal processing fee is required.

1. **Ms R is a 50-year-old woman who has been diagnosed with major depressive disorder (MDD) and also has subsyndromal hypomania. Could the *DSM-5* mixed features specifier be applied to Ms R?**
   a. No, it applies only to bipolar disorder
   b. Yes, it applies to both bipolar disorder and MDD
2. **Mr D is a 52-year-old man recently diagnosed with MDD. According to this set of MDD algorithms, Mr D should be evaluated for ___ during ongoing care.**
   a. Depression symptom severity
   b. Metabolic parameters
   c. Percentage of days of partial adherence or nonadherence
   d. All of the above
3. **Ms L is a 23-year-old college student. She's been diagnosed with a first major depressive episode. Her evaluation revealed no need for diagnostic specifiers (eg, psychotic features). Which of the following treatments would *not* be considered a reasonable first-line treatment for Ms L?**
   a. A selective serotonin reuptake inhibitor or serotonin-norepinephrine reuptake inhibitor
   b. Vortioxetine, bupropion, or mirtazapine
   c. Cognitive-behavioral therapy
   d. Aripiprazole