

2019–2020 Florida Best Practice Psychotherapeutic Medication Guidelines for Adults



The Impact of Social Determinants on Behavioral Health



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For treatment of mood disorders in pregnant and post-partum women visit **floridamedicaidmentalhealth.org** and see the *Florida Best Practice Recommendations for Women of Reproductive Age with Serious Mental Illness and Comorbid Substance Use Disorders*.

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Purpose of the Guidelines

INTRODUCTION

Social determinants of health—defined by Healthy People 2020 as the conditions in which people are born, work, live, grow, and age—are increasingly recognized for their impact on physical and mental health outcomes (Office of Disease Prevention and Health Promotion, “Social Determinants,” 2019). Individuals who suffer from severe behavioral health disorders are at greater risk for lower educational achievement, decreased productivity, poverty, homelessness, substance use, involvement with the justice system, poorer physical health status, and overall lower quality of life. Likewise, individuals who experience social inequities such as poverty, housing instability, food insecurity, and lack of access to health services are at greater risk for developing mental health conditions such as depression and anxiety and suffering from poorer physical health.

Mental health conditions affect nearly one in five adults, or 47.7 million people in the United States (National Institute of Mental Health, 2017). Partnerships between primary care and behavioral health providers have demonstrated effectiveness in improving treatment outcomes for behavioral health conditions such as depression and physical health comorbidities such as cardiovascular disease (University of Washington Advancing Integrated Mental Health Solutions, “Why practice collaborative care,” 2019). Yet, access to care is an ongoing concern due to the shortage of specialists required to address the growing need for behavioral health services. According to the most recent data published by the National Institute of Mental Health, less than half of adults with any mental health condition received behavioral health care (National Institute of Mental Health, 2017). To address these gaps, primary care clinicians are increasingly tasked with providing behavioral health services in the primary care setting, particularly in areas of critical need, since they serve as the first point of contact into the healthcare system. In the context of these challenges, providing quality care is especially daunting in the absence of clear, concise, evidence-based treatment recommendations.

PURPOSE

The purpose of the **2019–2020 Florida Best Practice Psychotherapeutic Medication Guidelines for Adults** is to guide clinicians who manage adults diagnosed with behavioral health conditions. These guidelines have evolved to reflect the most recent state of evidence, together with expert consensus when evidence is lacking. The guidelines cover a range of conditions that providers encounter in their clinical practice, including treatment of bipolar disorder, major depressive disorder, and schizophrenia. In this most recent iteration of the best practice guidelines, special consideration was given to treatment of behavioral health conditions in the primary care setting and addressing the social factors that impact behavioral health status and treatment outcomes.

PROCESS FOR CREATING THE GUIDELINES

The Florida Medicaid Drug Therapy Management Program for Behavioral Health organizes a diverse group of stakeholders known as the Florida Expert Panel every two years to update the Florida Best Practice Psychotherapeutic Medication Guidelines for Adults. This year’s Expert Panel was comprised of nationally recognized experts, academicians, medical directors of Florida Medicaid Managed Medical Assistance (MMA) health plans and community mental health centers, primary care providers, and pharmacists.

Organization

The 2019 Florida Expert Panel met in Tampa, Florida on November 1-2, 2019 to review and update the 2017 Florida Best Practice Psychotherapeutic Medication Guidelines for Adults. For each behavioral health condition, a psychiatrist who is a nationally recognized content expert conducted a full literature review, presented findings to the expert panel, and suggested revisions based on the current scientific evidence base. The panel then discussed the guidelines and proposed changes, and reached a consensus about whether or not to revise and adopt a particular set of revisions. The final guidelines are therefore a product of a thorough literature review with an emphasis on the highest level of clinical evidence (e.g., randomized controlled trials, systematic reviews), expert consensus, and consideration of safety and efficacy. The names of the meeting attendees and meeting presentations are available on the Florida Medicaid Drug Therapy Management Program for Behavioral Health's website at floridamedicaidmentalhealth.org. Financial disclosures are available upon request.

ORGANIZATION

The **2019–2020 Florida Best Practice Psychotherapeutic Medication Guidelines for Adults** are based on a thorough literature review of the latest evidence, and, when evidence is lacking, clinical consensus on best practice recommendations. When scientific evidence is absent or findings are mixed, the guidelines note the absence of clear evidence and advise caution in treatment.

The guidelines are organized by levels of treatment recommendations, beginning with Level 1. Recommendations for each section (Levels 1, 2, 3, and 4) are categorized hierarchically based on the strength of evidence for the efficacy and safety regarding a particular treatment option. Thus, Level 1 has stronger empirical evidence for efficacy and/or safety than Level 2, and so forth.

A description of the guideline process and assignment of levels of recommendation are provided below to explain the bases for each level of treatment recommendations:

- **Level 1:** Initial treatment for which there is established efficacy and relative safety for the treatment recommendations based on replicated, large randomized controlled trials and/or meta-analyses.
- **Level 2:** Considered if Level 1 is ineffective and/or not well tolerated. Compared to Level 1, data on efficacy and/or safety in Level 2 are less robust based on smaller randomized controlled trials, cohort studies, or systematic reviews of Level 2 studies.
- **Level 3:** Considered if Levels 1 and 2 are ineffective and/or not well tolerated. Treatments at this level have more limited efficacy data and/or more tolerability limitations than Levels 1 and 2. Data are from case-control studies, case series, or systematic reviews of Level 3 studies.
- **Level 4:** Considered if Levels 1 through 3 are ineffective and/or not well tolerated; treatments are not well supported and are listed because of expert opinion and/or use in clinical practice.

Disclaimer

DISCLAIMER

The **2019–2020 Florida Best Practice Psychotherapeutic Medication Guidelines for Adults** are based on the current state of scientific knowledge on the safety and effectiveness of various treatment options, as well as on clinical consensus judgements when research is lacking. The inevitable changes in the state of scientific knowledge require that periodic review, updates, and guideline revisions will be necessary. Treatment recommendations may not apply to all patients and must be tailored to the individual patient.

Proper use, adaptation, modifications, or decisions to disregard these or other guidelines, in whole or in part, are entirely the responsibility of the clinician who uses these guidelines. *The authors and expert panel members bear no responsibility for treatment decisions and outcomes based on the use of these guidelines.*



Treatment guidelines are available on our Program website: floridamedicaidmentalhealth.org

- Best Practice Psychotherapeutic Medication Guidelines for Adults
- Autism Spectrum Disorder & Intellectual Developmental Disorder: Psychotherapeutic Medication Recommendations for Target Symptoms in Children and Adolescents
- Best Practice Recommendations for Women of Reproductive Age with Severe Mental Illness and Comorbid Substance Use Disorders
- Best Practice Psychotherapeutic Medication Guidelines for Children and Adolescents
- Monitoring Physical Health and Side-Effects of Psychotherapeutic Medications in Adults and Children: An Integrated Approach

If you would like hard copies of the guidelines, please email sabrinasingh@usf.edu

Principles of Practice

COMPREHENSIVE ASSESSMENT

Conduct a comprehensive assessment. Rule out medical causes of behavioral symptoms. Use validated measures to assess and track psychiatric symptoms and impairment.

- A comprehensive mental health assessment includes:
 - ◆ Assessment of risk of harm to self or others
 - ◆ Assessment of the full range of psychiatric symptoms and disorders, as well as impairment from these symptoms and disorders
 - ◆ A thorough mental status exam
 - ◆ A full medical history
 - ◆ A relevant medical work-up and physical examination
 - ◆ Assessment of substance use, including tobacco use
 - ◆ Assessment of family psychiatric history, which includes psychiatric symptoms/ treatment of family members, including substance use and treatment
 - ◆ Assessment for social determinants of health (e.g., housing instability/homelessness, food insecurity, education level, employment status)
- Ongoing management of behavioral health conditions includes:
 - ◆ Use of measurement-based care to measure and monitor symptoms and side effects
 - ◆ Close follow-up after psychotherapeutic medication prescribing to assess medication tolerability
 - ◆ Assessment of benefits and risks of treatment, including review of boxed warnings
 - ◆ Patient education of the benefits and risks of treatment, including review of boxed warnings
 - ◆ Monitoring of physical health parameters (See Program publication Monitoring Physical Health and Side-Effects of Psychotherapeutic Medications in Adults and Children: An Integrated Approach available at floridamedicaidmentalhealth.org.)
 - ◆ Assessment of social support system (housing, family, other caregivers)
 - ◆ Evaluation of threats to continuity of care (financial burden, housing instability, access to medication, medication adherence, etc.)
 - ◆ Provision of patient tools/support for recovery and self-management

Notes:

- Effort should be made to communicate between primary care providers, psychiatrists, case workers, and other team members to ensure integrated care
- Incorporate collaborative/shared treatment decision-making with patients, family and caregivers
- Written informed consent should be obtained from the patient or the individual legally able to consent to medical interventions (e.g., pharmacotherapy), and documented in the chart

Principles of Practice (continued)

ADJUNCTIVE PSYCHOSOCIAL TREATMENTS (AS INDICATED)

- Individual and family psychoeducation
- Cognitive-behavioral therapy (CBT)
- Interpersonal psychotherapy (IPT)
- Interpersonal and social rhythm therapy (IPSRT)
- Family-focused therapy
- Group psychoeducation (especially for bipolar disorder)
- Social skills training (especially in schizophrenia)
- Cognitive remediation/rehabilitation (to improve attention, memory, and/or executive function)

Note on pharmacogenomics testing: Limited data exists examining whether patient care that integrates pharmacogenomic test information results in better or safer treatment.

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 information to supplement clinical judgement. 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/or 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:

floridamedicaidmentalhealth.org.

- Beck Depression Inventory (BDI)
- Brief Psychiatric Rating Scale (BPRS)
- Clinical Global Impression (CGI) Scale
- Clinician-Rated Dimensions of Psychosis Symptom Severity (CRDPSS)
- Hamilton Rating Scale for Depression (HAM-D)
- Montgomery-Asberg Depression Rating Scale (MADRS)
- Patient Health Questionnaire (PHQ-9)
- Positive and Negative Syndrome Scale (PANSS)
- Quick Inventory of Depression Symptomatology (QIDS)
- Young Mania Rating Scale (YMRS)

Principles of Practice *(continued)*

Table 1. Assessment Scales for Adult Behavioral Health Conditions

Measures	Bipolar Acute Depression	Bipolar Acute Mania	Bipolar 1 Cont/Main Therapy	Major Depression	Major Depression with Mixed Features	Major Depression with Psychosis	Schizophrenia
Beck Depression Inventory (BDI)	✓	—	—	✓	✓	✓	—
Brief Psychiatric Rating Scale (BPRS)	—	—	—	—	—	✓	✓
Clinical Global Impression (CGI) Scale	—	—	—	—	✓	—	✓
Clinician-Rated Dimensions of Psychosis Symptom Severity (CRDPSS)	—	—	—	—	—	✓	✓
Hamilton Rating Scale for Depression (HAM-D)	—	✓	—	—	—	✓	—
Montgomery-Asberg Depression Rating Scale (MADRS)	✓	✓	✓	—	✓	✓	—
Patient Health Questionnaire (PHQ-9)	✓	—	✓	✓	✓	—	—
Positive and Negative Syndrome Scale (PANSS)	—	—	—	—	—	✓	✓
Quick Inventory of Depression Symptomatology (QIDS)	✓	—	✓	✓	✓	—	—
Young Mania Rating Scale (YMRS)	✓	✓	✓	—	✓	—	—

**Notes: The recommendations in this table are based on the evidence-base and clinical consensus. The Montgomery-Asberg Depression Rating Scale (MADRS) and Hamilton Rating Scale for Depression (HAM-D) can also be used to assess symptoms of depression in major depressive disorder. Although the MADRS and HAM-D do not assess manic symptoms, these scales are recommended to evaluate depression symptoms in individuals presenting with bipolar mania (e.g., to rule out bipolar disorder – mixed features) and to assess for depressive symptoms among individuals on maintenance treatment for bipolar disorder.*

Principles of Practice (continued)

LIST OF ANTIPSYCHOTIC MEDICATIONS AVAILABLE IN THE UNITED STATES:

- First Generation Antipsychotics (FGAs): chlorpromazine, fluphenazine*, haloperidol*, loxapine, perphenazine, thioridazine, thiothixene, and trifluoperazine
- Second Generation Antipsychotics (SGAs): aripiprazole*, asenapine, brexpiprazole[†], cariprazine[†], clozapine, iloperidone, lurasidone, olanzapine*, paliperidone*, quetiapine, risperidone*, and ziprasidone

Notes:

Medications indicated by a single asterisk (*) are available in long-acting injectable formulations (refer to list below).

[†]Brexpiprazole and cariprazine were introduced in 2015.

LIST OF LONG-ACTING INJECTABLE ANTIPSYCHOTIC (LAI) MEDICATIONS AVAILABLE IN THE UNITED STATES:

- First Generation Antipsychotics (FGAs): fluphenazine decanoate, haloperidol decanoate
- Second Generation Antipsychotics (SGAs): aripiprazole monohydrate, aripiprazole lauroxil, olanzapine pamoate, paliperidone palmitate, risperidone microspheres

TREATMENT WITH ANTIPSYCHOTIC MEDICATION

Selection of antipsychotic medication with well-informed patients should be made on the basis of evidence-based guideline recommendations for a particular behavioral health condition, prior individual treatment response, side-effect experience, medication side-effect profile, and long-term treatment planning. Treatment with antipsychotic medications should take into account the following:

- First generation antipsychotics (FGAs) and second generation antipsychotics (SGAs) are heterogeneous within the class and differ in many properties, such as efficacy, side-effects, and pharmacology.
- Antipsychotics carry extrapyramidal symptoms (EPS) liability and metabolic effects.
- Caution should be used in prescribing antipsychotic medication in the context of dementia, anxiety disorders, and impulse control disorders. For these conditions, antipsychotic utilization should be:
 - ◆ Aimed at target symptoms
 - ◆ Prescribed only after other alternative treatments have been tried
 - ◆ Used in the short-term
 - ◆ Monitored with periodic re-evaluation of benefits and risks
 - ◆ Prescribed at the minimal effective dose

Note:

The Food and Drug Administration (FDA) has issued a boxed warning that elderly patients with dementia-related psychosis treated with FGAs or SGAs have an increased risk of death.

Principles of Practice (continued)

ACHIEVING OPTIMAL OUTCOMES WITH CURRENTLY AVAILABLE ANTIPSYCHOTICS

STEP 1 – Considerations for selecting the most appropriate antipsychotic for a particular patient:

- ◆ Equivalent efficacy across agents
- ◆ Individual variability in response
- ◆ No reliable pre-treatment predictor of individual response to different agents
- ◆ Different agents have different side-effects and safety profiles
- ◆ Individual patients have different vulnerabilities and preferences
- ◆ Risk of non-adherence to oral antipsychotics

STEP 2 – Proper antipsychotic trial sequence:

- ◆ Begin with systematic 6 to 10 week trial of one antipsychotic with optimal dosing.
- ◆ If inadequate response, follow with systematic trial of monotherapy with one or more antipsychotics at adequate dose and duration.
- ◆ If inadequate response, follow with a trial of clozapine or a long-acting antipsychotic.
- ◆ Follow with a trial of clozapine, if not tried before.

Note: Recent evidence suggests that long-acting injectable antipsychotic medications should be offered early as a treatment option for all individuals diagnosed with schizophrenia to reduce the risk of non-adherence, prevent future relapse/deterioration, and improve treatment outcomes.

- ◆ If insufficient response with the previously listed therapies, consider other strategies (e.g. antipsychotic polypharmacy).

Principles of Practice *(continued)*

STEP 3 - Good practice guidelines for ongoing antipsychotic treatment:

- ◆ Measurement-based individualized care
- ◆ Repeated assessment of efficacy using reliably defined treatment targets (use standard rating scales, e.g. CRDPSS, CGI, BPRS, PANSS)
- ◆ Careful assessment and measurement of adverse effects
- ◆ Care consistent with health monitoring protocols
- ◆ Standard protocols customized to individual vulnerabilities/needs and specific agent
- ◆ Ongoing collaboration with patient in decision-making

Notes:

CRDPSS = Clinician-Rated Dimensions of Psychosis Symptom Severity; CGI = Clinical Global Impressions Scale; BPRS = Brief Psychiatric Rating Scale; PANSS = Positive and Negative Syndrome Scale

Box 1.

Factors that Contribute to Poor Medication Adherence

REMEMBER TO ASSESS FOR MEDICATION ADHERENCE

Factors that contribute to poor medication adherence include:

- ◆ Poor health literacy
- ◆ Lack of involvement in the treatment decision-making process
- ◆ Complex drug regimens
- ◆ Ineffective communication about adverse effects
- ◆ Limited access to care

Resources

Below is a list of national and local resources for adults with serious mental illness (SMI).

NATIONAL RESOURCES:

- American Psychiatric Association: <https://www.psychiatry.org/>
- American Psychological Association: <https://www.apa.org/>
- Brain and Behavior Research Foundation: <http://bbfndoundation.org/>
- National Alliance on Mental Illness (NAMI): <https://www.nami.org/>
- National Council for Behavioral Health: <https://www.thenationalcouncil.org/>
- Depression and Bipolar Support Alliance (DBSA): <http://www.dbsalliance.org/>
- National Institute of Mental Health: <https://www.nimh.nih.gov/index.shtml>
- Mental Health America (MHA): <http://www.mentalhealthamerica.net/>
- Substance Abuse and Mental Health Services Administration (SAMHSA): <http://www.samhsa.gov/>
- Suicide Prevention Resource Center: <http://www.sprc.org/>
- U.S. Department of Health and Human Services: <https://www.mentalhealth.gov/>
- Hearing Voices Network: <http://www.hearingvoicesusa.org/>

LOCAL RESOURCES:

- Florida Medicaid Drug Therapy Management Program for Behavioral Health: floridamedicaidmentalhealth.org
- Aunt Bertha Web-Based Resource Guide: <https://floridamedicaidmentalhealth.auntbertha.com/>
- Florida Academy of Family Physicians (FAFP): <http://www.fafp.org/>
- Florida Association of Nurse Practitioners (FLANP): <http://flanp.org/>
- Florida Council for Community Mental Health (FCCMH): <http://www.fccmh.org/>
- Florida Medical Association (FMA): <http://www.flmedical.org/>
- Florida Osteopathic Medical Association (FOMA): <http://www.foma.org/>
- Florida Psychiatric Society (FPS): <http://www.floridapsych.org/>
- Florida Society of Neurology (FSN): <http://fsn.aan.com/>
- National Alliance on Mental Illness (NAMI) Florida: <http://www.namiflorida.org/>
- Peer Support Coalition of Florida: <https://www.peersupportfl.org/>

For updated links to resources, visit floridamedicaidmentalhealth.org.

Summary: The Social Determinants of Mental Health

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WHAT ARE SOCIAL DETERMINANTS OF MENTAL HEALTH?

Social determinants of health are societal problems affecting communities, families, and individuals that interfere with achieving optimal health and that increase risk for illnesses. Extensive research documents the social determinants that underpin diseases like diabetes, cardiovascular disease, chronic obstructive pulmonary disease, and sexually transmitted infections. The same societal problems that comprise social determinants of health are also social determinants of mental health. That is, the determinants that increase risk for diabetes, for example, also increase risk for psychiatric disorders such as major depressive disorder, and for substance use disorders like alcohol use disorder and opioid use disorder. While the social determinants are seen as “the causes of the causes” (predating and predicting onset of illness), they are also drivers of poorer course and outcomes among those with existing conditions.

Before further defining the social determinants of mental health, three conceptual points are noteworthy. First, the social determinants are responsible for health inequities—defined as differences in health status that are the result of unjust, unfair, and avoidable social and economic policies—as well as mental health inequities. Thus, effectively working to address the social determinants of mental health will not only reduce risk and prevalence, but will lead to the reduction and ultimately the eradication of mental health inequities. Second, the social determinants perspective gives us a path for pursuing prevention. That is, in addition to the usual categorizations of prevention (primary, secondary, and tertiary, as well as the more recent framework of universal, selective, and indicated preventive interventions), the social determinants framework gives the mental health field an additional set of lenses for understanding how to engage in the prevention of mental illnesses and substance use disorders, and the promotion of mental health. Third, although it is difficult to prove, it is likely that the social determinants have a more potent effect on mental health and mental illnesses than they do on physical health and physical illnesses. This is partly because the mechanism is relatively easy to trace (e.g., from ongoing psychological stress that the social determinants cause to altered physiologic functioning). It also relates to the unfortunate fact that, because of stigma and discrimination against individuals with serious mental illnesses, those individuals tend to experience the very social outcomes (e.g., unemployment, housing instability, poor access to healthcare) that are the social determinants of course and outcomes of both mental and physical conditions.

Summary: The Social Determinants of Mental Health *(continued)*

ENUMERATING THE SOCIAL DETERMINANTS OF MENTAL HEALTH

- In considering the social determinants of mental health more specifically, at least 16 different types of social determinants (although many are interconnected and interact closely with one another) can be identified, which can be placed into four broad categories. The first includes pervasive, highly detrimental U.S. societal problems that should be top priorities, from a health perspective, of policymaking and policy change:
 - ◆ Adverse early life experiences (traumatic events) and childhood maltreatment
 - ◆ Discrimination (based on race and ethnicity, gender, LGBTQ status, religion, immigrant status, disability, age, etc.) and the related social exclusion and social isolation
 - ◆ Exposure to conflict, violence, shootings, war, forced migration, immigration trauma, and related issues
 - ◆ Involvement and interaction with the criminal justice system
- Another category pertains to socioeconomic status and is intimately related to opportunities for accruing wealth (and thus for optimizing health):
 - ◆ Low educational attainment, poor quality of education, and educational inequalities
 - ◆ Unemployment, under-employment, and job insecurity
 - ◆ Poverty, income inequality, and wealth inequality
 - ◆ Area-level poverty and concentrated neighborhood poverty
- Yet another category relates to basic needs in terms of housing, food, transportation, and health care:
 - ◆ Homelessness, poor housing quality, and housing instability
 - ◆ Food insecurity and poor dietary quality
 - ◆ Poor or unequal access to transportation
 - ◆ Being uninsured, being under-insured, loss of insurance, and poor access to health care
- The final category concerns the immediate and global physical environment:
 - ◆ Adverse features of the built environment (e.g., the transportation infrastructure, the energy infrastructure, building design, city planning, extent of access to natural environments and green space)
 - ◆ Neighborhood disorder, disarray, and disconnection
 - ◆ Exposure to pollution (air, water, and soil pollution)
 - ◆ Exposure to the impacts of global climate change

The social determinants underpin physical health and mental health conditions through diverse mechanisms. For example, at the individual level, struggling with social needs (such as food insecurity) leads to chronic psychological stress, which can impact upon physiological stress response systems. They are also associated with reduced options (which are sometimes naively referred to as “poor choices”); food insecurity is associated with a reliance on an energy-dense, micronutrient-deficient diet (as limited food dollars are used to purchase the most calories in the

Summary: The Social Determinants of Mental Health *(continued)*

most efficient and cost-effective way). In addition to their direct effects, social determinants likely interact with genetic constitution in complex ways, including gene-by-environment interactions and epigenetics.

UNDERSTANDING THE UNDERPINNINGS OF THE SOCIAL DETERMINANTS OF MENTAL HEALTH

Each of the 16 types of social determinants can have a negative impact on health, can increase risk for illnesses, and can worsen outcomes among those with existing illnesses; each can also make it harder to attain optimal mental health, which is more than just the absence of mental illness. The social determinants of mental health increase risk for and prevalence of mental illnesses and substance use disorders, and among those living with a behavioral health disorder, they complicate the course and worsen outcomes. As noted, the social determinants of mental health are interconnected—individuals, families, or communities are often affected by multiple social determinants at the same time. That co-occurrence suggests common underlying factors that, if addressed at a deeper level, would likely help to address many social determinants rather than one at a time. Based on one conceptualization (Compton & Shim, 2015), the common, unifying foundation setting the stage for each of the social determinants is unfair and unjust distribution of opportunity. Opportunity pertains to power, empowerment, voice, access to resources, and advantages. At an even deeper level, two fundamental elements consistently drive the unfair and unjust distribution of opportunity: public policies (those societal conventions that are codified, such as laws, ordinances, rules, regulations, and court decisions), and social norms (those societal conventions that are imprinted upon minds rather than being printed on paper: the attitudes, biases, and opinions that groups of people have toward other groups of people). Addressing the social determinants of mental health ultimately requires changing public policies and changing social norms. Importantly, public policies shape social norms, and social norms shape public policies. As such, although both must be addressed for us to achieve most robust results, changing one is likely to have some impact on the other.

REFERENCE:

Compton MT and Shim RS, Ed. The Social Determinants of Mental Health. Washington, DC: American Psychiatric Publishing; 2019. ISBN-13: 978-1-58562-477-5.

DSM-5 Criteria: Bipolar Disorders

Box 2.

DSM-5 Diagnosis: Bipolar I Disorder

BIPOLAR I DISORDER:

For a diagnosis of bipolar I disorder, it is necessary to meet the following criteria for a manic episode. The manic episode may have been preceded by and may be followed by hypomanic or major depressive episodes.

Manic Episode:

- ◆ A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary).
- ◆ During the period of mood disturbance and increased energy or activity, 3 (or more) of the following symptoms (4 if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior:
 - ◇ Inflated self-esteem or grandiosity
 - ◇ Decreased need for sleep (e.g., feels rested after only 3 hours of sleep)
 - ◇ More talkative than usual or pressure to keep talking
 - ◇ Flight of ideas or subjective experience that thoughts are racing
 - ◇ Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed
 - ◇ Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless, non-goal-directed activity)
 - ◇ Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)
- ◆ The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.
- ◆ The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or to another medical condition.

Note: A full manic episode that emerges during antidepressant treatment [e.g., medication, electroconvulsive therapy (ECT)], but persists at a fully syndromal level beyond the physiological effect of treatment is sufficient evidence for a manic episode, and therefore, a bipolar I diagnosis.

DSM-5 Criteria: Bipolar Disorders (continued)

Box 3.

DSM-5 Diagnosis: Bipolar II Disorder

BIPOLAR II DISORDER:

- ◆ Criteria have been met for at least one hypomanic episode and at least one major depressive episode
- ◆ There has never been a manic episode
- ◆ The occurrence of the hypomanic episode(s) and major depressive episode(s) is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified or unspecified schizophrenia spectrum and other psychotic disorder.
- ◆ The symptoms of depression or the unpredictability caused by frequent alternation between periods of depression and hypomania causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

For a diagnosis of bipolar II disorder, it is necessary to meet the following criteria for a current or past hypomanic episode and the criteria for a current or past major depressive episode (See Box 4 on page 30 for Major Depressive Episode criteria).

Hypomanic Episode:

- ◆ A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least 4 consecutive days and present most of the day, nearly every day.
- ◆ During the period of mood disturbance and increased energy and activity, 3 (or more) of the above symptoms (4 if the mood is only irritable) have persisted, represent a noticeable change from usual behavior, and have been present to a significant degree.
- ◆ The episode is associated with an unequivocal change in functioning that is uncharacteristic of the individual when not symptomatic.
- ◆ The disturbance in mood and the change in functioning are observable by others.
- ◆ The episode is not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization. If there are psychotic features, the episode is, by definition, manic.
- ◆ The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment).

Note: A full hypomanic episode that emerges during antidepressant treatment (e.g., medication, ECT) but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a hypomanic episode diagnosis. However, caution is indicated so that one or two symptoms (particularly increased irritability, edginess or agitation following antidepressant use) are not taken as sufficient for a diagnosis of a hypomanic episode nor necessarily indicative of a bipolar diathesis.

Treatment of Acute Bipolar Disorder - Depression

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 primary therapeutic objectives of bipolar disorder care are to achieve symptomatic remission, promote syndromal recovery, prevent recurrence, and facilitate full functional recovery.

- Selection of acute treatment should take maintenance treatment goals into account.
- Be aware of safety and tolerability concerns, evidence for maintenance use, and acute efficacy.
- Revisit the appropriateness of current regimen (e.g. inappropriate polypharmacy)

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

Level 1 Initial treatment:

- ◆ Lurasidone or cariprazine monotherapy*
**Note: Lurasidone and cariprazine have better metabolic profiles than quetiapine.*
- ◆ Lamotrigine monotherapy
- ◆ Quetiapine monotherapy - *If the patient has bipolar II depression*
- ◆ Lithium monotherapy
- ◆ Lurasidone or lamotrigine** adjunctive to lithium or divalproex if index agent (lithium or divalproex) has been previously prescribed and optimized. Adjunctive data for cariprazine not available, but cariprazine could be considered as alternative adjunct.
***Caution: There is a drug-drug interaction with use of lamotrigine and divalproex together that requires reducing the lamotrigine dose by 50% of the typical lamotrigine dose. For dosing recommendations, refer to Table 2 on pages 24–25.*
- ◆ Do not utilize conventional antidepressants (e.g., SSRIs, SNRIs, TCAs, MAOIs) as a first-line therapy.


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

- ◆ Divalproex + lurasidone
- ◆ Olanzapine + fluoxetine (bipolar I disorder)
**Note: Tolerability limitations include weight gain and metabolic concerns.*
- ◆ Two (2) drug combination of Level 1 medications but **NOT TWO** antipsychotic medications.
**Note: Efficacy limitations, relatively few positive randomized controlled trials.*

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

- ◆ Electroconvulsive therapy (ECT)
**Note: Consideration is merited due to clinical need, despite even greater efficacy/tolerability limitations than Level 1 and 2 treatments.*

Treatment of Acute Bipolar Disorder - Depression *(continued)*

	<p>Level 4 If Levels 1 – 3 are ineffective and/or not well tolerated:</p> <ul style="list-style-type: none">◆ Intravenous racemic ketamine and/or esketamine◆ FDA-approved agent for bipolar disorder + conventional antidepressant (e.g., SSRI)*◆ Pramipexole◆ Adjunctive: modafinil, thyroid hormone (T3), or stimulants◆ Three (3) drug combination◆ Transcranial magnetic stimulation (TMS) <p><i>*Notes:</i></p> <ul style="list-style-type: none">• <i>There is inadequate information (including negative trials) to recommend adjunctive antidepressants, aripiprazole, ziprasidone, levetiracetam, armodafinil, or omega-3 fatty acids for bipolar depression.</i>• <i>Antidepressant monotherapy is not recommended in bipolar I depression; recommendation is for adjunctive mood stabilizer with antidepressant.</i>• <i>The safety and efficacy of antidepressant monotherapy in bipolar II depression is uncertain but may be appropriate in select circumstances.</i>
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Treatment of Acute Bipolar Disorder - Mania

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 primary therapeutic objectives of bipolar disorder care are safety, symptomatic improvement, and patient psychoeducation.

- Selection of acute treatment should take maintenance treatment goals into account.
- Be aware of safety and tolerability concern, evidence for maintenance use, and acute efficacy.

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

Level 1A Initial Treatment:

Mild to moderate severity and/or not requiring hospitalization

- ◆ Lithium* monotherapy
- ◆ Monotherapy with aripiprazole, asenapine, divalproex*, quetiapine, risperidone, ziprasidone, or cariprazine.

Severe and/or requiring hospitalization

- ◆ Lithium* or divalproex* + aripiprazole, asenapine, quetiapine, or risperidone
- ◆ Electroconvulsive therapy (ECT) is recommended if medical emergency/patient welfare at risk and pharmacotherapy is insufficient.

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

Mild to moderate severity

- ◆ Monotherapy with either haloperidol or olanzapine


Level 2 If Levels 1A and 1B are ineffective and/or not well tolerated:

- ◆ Combination treatment with lithium* + divalproex*
- ◆ Combination with lithium* and/or divalproex* + second generation antipsychotic (SGA) other than clozapine
- ◆ Carbamazepine* monotherapy

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

- ◆ Electroconvulsive therapy (ECT)
- ◆ Clozapine + lithium* or divalproex*
- ◆ Lithium* + carbamazepine*
- ◆ Divalproex* + carbamazepine*

Treatment of Acute Bipolar Disorder - Mania (continued)

	<p>Level 4 If Levels 1 – 3 are ineffective and/or not well tolerated:</p> <ul style="list-style-type: none">◆ A three (3)-drug combination of Level 1, 2, and 3. Drugs may include first generation antipsychotic (FGA) or second generation antipsychotic (SGA) but NOT TWO antipsychotic medications. <i>Example:</i> Lithium* + (divalproex* or carbamazepine*) + antipsychotic
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Notes:

*Caution should be used when prescribing lithium, lamotrigine, divalproex or carbamazepine to women of reproductive age due to increased risk 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 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 clinicians.

Data for use of paliperidone to treat bipolar mania are mixed. Paliperidone > 6mg has some data supporting efficacy.

Benzodiazepines may be used as an adjunct treatment for acute treatment of bipolar mania.

Bipolar 1 Disorder Continuation / Maintenance Therapy

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 list of possible treatments in the prevention of bipolar disorder is comprised of many treatment options; therefore, the regimen that stabilizes a patient should be strongly considered for continuation and maintenance (monitoring for efficacy and adverse events).

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

Level 1 Initial Treatment:

- ◆ Periodic evaluation: frequency based on clinical needs
- ◆ Continue with effective and well-tolerated treatment
- ◆ Lithium* monotherapy
- ◆ Quetiapine monotherapy
- ◆ Lamotrigine* (evidence strongest for prevention of depression)
- ◆ If initially stabilized on divalproex**†, maintain.
- ◆ Oral aripiprazole or aripiprazole long-acting injectable, long-acting risperidone monotherapy
- ◆ Quetiapine (for recurrence prevention) or ziprasidone (for relapse prevention) adjunctive to (lithium* or divalproex**†)
- ◆ Asenapine monotherapy
- ◆ Manual-based psychotherapy (e.g., interpersonal social rhythm therapy, CBT, mindfulness best evidence along with psychoeducation during the maintenance phase)

†Note: Be aware that there are limited data on long-term efficacy of divalproex.



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


- ◆ Olanzapine monotherapy
- ◆ Olanzapine adjunctive to lithium* or divalproex**†

Level 2B If Levels 1 and 2A are ineffective and/or not well tolerated:

- ◆ Continue effective and well-tolerated acute treatment(s) if not listed in Level 1
- ◆ Lithium* and divalproex**† combination
- ◆ Follow acute mania/bipolar depression guidelines to achieve remission or partial remission

Bipolar 1 Disorder Continuation / Maintenance Therapy

(Continued)

	Level 3 If Levels 1 and 2 are ineffective and/or not well tolerated: <ul style="list-style-type: none">◆ Adjunctive clozapine (avoid combining with another antipsychotic)◆ Electroconvulsive therapy (ECT)[†]
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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 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.

[†]Long-term efficacy data are limited for the following: divalproex monotherapy, carbamazepine (drug interaction risk), antidepressants, and electroconvulsive therapy (inconvenience/expense).

Table 2. Recommended Medications for the Treatment of Bipolar Disorder – Mood Stabilizers

Medication	Dosage	Comments
Lithium	<p>In acute mania: 1,200–2,400 mg/day (serum level 0.8–1.2 mEq/L)</p>	<ul style="list-style-type: none"> ◆ Initial titration for tolerability: <ul style="list-style-type: none"> ◇ Start 600–900 mg/day, increase 300 mg/day every 5 days. ◇ Check levels 5 days after initiation/dose change (ideally, trough lithium levels 12 hours after last dose). ◇ Check blood levels more frequently if signs or suspicion of clinical toxicity. ◆ Lower doses/levels may be necessary in non-manic compared to manic patients. ◆ Monitor renal and thyroid functions. ◆ For maintenance, some patients require serum levels of 0.8 to 1.2 mEq/L, others can be maintained with lower levels, but not below 0.6 mEq/L. ◆ In older individuals, start with lower lithium dose, titrate more slowly, and target lower serum lithium levels.
Divalproex	<p>In acute mania: 5–60 mg/kg/day; 1,000–2,500 mg/day (serum level 85–125 µg/mL)</p>	<ul style="list-style-type: none"> ◆ Initial dosing: <ul style="list-style-type: none"> ◇ Initial loading may be tolerated, but some patients need initial titration for tolerability. ◇ Lower doses/levels may be necessary in non-manic compared to manic patients. ◇ Check levels 48 hours after initiation and adjust dose accordingly. ◆ Side-effects (especially gastrointestinal) are more evident above 100 µg/ml. ◆ More teratogenic than other mood stabilizers. ◆ Serious side effects include hepatotoxicity, thrombocytopenia, pancreatitis, and hyperammonemic encephalopathy.

Table 2. Recommended Medications for the Treatment of Bipolar Disorder – Mood Stabilizers (continued)

<p>Carbamazepine</p>	<p>In acute mania: 200–1,600 mg/day (serum level 6–12 µg/mL)</p>	<ul style="list-style-type: none"> ◆ Initial titration for tolerability due to hepatic auto-induction: <ul style="list-style-type: none"> ◇ Start 200–400 mg/day and increase 200 mg/day every 3 days. Lower doses/levels may be necessary in non-manic compared to manic patients. ◇ Monitor for blood dyscrasias and serious rash. ◇ Screen individuals of Asian descent for HLA-B*1502 (serious rash risk indicator) due to high risk for Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). ◇ Patients testing positive for the HLA-B*1502 allele should not be treated with carbamazepine unless benefits clearly outweigh risks. ◆ Carbamazepine decreases serum levels of multiple other CYP450-metabolized drugs due to induction of CYP450 enzymes 3A4, 1A2, 2C9, and 2C19.
<p>Lamotrigine</p>	<p>In bipolar maintenance: 100–400 mg/day</p>	<ul style="list-style-type: none"> ◆ Initial titration to reduce risk of Stevens-Johnson syndrome and Toxic Epidermal Necrolysis (TEN) [serious rash]: <ul style="list-style-type: none"> ◇ Start 25 mg/day (12.5 mg/day if taken with divalproex). ◇ Increase by 25 mg/day (12.5 mg/day if taken with divalproex) after 2 and 4 weeks and weekly thereafter. Initial target dose 200 mg/day, but final doses may be 100–400 mg/day. ◆ May be used in some patients with acute bipolar depression (despite acute efficacy limitation) due to good tolerability and depression prevention efficacy.

*mg/day= milligrams per day; mEq/L = milliequivalents per Liter; mg/kg/day = milligram per kilogram per day; µg/ml = microgram per millimeter

Table 3. Recommended Medications for the Treatment of Bipolar Disorder – Second Generation Antipsychotics (SGAs) and Antidepressants

Medication	Dosage	Comments
Second Generation Antipsychotics (SGA)	<p>In acute mania:</p> <ul style="list-style-type: none"> • Aripiprazole: 15–30 mg/day • Asenapine: 10–20 mg/day • Olanzapine: 6–20 mg/day • Paliperidone 3–12 mg/day • Quetiapine: 400–800 mg/day • Risperidone: 2–6 mg/day • Ziprasidone: 80–160 mg/day <p>In acute bipolar depression:</p> <ul style="list-style-type: none"> • Quetiapine: 200–600 mg/day • Olanzapine/Fluoxetine: 3 mg/12.5 mg–12 mg/50 mg per day • Lurasidone: 40–120 mg/day • Clozapine: 50–400 mg/day (if treatment resistant) 	<ul style="list-style-type: none"> ◆ Initial titration may be necessary for tolerability. Lower doses may be necessary in depressed patients (e.g., quetiapine 300 mg/day). Ziprasidone should be taken with food. Asenapine is sublingual. ◆ Monitor for side effects, including sedation (especially with quetiapine and clozapine), weight gain (especially with olanzapine and clozapine), akathisia (especially with aripiprazole and ziprasidone) and extrapyramidal symptoms (EPS), especially with risperidone. Monitor weight and body mass index (BMI) at each visit and laboratory metabolic indices at baseline, 3 months, and yearly thereafter.
Antidepressants	<p>In acute bipolar depression:</p> <p>As dosed for major depression. (No specific dosing recommendations can be given for bipolar depression.)</p>	<ul style="list-style-type: none"> ◆ Larger trials have not found a benefit of antidepressant when added to mood stabilizers/antimanic for bipolar depression (other than olanzapine/fluoxetine combination). May be used in combination with antimanic drugs in some patients with acute bipolar depression, but should not be prescribed as monotherapy in patients with bipolar I disorder due to manic switch risk. ◆ Serotonin-norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs) may have greater manic switch risk. ◆ Antidepressant carry an FDA boxed warning for increased suicidality risk in pediatric and young adult patients (under age 25). May be continued in patients who are on antidepressants and have stable mood.

*mg/day = milligrams per day

Summary for Treatment of Bipolar Disorder *(continued)*

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INTRODUCTION

Bipolar disorder (BD) is a severe, lifelong group of disorders with an estimated prevalence of approximately 2%. Approximately three-quarters of individuals with BD exhibit features of the disorder prior to the age of 25 highlighting the neurodevelopmental aspects of the disorder as well as the importance for screening and timely diagnosis, especially in younger populations presenting in clinical settings with clinically significant depressive and anxiety symptoms. Misdiagnosis representing a conflation of both false positives and false negatives continue to be one of the greatest unmet needs in BD. The consequences of missed and delayed diagnosis are protean and include the accumulation of comorbidities (e.g., obesity, substance abuse), unmitigated suicide risk, erroneous treatment selections, human suffering, and increased morbidity.

The panel agreed that screening for BD is essential for any person presenting with mood related symptoms and/or in clinical scenarios wherein conventional treatments for a mood disorder are inadequate. Results from longitudinal studies consistently report that most individuals with BD exhibit depression, depressive symptoms, and/or episodes as the predominant presentation of the illness as well as polarity at first presentation. Consequently, many adults with BD transition from the diagnosis of Major Depressive Disorder (MDD) to BD over multiple years of prospective follow-up. For example, it is reported that approximately 1% of adults with “MDD” transition to BD annually underscoring the importance of vigilance for hypo/manic presentations in adults originally diagnosed with having MDD.

In addition to misdiagnosis as well as delayed diagnosis, insufficient attention to comorbidity in BD is identified as an unmet need. Adults with BD are affected by a large number of medical and mental comorbidities with at least half of patients meeting criteria for three or more concurrent conditions. It is not uncommon for the comorbid conditions to be a phenomenological antecedent to BD and, not infrequently, obscuring the underlying diagnosis of BD.

Similar to adults with MDD, it is recognized that the vast majority of adults with BD are not achieving full syndromal and functional recovery. This deficiency is in part explained by inadequate/inappropriate treatments, treatment non-concordance, as well as insufficient attention to comorbidities and relevant psychosocial factors. It is additionally recognized that for a substantial population of adults with BD, enduring deficits across multiple domains of cognitive function remain a source of distress and mediator of functional impairment. In some cases, the severity, persistence, and complexity of cognitive impairment in BD phenotypically mimics attention deficit hyperactivity disorder (ADHD). Hitherto, there are no United States Food and Drug Administration (FDA)-approved treatments for cognitive dysfunctions in BD nor are there any evidence-based and proven treatments for cognitive impairment in BD.

Results from the extant literature indicate that outcomes in BD are optimal when individuals are diagnosed timely and accurately and receive guideline-informed measurement based, integrated, and multidisciplinary care. For individuals with treatment-resistant BD, evidence also supports cognitive and functional remediation as a manual-based intervention. Response rates to conventional treatments for BD, both pharmacologic and psychosocial, are diminished

Summary for Treatment of Bipolar Disorder *(continued)*

in subpopulations with higher episode frequency. Moreover, populations with greater episode frequency exhibit greater susceptibility to additional disorders including, but not limited to, cardiovascular disease, obesity, and dementia.

PRINCIPLES OF TREATMENT

The unmet need regarding timely and accurate diagnosis instantiates the importance of using screening tools (e.g., Mood Disorder Questionnaire; MDQ) in adults with BD. Screening should take place at initial assessments and any scenarios wherein inadequate outcomes are being observed. Screening does not supplant a careful and comprehensive clinical evaluation which is sine qua non to establishing the diagnosis of BD. The use of measurement to track symptoms (e.g., mood diaries) is encouraged and attempts to prevent comorbidities should be a clinical focus at initial presentations. Recognition that BD is an independent risk factor for cardiovascular disease further underscores the importance of holistic approaches to the assessment, prevention, and management of BD. Individuals with BD report much higher rates of physical and sexual trauma in the recent or distant past as well as describe psychosocial stressors as associated with episode recurrence. In addition to targeting key features of BD, the management of BD also needs to include psychoeducation, improvement of diagnosis and treatment literacy, conflict and stress management skills, as well as lifestyle improvement with focus on diet as well as sleep hygiene.

PHARMACOLOGIC TREATMENT OF ACUTE BIPOLAR DEPRESSION

The panel recommends cariprazine and lurasidone monotherapy as initial treatment for bipolar depression. Lurasidone is also recommended in combination with lithium or divalproex. The panel recognizes that lurasidone is not FDA-approved for mania; cariprazine and quetiapine are approved for acute bipolar mania/mixed states. Cariprazine was FDA approved in 2019 for the acute treatment of bipolar depression. The panel recognizes that cariprazine and lurasidone have lower propensity to weight gain and are metabolically similar to placebo in the treatment of adults with BD. These observations differentiate these second-generation antipsychotics (SGAs) from quetiapine and olanzapine-fluoxetine combination which are susceptible to clinically significant weight gain and/or metabolic shift. It was the view of the panel that consideration of weight gain and metabolics is paramount in selecting treatments for bipolar depression. The panel also recommends lithium or lamotrigine as possible first-line treatments for bipolar depression. The anti-suicide effects of lithium, not seen with other FDA-approved treatments for BD, are an important attribute of lithium.

The panel recognizes that antidepressant monotherapy in Bipolar I Disorder is to be discouraged. Conventional antidepressants are not recommended in Bipolar I Disorder for adults manifesting mixed features, rapid cycling, and/or histories of previous antidepressant-associated emergence of hypo/mania. For adults with Bipolar II Disorder, preliminary evidence suggests that some adults may be safely and effectively treated with antidepressant monotherapy. The lack of empirically supported response predictors to antidepressant monotherapy in BD implies that it is unknown a priori which individuals with Bipolar II Disorder may be safely treated with antidepressant monotherapy. The panel also recognizes that there is a paucity of long-term treatments with antidepressants in BD. The recommendation to continue antidepressants will be determined on an individual basis.

Summary for Treatment of Bipolar Disorder (continued)

PHARMACOLOGIC TREATMENT OF ACUTE BIPOLAR MANIA

The **2019-2020 Florida Best Practice Psychotherapeutic Medication Guidelines for Adults** has retained similar guidance with respect to pharmacologic treatments of bipolar mania. Bipolar mania is recognized as a medical emergency requiring, in many cases, a higher intensity of treatment. Safety is of paramount importance of mania and, where applicable, inpatient stay and specialist consultation is encouraged. The panel also recognizes that for many adults with bipolar mania, the predominant presentation is dysphoric and mixed with many adults manifesting non-specific symptoms (e.g., anxiety, agitation, irritability, anger) that often obscure the underlying diagnosis of mania. SGA monotherapy as well as lithium or divalproex are recommended in cases of mania of milder severity (e.g., non-psychotic mania). In situations where patients have severe mania (e.g., psychosis, need for hospitalization), combination SGA and additional mood stabilizing agent (e.g., lithium) is recommended.

MAINTENANCE PHARMACOLOGICAL TREATMENT OF BIPOLAR DISORDER

More than 90% of individuals with BD will experience recurrence of illness. Episode recurrence in BD is highly associated with progressive changes to brain structure and function, as well as the accumulation of multiple comorbidities. Further evidence also suggests that greater episode frequency is associated with more pronounced cognitive deficits in BD. Moreover, it is not frequent in BD to witness a phenomenological shift across time where patients manifest increasing depressive symptom burden. A clinical impression awaiting cogent empirical confirmation is that, increasingly, clinicians are encountering a higher percentage of individuals with BD presenting with mixed features during the acute or maintenance phase. It is uncertain what is causing this, but, certainly, antidepressant utilization, drug and alcohol misuse and obesity are contributing causes. For most adults with BD, multi-year/lifetime pharmacotherapy is recommended, integrated with lifestyle interventions targeting healthful living, diet, exercise, and sleep hygiene. For many adults, manual-based psychosocial treatments (e.g., cognitive therapy), interpersonal social rhythm therapy and psychoeducation, are critical adjuncts to pharmacotherapy to improve overall psychosocial function and wellbeing. During the acute and maintenance phase of BD, careful attention to suicidality is paramount.

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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.

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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DSM-5 Criteria: Schizophrenia

Box 5.

DSM-5 Diagnosis: Schizophrenia

- ◆ Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be delusions, hallucinations or disorganized speech:
 - ◇ Delusions
 - ◇ Hallucinations
 - ◇ Disorganized speech (e.g., frequent derailment or incoherence)
 - ◇ Grossly disorganized or catatonic behavior
 - ◇ Negative symptoms (i.e., diminished emotional expression or avolition)
- ◆ Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet the above criteria (i.e., active phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested only by negative symptoms or by two or more symptoms listed above present in an attenuated form.
- ◆ For a significant portion of time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is a failure to achieve expected level of interpersonal, academic, or occupational functioning).
- ◆ Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out.
- ◆ The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.
- ◆ If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least 1 month (or less if successfully treated).

Treatment of Schizophrenia

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.

Most importantly, assess social support system (housing, family, other caregivers) and evaluate threats to continuity of care (access to medication, adherence, etc.).

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




	<p>Level 1 Initial Treatment:</p> <ul style="list-style-type: none"> ◆ Monotherapy with an antipsychotic (SGA) other than clozapine*—either oral, or oral antipsychotic followed by the same SGA-LAI (if tolerable and sufficiently efficacious) ◆ If initial trial of antipsychotic monotherapy unsuccessful, try monotherapy with another SGA antipsychotic (either oral or LAI) with low metabolic adverse effects. <p><i>*Note: Balance efficacy, side-effects, individual vulnerabilities and preferences. Select a medication with lower metabolic risk, lower risk of extrapyramidal symptoms (EPS), sedation, and sexual side-effects. For more detail on LAIs, refer to page 43.</i></p>
	<p>Level 2A If non-adherent or refractory to Level 1:</p> <ul style="list-style-type: none"> ◆ Long-acting injectable antipsychotic medication (LAI)
	<p>Level 2B If Level 1 is ineffective in at least two antipsychotic trials:</p> <ul style="list-style-type: none"> ◆ Clozapine
	<p>Level 3 If Levels 1 and 2 are ineffective and/or not well tolerated:</p> <ul style="list-style-type: none"> ◆ Diagnostic review and/or consultation ◆ Clozapine if not tried earlier ◆ Antipsychotic, including clozapine + electroconvulsive therapy (ECT) ◆ Augmentation of clozapine with aripiprazole, lamotrigine, topiramate or if partial or incomplete response to clozapine
	<p>Level 4 If Levels 1, 2, and 3 are ineffective and/or not well tolerated:</p> <ul style="list-style-type: none"> ◆ Two antipsychotics, ideally with different pharmacological mechanisms* and side-effect profiles (evidence is weak) ◆ First generation antipsychotic use <p><i>*Full antagonist with partial agonist; loose binding with tight binding</i></p>

Table 4. Recommended Medications for the Treatment of Schizophrenia: Oral Antipsychotics

Medication	Chlorpromazine Equivalents ^a	Acute Therapy	Maintenance Therapy ^b
First Generation Antipsychotics (FGAs)			
Chlorpromazine	100	300–1,000 mg/day	300–800 mg/day
Fluphenazine HCl	2	5–20 mg/day	5–15 mg/day
Haloperidol	2	5–20 mg/day	6–12 mg/day
Loxapine	10	30–100 mg/day	30–60 mg/day
Molindone	10	30–100 mg/day	30–60 mg/day
Perphenazine	8	16–80 mg/day	16–64 mg/day
Thiothixene	5	15–50 mg/day	15–30 mg/day
Trifluoperazine	5	15–50 mg/day	15–30 mg/day
Second Generation Antipsychotics (SGAs)			
Aripiprazole	N/A	10-30 mg/day	10–30 mg/day
Asenapine	N/A	10–20 mg/day	10–20 mg/day
Brexpiprazole	N/A	2–4 mg/day	2–4 mg/day
Cariprazine	N/A	1.5–6 mg/day	3–6 mg/day
Clozapine	N/A	150–800 mg/day	150–800 mg/day
lloperidone	N/A	12–24 mg/day	12–24 mg/day
Lurasidone	N/A	40–160 mg/day	40–160 mg/day
Olanzapine	N/A	10–30 mg/day	10–20 mg/day
Paliperidone	N/A	3–12 mg/day	3–12 mg/day
Quetiapine	N/A	300–800 mg/day	300–800 mg/day
Risperidone	N/A	2–8 mg/day	2–8 mg/day
Ziprasidone	N/A	80–240 mg/day	80–160 mg/day

Notes:

Recommendations may be below FDA maximum approved doses but are based on current evidence and expert consensus.

Consider lower doses for first episode due to better response and higher side effects to medications in pharmaceutically naïve patients. Use atypical antipsychotics and avoid haloperidol completely due to well-documented neuronal cell death caused by haloperidol (and also fluphenazine and perphenazine). Thioridazine is not recommended due to concerns about ventricular arrhythmias (Torsades de Pointes).

^aApproximate dose equivalent to 100 mg of chlorpromazine (relative potency); it may not be the same at lower versus higher doses. Chlorpromazine equivalent doses are not relevant to the second generation antipsychotics and therefore are not provided for these agents.

^bDrug-drug interactions (DDIs) can impact dosing. Maintenance dose should generally be no less than half of the initial clinically effective dose, as that can result in reduced effectiveness of relapse prevention.

Treatment of Schizophrenia with Long-Acting Injectable Antipsychotic Medications (LAIs)

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 a comprehensive assessment and use measurement-based care as found in the Principles of Practice on pages 6–11.

Assess social determinants (housing, family, other caregivers) and evaluate threats to continuity of care (access to medication, adherence, etc.).

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

Level 1 Initial Treatment:

- ◆ After stabilization or obtaining sufficient evidence for efficacy and tolerability, offer any of the following long-acting injectable antipsychotics (LAI). Base the selection on past efficacy and tolerability patterns to specific oral or LAI, expected tolerability advantages*, desired injection intervals, and procedural (oral overlap needed- yes versus no)/logistic/access/cost considerations:
 - ◇ Aripiprazole monohydrate
 - ◇ Aripiprazole lauroxil
 - ◇ Paliperidone palmitate
 - ◇ Risperidone microspheres
 - ◇ Risperidone extended release subcutaneous injectable.
- ◆ If initial, adequate trial (minimum 3 to 4 months) of LAI is unsuccessful, try monotherapy with another LAI from the above group or address potential reasons for efficacy difficulty on the LAI. Refer to Figure 1: Management of Breakthrough Psychosis with LAI for options to consider if psychotic symptoms persist despite adequate medication trial.

**Note: Balance efficacy, side-effects, individual vulnerabilities and preferences. Select medication with lower propensity for metabolic and extrapyramidal side-effects.*



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

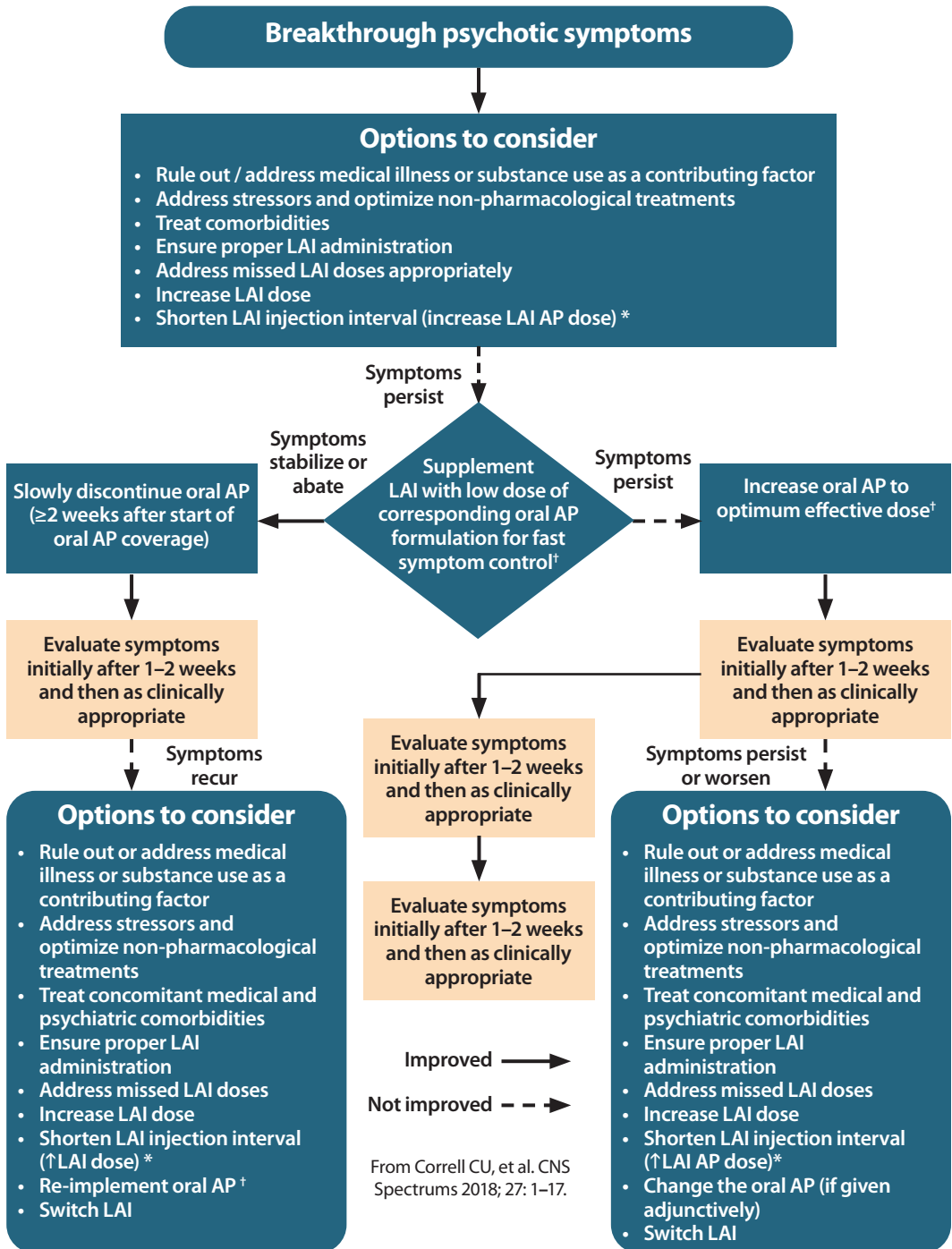
- ◆ Consider LAI with greater adverse effect risk [olanzapine: post-injection delirium/sedation syndrome (PDSS); FGA-LAIs: EPS, TD]
 - ◇ Olanzapine pamoate
 - ◇ Fluphenazine decanoate
 - ◇ Haloperidol decanoate



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

- ◆ Diagnostic review and/or consultation
- ◆ Consider switch to an oral antipsychotic not available as an LAI (if adherence can be assured)
- ◆ Clozapine if not tried earlier
- ◆ LAI + electroconvulsive therapy (ECT) or oral antipsychotic
- ◆ Clozapine + ECT

Figure 1. Management of Breakthrough Psychosis with Long-Acting Injectable Antipsychotics (LAIs)



*Off-label strategy; based on expert opinion.

†Caution should be exercised with this strategy, because data on the safety of concomitant use of LAI and oral APs are limited, especially over extended periods of time.

**Table 5. Recommended Medications for the Treatment of Schizophrenia:
Long-Acting Injectable Antipsychotics**

Medication	Dose Interval	Dosage Strengths/Forms	Starting Dose	Maintenance Dose	Oral Supplementation	Time to Peak	Steady State
First-Generation Long-Acting Injectable Antipsychotics*							
Fluphenazine decanoate	Varies	25 and 100 mg/mL ampoules/vials/syringes	Varies, 12.5 mg	Varies, 12.5 to 100 mg	No	2 to 4 days	2 to 3 months
Haloperidol decanoate	4 weeks	50 and 100 mg/mL ampoules	Varies, 50 mg	Varies, 300 mg	No	6 to 7 days	2 to 3 months
Second-Generation Long-Acting Injectable Antipsychotics*							
Aripiprazole monohydrate (Ablify/Maintena®)	Monthly	300, 400 mg vial kits and dual-chamber syringe	400 mg	400 mg (300 to 400 mg)	2 weeks	5 to 7 days	400 mg: 4 to 8 months 300 mg: 3 to 4 months
(Aripiprazole lauroxil (Aristada®))	Monthly for 441 mg dose; monthly to every 6 weeks for 882 mg dose; bimonthly for 1,064 mg dose	441; 662; 882; 1,064 mg prefilled syringes	Varies 441 mg to 1,064 mg**	Varies, 441 to 882 mg	3 weeks if Aristada Initio® is not administered at the beginning of treatment. If initiating treatment with Aristada Initio®, 1 day oral supplementation with aripiprazole 30 mg tablet is required.	4 days	4 to 6 months

Table 5. Recommended Medications for the Treatment of Schizophrenia: Long-Acting Injectable Antipsychotics (continued)

Medication	Dose Interval	Dosage Strengths/Forms	Starting Dose	Maintenance Dose	Oral Supplementation	Time to Peak	Steady State
Aripiprazole lauroxil (Aristada Initio®)	Once at the beginning to initiate aripiprazole lauroxil (Aristada®) treatment	675 mg	675 mg	Not applicable (N/A)	1 day (aripiprazole 30 mg tablet)—therapeutic levels in 4 days	27 days	With single IM injection of Aristada initio® and 30 mg oral aripiprazole at time of first Aristada® dose, aripiprazole concentration reaches therapeutic levels within 4 days
Olanzapine pamoate† (Zyprexa Relprevv®)	2 to 4 weeks	210, 300, 405 mg vial kits	Varies, up to 300 mg every 2 weeks	Varies, up to 300 mg every 2 weeks	No	4 days	3 months
Paliperidone palmitate (Invega Sustenna®)	Monthly	39, 78, 117, 156, 234 mg prefilled syringes	234 mg (day 1) + 156 mg (day 8) Deltoid only	117 mg (39 to 234 mg)	No	13 days	7 to 11 months
Paliperidone palmitate (Invega Trinza®)	Once every 3 months	273, 410, 546, 819 mg prefilled syringes	Depends on once-monthly paliperidone palmitate (Invega Sustenna®) dose	Varies, 273 to 819 mg	No	30 to 33 days	Continues steady state at equivalent dose

Medication	Dose Interval	Dosage Strengths/Forms	Starting Dose	Maintenance Dose	Oral Supplementation	Time to Peak	Steady State
Risperidone microspheres (Risperdal Consta®)	Once every two weeks	12.5, 25, 37.5, 50 mg vial kits	Varies, 12.5 mg to 25 mg	Varies, 12.5 mg to 50 mg	3 weeks	4-6 weeks	Steady state reached after 4 injections and maintained for 4-6 weeks after last injection
Risperidone extended release subcutaneous injectable (Perseris®)	Monthly	90 mg, 120 mg powder and liquid filled syringes	90 mg, 120 mg	90 mg, 120 mg	No	4-48 hours	4-6 weeks

Adapted and updated from: Correll CU, Kane JM, Citrome LL. Epidemiology, Prevention, and Assessment of Tardive Dyskinesia and Advances in Treatment. *J Clin Psychiatry*. 2017 Sep/Oct;78(8):1136-1147.

Notes:

For the most updated Florida Medicaid Preferred Drug List, visit https://ahca.myflorida.com/medicaid/Prescribed_Drug/pharm_thera/fmpdli.shtml.

*First-generation long-acting injectable antipsychotic medications (fluphenazine decanoate and haloperidol decanoate) have an oil base. Second-generation long-acting injectable antipsychotic medications (aripiprazole monohydrate, aripiprazole lauroxil, olanzapine pamoate, 1-month and 3-month paliperidone palmitate, and risperidone microspheres) have a water base.

** Initial Aristada® dose is based on current oral aripiprazole dose as follows: If oral aripiprazole dose is 10 mg/day, initial Aristada® dose is 441 mg once monthly. If oral aripiprazole dose is 15 mg/day, initial Aristada® dose is either 882 mg once monthly, 882 mg Aristada every 6 weeks, or 1,064 mg Aristada® every 2 months. If oral aripiprazole dose is ≥20 mg/day, initial Aristada® dose is 882 mg once monthly.

#Olanzapine pamoate (Zyprexa Relprevv) requires prescriber certification and patient enrollment with the Risk Evaluation and Mitigation Strategy (REMS) program. Administration of olanzapine pamoate requires at least 3-hours of post-injection monitoring for post-injection delirium/sedation syndrome (PDSS). Olanzapine has been found to cause more weight gain and related metabolic side effects than other SGAs.

Summary: Treatment of Schizophrenia with LAIs

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MAIN QUESTIONS:

1. Are LAIs more effective than placebo?

Yes.

All approved LAIs have demonstrated efficacy for people with schizophrenia. In the USA (Correll et al., 2017), these agents include:

- ◆ First-generation antipsychotics:
 - ◇ Fluphenazine decanoate
 - ◇ Haloperidol decanoate
- ◆ Second-generation antipsychotics:
 - ◇ Aripiprazole monohydrate
 - ◇ Aripiprazole lauroxil
 - ◇ Olanzapine pamoate
 - ◇ Paliperidone palmitate
 - ◇ Risperidone microspheres
 - ◇ Risperidone extended release subcutaneous injectable

2. Are LAIs more effective than oral antipsychotics?

Yes, in many studies and settings, with some non-differential results, but very rare/virtually no data indicating better efficacy for oral antipsychotics.

Efficacy of LAIs versus oral antipsychotics depends on the study design and included population (Correll et al., 2016). In randomized clinical trials (RCTs) that include patients with better illness insight, less severity/complexity of the disease and better/monitored adherence, LAIs were not more efficacious than placebo (Kishimoto et al., 2014). In mirror image studies (Kishimoto et al., 2013) and cohort/database studies (Kishimoto et al., 2018) that enroll more generalizable patients, LAIs were superior to oral antipsychotics regarding relapse, hospitalization, and all-cause discontinuation risk, despite greater illness severity in patients started on LAIs versus oral antipsychotics in real-world studies. Additionally, LAIs have been associated with a 20–30% reduced all-cause mortality versus oral antipsychotics (Taipale et al., 2018).

Summary: Treatment of Schizophrenia with LAIs (continued)

3. Are LAIs tolerable?

Yes.

Generally, the adverse effects of LAIs are predictable from knowledge of the adverse effect potential of the oral counterpart and can be tested in an individual patient during lead in treatment with the oral antipsychotic.

Comparing 119 adverse events in patients randomized to an LAI or the same medication given in an oral formulation, 115 (97%) were not different, including discontinuation due to adverse event or mortality. Regarding 3 adverse effects [akinesia, (stiffness) with first generation antipsychotics (FGAs), increase in low density lipoprotein cholesterol, and anxiety], oral antipsychotics had lower events, while prolactin levels and hyperprolactinemia were lower in LAI treated patients (Misawa et al., 2016). Injection pain and injection site reactions are generally mild and infrequent (Correll et al., 2016).

Based on data with FGA-LAIs, there is no current indication that the outcome of neuroleptic malignant syndrome is worse when it occurs during LAI versus oral antipsychotic treatment, as management is symptomatic (Glazer and Kane, 1992).

An exception from the rules above is olanzapine pamoate, which is highly blood soluble and which can, in 1/1,100–1,200 injections, lead to a post-injection somnolence, sedation, and coma syndrome (known as post injection delirium/sedation syndrome, or PDSS). Therefore, at least 3 hours of post-injection observation for the duration of treatment with olanzapine pamoate is required.

4. Are there special populations in whom LAIs should especially be considered or not considered?

While prior guidelines relegated LAI use to a third-tier treatment step, unless patients were non-adherent, had multiple relapses or preferred LAIs, recent evidence and guidance includes offering LAIs to potentially all patients as a treatment option and also considering them for prevention of future non-adherence and relapse/deterioration (Llorca et al., 2013; Malla et al., 2013; Correll et al., 2016; Brugnoli et al., 2016; Galletly et al., 2016; Howes et al., 2017; Sajatovic et al., 2018).

- ◆ Populations and clinical scenarios in which first-line use of LAIs should be considered include:
 - ◇ Past or current nonadherence leading to deterioration
 - ◇ Low illness insight
 - ◇ Poor cognition
 - ◇ Dangerousness
 - ◇ Homelessness
 - ◇ Poor support system
 - ◇ Suicidality

Summary: Treatment of Schizophrenia with LAIs (continued)

- ◆ Emerging areas of first-line use of LAIs include:
 - ◇ High level of insight
 - ◇ High functioning (to prevent loss of function)
 - ◇ Anticipated nonadherence over time
 - ◇ Stabilized first episode and early phase patients (high future non-adherence risk, most to lose from future potential relapse)
 - ◇ Treatment-refractory patients who may be “pseudo-resistant” due to covert levels of non-adherence

The only contraindication for deep intramuscular injectable LAIs is significant anticoagulation, presenting a risk for internal bleeding/large hematomas. Needle phobia should be addressed with cognitive behavioral therapy (CBT).

5. How should break-through symptoms during LAI treatment be addressed?

Review and address non-pharmacologic reasons for exacerbation, such as substance use, other comorbid psychiatric or medical illness, psychosocial stressors, etc. Rule out drug-drug interactions and inappropriate injection (insufficient mixing prior to injection, lack of deep intramuscular injection, accumulation of late injection visits, etc.) (Correll et al., 2018).

If the above does not resolve the issue or immediate action is needed, add the same antipsychotic in oral formulation in an attempt to increase the dose. Generally, try to avoid polypharmacy with different antipsychotics, as the evidence for efficacy and safety is lacking (Galling et al., 2017; Correll et al., 2017).

If efficacy is reestablished and the higher dose is tolerated, at the next injection interval, use a higher LAI dose that corresponds to that combined LAI + oral dose. If already at the highest dose, consider changing injection site (deltoid injections lead to higher peak levels but shorter half-life, gluteal injection leads to lower peak levels but longer half-life), change to shortest FDA-approved injection interval (if not already done), or consider off-label strategy of shortening the injection interval (Correll et al., 2016; Correll et al., 2018).

6. How should LAIs best be offered in clinical care?

LAIs need to be destigmatized and presented not as a last resort or in a punitive or mistrustful way, but rather as a highly effective treatment option that offers for many patients a greater likelihood of stability and improved ability to focus on recovery. Data suggest that motivational interviewing and shared decision making, which do not pass the decision simply back to the patient, but that present the evidence and advantages in a respectful and authoritative (yet not authoritarian) way, may yield best results (Correll et al., 2016; Weiden et al., 2017). Inclusion of caregivers/significant others and/or peer counselors should also be considered (Correll et al., 2016). Furthermore, buy-in by and training of all team members can yield very high acceptance of LAIs, with such training, including role play, having been shown to result in at least one LAI injection within 3 months of service engagement in >75% of first-episode and early-phase patients with schizophrenia (Kane et al., 2019).

Summary: Treatment of Schizophrenia with LAIs (continued)

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Treatment Update: Medications Approved for Tardive Dyskinesia

Tardive dyskinesia (TD) is a chronic movement disorder characterized by involuntary, repetitive jerking or writhing movements (choreoathetoid movements) of the face, tongue, lips, torso, or extremities that is most commonly associated with antipsychotic medication treatment for at least a few months. In some cases, tardive dyskinesia may be diagnosed if choreoathetoid movements occur after antipsychotic medication dose reduction or treatment discontinuation when symptoms are not time-limited and persist beyond 4 to 8 weeks.

WHAT MEDICATIONS ARE CURRENTLY APPROVED BY THE FOOD AND DRUG ADMINISTRATION (FDA) TO TREAT TARDIVE DYSKINESIA?

In 2017, valbenazine (Ingrezza™) and deutetrabenazine (Austedo™) became the first FDA-approved agents to treat tardive dyskinesia. Valbenazine and deutetrabenazine are vesicular monoamine transporter-2 (VMAT2) inhibitors. VMAT2 inhibitors block the vesicular monoamine transporter protein from storing and releasing dopamine. Less dopamine storage and release theoretically reduces overstimulation of dopamine receptors in the motor striatum, leading to reduction in the abnormal involuntary movements associated with tardive dyskinesia.

HOW ARE VMAT2 INHIBITORS DOSED?

Drug Name	Dose Form and Strength	Recommended Dosing	FDA-Approval Date for Tardive Dyskinesia
Valbenazine (Ingrezza™)	40 mg capsule	Initial dose of 40 mg/day. Increase to 80 mg once daily after 1 week	April 2017
Deutetrabenazine (Austedo™)	6 mg, 9 mg, and 12 mg tablets	Initial dose of 12 mg/day; titrate at a weekly interval by 6 mg/day until symptoms improvement, and tolerability, up to a maximum of 48 mg/day given in two divided doses.	August 2017

Notes: Valbenazine is currently not on the Medicaid preferred drug list. Deutetrabenazine requires a prior authorization. For updates on the Florida Medicaid preferred drug list, visit https://ahca.myflorida.com/Medicaid/Prescribed_Drug/pharm_thera/fmpdl.shtml.

WHAT ARE THE MOST COMMON SIDE-EFFECTS ASSOCIATED WITH VMAT2 INHIBITORS?

The most common side effects reported with valbenazine and deutetrabenazine were fatigue and somnolence. Deutetrabenazine has a boxed warning for increased risk of depression and suicidality in patients with Huntington disease. Other common side effects associated with VMAT2 inhibitors include anticholinergic effects (dry mouth, constipation, blurred vision, urinary retention), headache, akathisia, and gait disturbances.

List of Abbreviations

- AHCA:** Florida Agency for Healthcare Administration
- AP:** Antipsychotic
- BDI:** Beck Depression Inventory
- BMI:** Body Mass Index
- BPRS:** Brief Psychiatric Rating Scale
- CBT:** Cognitive-Behavioral Therapy
- CGI:** Clinical Global Impression Scale
- CMHC:** Community Mental Health Center
- CRDPSS:** Clinician-Rated Dimensions of Psychosis Symptom Severity
- CYP450:** Cytochrome p450
- DDI:** Drug-Drug Interaction
- DSM:** Diagnostic and Statistical Manual
- ECT:** Electroconvulsive Therapy
- EPS:** Extrapyramidal Symptoms
- FAFP:** Florida Academy of Family Physicians
- FCCMH:** Florida Council for Community Mental Health
- FDA:** Food and Drug Administration
- FGA:** First Generation Antipsychotic
- FLANP:** Florida Association of Nurse Practitioners
- FMA:** Florida Medical Association
- FOMA:** Florida Osteopathic Medical Association
- FPS:** Florida Psychiatric Society
- FSN:** Florida Society of Neurology
- HAM-D:** Hamilton Rating Scale for Depression
- IPSRT:** Interpersonal and Social Rhythm Therapy
- IPT:** Interpersonal psychotherapy
- LAI:** Long-Acting Injectable Antipsychotic
- MADRS:** Montgomery-Åsberg Depression Rating Scale
- MAOI:** Monoamine Oxidase Inhibitor
- MDD:** Major Depressive Disorder

List of Abbreviations (*continued*)

mEq/L: milliequivalents per Liter

mg: milligram

mg/day: milligrams per day

mg/kg/day: milligrams per kilogram per day

MHA: Mental Health America

MMA: Medicaid Managed Medical Assistance

NAMI: National Alliance on Mental Illness

NCD: Non-communicable Chronic Disease

NDMDA: National Depressive and Manic Depressive Association

NIMH: National Institute of Mental Health

PANSS: Positive and Negative Syndrome Scale

PDSS: Post-Injection Delirium/Sedation Syndrome

PHQ-9: Patient Health Questionnaire

PRO: Patient Reported Outcome

QIDS: Quick Inventory of Depression Symptomatology

SAMHSA: Substance Abuse and Mental Health Services Administration

SGA: Second Generation Antipsychotic

SJS: Stevens-Johnson Syndrome

SNRI: Serotonin Norepinephrine Reuptake Inhibitor

SSRI: Selective Serotonin Reuptake Inhibitor

T3: Triiodothyronine

TCA: Tricyclic Antidepressant

TD: Tardive Dyskinesia

TEN: Toxic Epidermal Necrolysis

TMS: Transcranial Magnetic Stimulation

µg/mL: micrograms per milliliter

VMAT2: Vesicular Monoamine Transporter-2

VNS: Vagus Nerve Stimulation

YMRS: Young Mania Rating Scale

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- Resources include health, housing, food banks, transportation, and other services.

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Search for behavioral and physical health services and community resources including housing, food banks, and transportation.

Zip

Enter zip code of interest here and click "search"

- Click the specific category of interest (e.g., food, housing, transit, health) to view available resources, or enter a keyword to narrow the search.

Zip or keyword or program

Select Language ▼

Type the keyword or name of the program here, or search by a different zip code.

FOOD HOUSING GOODS TRANSIT HEALTH MONEY CARE EDUCATION

- Click on the program of interest to view information such as services provided, location, hours, and contact information about that program.



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