2017-2018
Florida Best Practice
Psychotherapeutic Medication Guidelines for Adults
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- Resources and tools

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For treatment of mood disorders in pregnant and post-partum women visit [medicaidmentalhealth.org](http://medicaidmentalhealth.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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INTRODUCTION

The most recent estimate of the prevalence of any mental illness among adults in the United States is 43.4 million, or 17.9% of all adults according to the National Institute of Mental Health (NIMH). Approximately 1 in 25 adults in the U.S.—9.8 million people, or 4.0% of all adults—experiences a serious mental illness that substantially interferes with or limits one or more major life activities (National Institute of Mental Health, 2015). Yet, lack of access to behavioral health care has been an ongoing concern, particularly in areas of critical need, due to increasing shortages in behavioral health specialists and rising demand for behavioral health services. To help bridge gaps in access to behavioral health care in the absence of specialists, primary care clinicians are tasked with providing behavioral health services, as they serve as the first point of contact into the healthcare system. Given these challenges, providing quality care is especially daunting in the absence of clear, concise evidence-based treatment recommendations.

PURPOSE

The goal of the 2017-2018 Florida Best Practice Psychotherapeutic Medication Guidelines for Adults is to provide a guide to clinicians, including psychiatrists and primary care providers, who use psychotherapeutic medications to treat adults with behavioral health conditions. The guidelines are intended as a starting point and provide rational approaches to help address some very challenging conditions. As always, the clinician and patient partnership prevails in the choice of treatment.

The guidelines cover a range of conditions that providers encounter in their clinical practice, including treatment of bipolar disorder, major depressive disorder, and schizophrenia. This year, the expert panel has also updated the guidelines to include recommendations on the use of long-acting injectable antipsychotic medications (LAIs) to inform and guide clinicians in the use of these medications as a treatment option in the management of schizophrenia.

PROCESS FOR CREATING THE GUIDELINES

Every two years, the Florida Medicaid Drug Therapy Management Program brings together a diverse array of stakeholders to update the Florida Best Practice Psychotherapeutic Medication Guidelines for Adults. This year’s group of stakeholders, known as the Florida 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 (CMHCs), psychiatrists, primary care providers, and pharmacists.

The 2017 Florida Expert Panel met in Tampa, Florida on November 3-4, 2017 to review and update the adult guidelines last published in 2015. For each disorder, a psychiatrist who is a nationally recognized content expert conducted a full literature review, presented the findings to the expert panel, and made suggestions to the panel on revising the guidelines based on the state of the scientific evidence. The panel then discussed the guidelines, proposed revisions, and reached a consensus about whether or not to revise and adopt a particular set of proposed revisions. Thus, the final guidelines are a product of an in-depth review of the literature with an emphasis on the highest level of clinical evidence (e.g., randomized controlled trials, systematic reviews), expert consensus on the strength of the evidence, and consideration of safety and efficacy. The names of
the meeting attendees and meeting presentations are available on the program website at medicaidmentalhealth.org. Financial disclosures are available upon request.

We are grateful to our dedicated panel of experts who have provided their expertise, editorial comments, and invaluable advice. We also would like to thank all external reviewers who took the time to make comments and point out areas needing clarity. The Florida Agency for Healthcare Administration (AHCA) is to be commended for its commitment to improving the behavioral health and well-being of underserved populations through the use of evidence-based treatment recommendations.

**Organization**

The 2017-2018 Florida Best Practice Psychotherapeutic Medication Guidelines for Adults are based on a thorough review of the research literature by the expert panel. When the scientific literature is absent or findings are mixed, the guidelines note and explain the absence of clear findings, and advise caution in treatment. Clinical tools recommended in these guidelines are available at medicaidmentalhealth.org. Recommended clinical rating scales are available in the public domain; those that are not are specifically noted.

The guidelines are organized by “levels” of treatment recommendations, beginning with Level 1. The treatment recommendations for each section (Levels 1, 2, 3, etc.) are categorized hierarchically based on the strength of the evidence for efficacy and safety regarding a particular agent or treatment option. Thus, Level 1 treatment 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 recommendations were recently published and are adapted here to explain the bases for each Level:

- Level 1 is initial treatment for which there is established efficacy and relative safety for the treatment recommendations (based on replicated, large randomized controlled trials).

- Level 2 is considered if Level 1 is ineffective and/or not well tolerated. Compared to Level 1, the data on treatment efficacy and/or safety in Level 2 are less robust (based on smaller randomized controlled trials, smaller effect sizes, etc.).

- Level 3 is 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.

- Level 4 is considered if Levels 1 through 3 are ineffective and/or not well tolerated; however, the treatments are not empirically supported at this time and are listed because of expert opinion and/or use in clinical practice.

It should be noted that the levels are not algorithms in which specific treatment decisions are mandatory. Instead, use of these guidelines should take into account the individuality of the patient and presenting symptoms. Although selecting treatments beginning with Level 1 and moving sequentially through the levels is encouraged, the treatment choice can start at any level and should be based on clinical judgment as well as the patient’s individual symptoms, needs, and preferences.
Disclaimer

DISCLAIMER

The 2017-2018 Florida Best Practice Psychotherapeutic Medication Guidelines for Adults are based on the current state of scientific knowledge at the time of publication on effective and appropriate care, as well as on clinical consensus judgments when research is lacking. The inevitable changes in the state of scientific information and technology mandate that periodic review, updating, and revisions will be necessary. These guidelines may not apply to all patients; therefore, each guideline must be adapted and 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: medicaidmentalhealth.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

medicaidmentalhealth.org
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:
  - Risk of harm to self or others
  - An assessment of the full range of psychiatric symptoms and disorders, as well as impairment from these symptoms and disorders
  - 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

- Ongoing management of behavioral health conditions includes:
  - Use of measurement-based care to measure and monitor symptoms and side-effects
  - 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 titled Monitoring Physical Health and Side-Effects of Psychotherapeutic Medications in Adults and Children: An Integrated Approach available at medicaidmentalhealth.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 exist 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: [medicaidmentalhealth.org](http://medicaidmentalhealth.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)
### Table 1. Assessment Scales for Adult Disorders

<table>
<thead>
<tr>
<th>Measures</th>
<th>Acute Depression</th>
<th>Bipolar Acute Mania</th>
<th>Bipolar 1 Cont/Main Therapy</th>
<th>Major Depression</th>
<th>Major Depression with Mixed Features</th>
<th>Major Depression with Psychosis</th>
<th>Schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beck Depression Inventory (BDI)</td>
<td>✓</td>
<td>−</td>
<td>−</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>−</td>
</tr>
<tr>
<td>Brief Psychiatric Rating Scale (BPRS)</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Clinical Global Impression (CGI) Scale</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>✓</td>
<td>−</td>
<td>✓</td>
</tr>
<tr>
<td>Clinician-Rated Dimensions of Psychosis Symptom Severity (CRDPSS)</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Hamilton Rating Scale for Depression (HAM-D)</td>
<td>−</td>
<td>✓</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>✓</td>
<td>−</td>
</tr>
<tr>
<td>Montgomery-Asberg Depression Rating Scale (MADRS)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>−</td>
<td>✓</td>
<td>✓</td>
<td>−</td>
</tr>
<tr>
<td>Patient Health Questionnaire (PHQ-9)</td>
<td>✓</td>
<td>−</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Positive and Negative Syndrome Scale (PANSS)</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Quick Inventory of Depression Symptomatology (QIDS)</td>
<td>✓</td>
<td>−</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Young Mania Rating Scale (YMRS)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>−</td>
<td>✓</td>
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</table>
LIST OF ANTIPSYCHOTIC MEDICATIONS AVAILABLE IN THE UNITED STATES:

- First Generation Antipsychotics (FGAs): chlorpromazine, fluphenazine*, haloperidol¹, loxapine, molindone, perphenazine, thioridazine, thiothixene, and trifluoperazine
- Second Generation Antipsychotics (SGAs): aripiprazole*, asenapine, brexiprazole†, cariprazine¹, 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).
¹Brexiprazole and cariprazine were introduced in 2015.

LIST OF LONG-ACTING INJECTABLE (LAI) ANTIPSYCHOTIC 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 prior individual treatment response, side-effect experience, medication side-effect profile, long-term treatment planning, and 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.

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

**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
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/](https://www.psychiatry.org/)
- Brain and Behavior Research Foundation: [http://bbrfoundation.org/](http://bbrfoundation.org/)
- National Council for Behavioral Health: [https://www.thenationalcouncil.org/](https://www.thenationalcouncil.org/)
- Mental Health America (MHA): [http://www.mentalhealthamerica.net/](http://www.mentalhealthamerica.net/)

**LOCAL RESOURCES:**

For updated links to resources, visit [medicaidmentalhealth.org](http://medicaidmentalhealth.org).
DSM-5 Criteria: Bipolar Disorders

Box 1.

**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.*
Box 2.

**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 3 on page 24 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

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

The primary therapeutic objectives of bipolar disorder care are remission, maintenance of remission, prevention of recurrence, and 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.

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

<table>
<thead>
<tr>
<th>Level 1</th>
<th>Established efficacy:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Optimize index mood stabilizer if already prescribed a mood stabilizer. Check blood levels if appropriate.</td>
<td></td>
</tr>
<tr>
<td>2. Quetiapine or lurasidone monotherapy*</td>
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<tr>
<td>*Notes: Only quetiapine has established efficacy for bipolar II disorder. Lurasidone has a better metabolic profile than quetiapine.</td>
<td></td>
</tr>
<tr>
<td>3. Lamotrigine monotherapy</td>
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<tr>
<td>4. Lurasidone or lamotrigine** adjunctive to lithium or divalproex if index mood stabilizer has been optimized.</td>
<td></td>
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<tr>
<td>**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 page 19.</td>
<td></td>
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<tr>
<td>5. Do not utilize conventional antidepressants (e.g., SSRIs, SNRIs, TCAs, MAOIs) as a first-line therapy.</td>
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<table>
<thead>
<tr>
<th>Level 2A</th>
<th>Established efficacy, but with safety concerns*:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Olanzapine + fluoxetine (bipolar I disorder)</td>
<td></td>
</tr>
<tr>
<td>*Note: Tolerability limitations include weight gain and metabolic concerns.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level 2B</th>
<th>Better tolerability, but limited efficacy*:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Lithium (bipolar 1 disorder)</td>
<td></td>
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<tr>
<td>2. 2 drug combination of above medications. Drugs may include either a first generation antipsychotic (FGA) or second generation antipsychotic (SGA) but NOT TWO antipsychotic medications</td>
<td></td>
</tr>
<tr>
<td>*Note: Efficacy limitations, relatively few positive randomized controlled trials.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level 3</th>
<th>If Levels 1 and 2 are ineffective and/or not well tolerated*:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Electroconvulsive therapy (ECT)</td>
<td></td>
</tr>
<tr>
<td>*Note: Consideration is merited due to clinical need, despite even greater efficacy/tolerability limitations than Level 1 and 2 treatments.</td>
<td></td>
</tr>
</tbody>
</table>
Level 4 If Levels 1 – 3 are ineffective and/or not well tolerated:
- Cariprazine
- FDA-approved agent for bipolar disorder + conventional antidepressant (e.g., SSRI)*
- Pramipexole
- Adjunctive: modafinil, thyroid hormone (T3), or stimulants
- 3 drug combination
- Transcranial magnetic stimulation (TMS)

*Notes:
- There is inadequate information (including negative trials) to recommend adjunctive antidepressants, aripiprazole, ziprasidone, levetiracetam, armodafinil, or omega-3 fatty acids for bipolar depression.
- Preliminary evidence is available for cariprazine in the treatment for bipolar I depression.
- Antidepressant monotherapy is not recommended in bipolar I depression; recommendation is for adjunctive mood stabilizer with antidepressant.
- Superiority (in other words, efficacy and safety) of antidepressant monotherapy versus adjunctive mood stabilizer with antidepressant for treatment of bipolar II depression is uncertain.
## Treatment of Acute Bipolar Disorder - Mania

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

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 concerns, 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  Established efficacy:

**Mild to moderate severity and/or not requiring hospitalization**
- Optimize mood stabilizer (lithium*, divalproex*, or carbamazepine*) if already prescribed. Check blood levels if appropriate.
- 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  Established efficacy, but with safety concerns**:

**Mild to moderate severity and/or not requiring hospitalization**
- Monotherapy with either haloperidol or olanzapine

**Severe and/or requiring hospitalization**
- Lithium* or divalproex* + 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)

Level 4 If Levels 1 – 3 are ineffective and/or not well tolerated:

- A three-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. Example: lithium* + (divalproex* or carbamazepine*) + antipsychotic

Notes:

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

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

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

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

Florida Clozapine Hotline
727-562-6762
Rhemsath@aol.com

The Clozapine Hotline is operated by Randolph Hemsath, M.D., Medical Director of Boley Centers, a CARF-accredited community mental health center in St. Petersburg, FL. Dr. Hemsath has over 30 years’ experience as a psychiatrist and extensive experience utilizing clozapine as an option for individuals with treatment-refractory schizophrenia.

The hotline is funded by the Florida Medicaid Drug Therapy Management Program for Behavioral Health through a contract with the Florida Agency for Healthcare Administration.

Calls and emails will be answered on non-holiday weekdays between 8:00am and 5:00pm. No registration is required and the service is free.
Bipolar 1 Disorder Continuation / Maintenance Therapy

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

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 treated by a non-psychiatrist.**

<table>
<thead>
<tr>
<th>Level 1</th>
<th>Established efficacy:</th>
</tr>
</thead>
<tbody>
<tr>
<td>✦ Periodic evaluation: frequency based on clinical needs</td>
<td></td>
</tr>
<tr>
<td>✦ Continue with effective and well-tolerated treatment</td>
<td></td>
</tr>
<tr>
<td>✦ Lithium* monotherapy</td>
<td></td>
</tr>
<tr>
<td>✦ Quetiapine monotherapy</td>
<td></td>
</tr>
<tr>
<td>✦ Lamotrigine* (evidence strongest for prevention of depression)</td>
<td></td>
</tr>
<tr>
<td>✦ If initially stabilized on divalproex†, maintain.</td>
<td></td>
</tr>
<tr>
<td>✦ Aripiprazole or aripiprazole long-acting injectable, long-acting risperidone monotherapy</td>
<td></td>
</tr>
<tr>
<td>✦ Quetiapine (for recurrence prevention) or ziprasidone (for relapse prevention) adjunctive to (lithium* or divalproex**)</td>
<td></td>
</tr>
<tr>
<td>✦ Asenapine monotherapy</td>
<td></td>
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</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Level 2A</th>
<th>Established efficacy, but with safety concerns**:</th>
</tr>
</thead>
<tbody>
<tr>
<td>✦ Olanzapine monotherapy</td>
<td></td>
</tr>
<tr>
<td>✦ Olanzapine adjunctive to lithium* or divalproex***</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level 2B</th>
<th>If Level 1 is ineffective and/or not well tolerated:</th>
</tr>
</thead>
<tbody>
<tr>
<td>✦ Continue effective and well-tolerated acute treatment(s) if not listed in Level 1</td>
<td></td>
</tr>
<tr>
<td>✦ Lithium* and divalproex*** combination</td>
<td></td>
</tr>
<tr>
<td>✦ Follow acute mania/bipolar depression guidelines to achieve remission or partial remission</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Level 3</th>
<th>If Levels 1 and 2 are ineffective and/or not well tolerated:</th>
</tr>
</thead>
<tbody>
<tr>
<td>✦ Adjunctive clozapine (avoid combining with another antipsychotic)</td>
<td></td>
</tr>
<tr>
<td>✦ Electroconvulsive therapy (ECT)†</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Notes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Caution should be used when prescribing lithium, lamotrigine, divalproex or carbamazepine to women of reproductive age due to increased risks to the fetus with use during pregnancy, including neural tube and other major birth defects. Please see Florida Best Practice Recommendations for Women of Reproductive Age with Serious Mental Illness and Comorbid Substance Use Disorders and online guideline on the Pharmacological Treatment of Mood Disorders During Pregnancy.</td>
</tr>
<tr>
<td>**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.</td>
</tr>
<tr>
<td>†Long-term efficacy data are limited for the following: divalproex monotherapy, carbamazepine (drug interaction risk), antidepressants, and electroconvulsive therapy (inconvenience/expense).</td>
</tr>
</tbody>
</table>

**medicaidmentalhealth.org**
<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>In acute mania: 1,200 - 2,400 mg/day</td>
<td>Initial titration for tolerability - start 600-900 mg/day, increase 300 mg/day every 5 days. Check levels 5 days after initiation/dose change. Check levels frequently if clinical toxicity. Monitor renal and thyroid functions. Lower doses/levels may be necessary in non-manic compared to manic patients. 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.</td>
</tr>
<tr>
<td>Divalproex</td>
<td>In acute mania: 5 - 60 mg/kg/day; 1,000 - 2,500 mg/day</td>
<td>Initial loading may be tolerated, but some patients need initial titration for tolerability. Check levels 48 hours after initiation and adjust dose accordingly. Side-effects (especially gastrointestinal) are more evident above 100μg/ml. More teratogenic than other mood stabilizers. Lower doses/levels may be necessary in non-manic compared to manic patients.</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>In acute mania: 200 - 1,600 mg/day</td>
<td>Initial titration for tolerability due to hepatic auto-induction: 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<em>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</em>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, 2C19, and 2C19.</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>In bipolar maintenance: 100 - 400 mg/day</td>
<td>Initial titration to reduce risk of Stevens-Johnson syndrome (serious rash): Start 25 mg/day (12.5 mg/day if taken with divalproex). Increase by 25mg/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.</td>
</tr>
</tbody>
</table>

*mg/day = milligrams per day; mEq/L = milliequivalents per Liter; mg/kg/day = milligram per kilogram per day; μg/ml = microgram per milliliter
### Table 3. Recommended Medications for the Treatment of Bipolar Disorder – Second Generation Antipsychotics (SGAs) and Antidepressants

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Second Generation Antipsychotics (SGA)</strong></td>
<td>In acute mania:</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>• Aripiprazole: 15 - 30 mg/day</td>
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<tr>
<td></td>
<td>• Asenapine: 10 - 20 mg/day</td>
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<tr>
<td></td>
<td>• Olanzapine: 6 - 20 mg/day</td>
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<tr>
<td></td>
<td>• Paliperidone 3 - 12 mg/day</td>
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<tr>
<td></td>
<td>• Quetiapine: 400 - 800 mg/day</td>
<td></td>
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<tr>
<td></td>
<td>• Risperidone: 2 - 6 mg/day</td>
<td></td>
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<tr>
<td></td>
<td>• Ziprasidone: 80 - 160 mg/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>In acute bipolar depression:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Quetiapine: 200 - 600 mg/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Olanzapine/Fluoxetine: 3 mg/12.5 mg - 12 mg/50 mg per day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Lurasidone: 40 - 120 mg/day</td>
<td></td>
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<tr>
<td></td>
<td>• Clozapine: 50 - 400 mg/day (if treatment resistant)</td>
<td></td>
</tr>
<tr>
<td><strong>Antidepressants</strong></td>
<td>In acute bipolar depression:</td>
<td>Larger trials have not found a benefit of antidepressants when added to mood stabilizers/antimanics 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.</td>
</tr>
<tr>
<td></td>
<td>As dosed for major depression. (No specific dosing recommendations can be given for bipolar depression.)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Larger trials have not found a benefit of antidepressants when added to mood stabilizers/antimanics 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.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Serotonin-norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs) may have greater manic switch risk.</td>
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<tr>
<td></td>
<td>Antidepressants 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 them and have stable mood.</td>
<td></td>
</tr>
</tbody>
</table>

*mg/day = milligrams per day
Pharmacological Treatment of Bipolar Disorder: 2017-2018 Update Summary

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Head, Mood Disorders Psychopharmacology Unit (MDPU), University Health Network
Chairman and Executive Director, Brain and Cognition Discovery Foundation (BCDF)
Director, Depression and Bipolar Support Alliance (DBSA), Chicago

INTRODUCTION

Bipolar disorders (BD) are associated with high rate of non-recovery, inter-episodic dysfunction, and chronicity. Mortality studies indicate that the rate of premature mortality is significantly elevated in bipolar disorder with a widening chasm in the mortality rate between affected individuals and persons in the general population. Convergent and replicated evidence indicates that utilization of a chronic disease model is an integral component to improving health outcomes in bipolar disorder, with salutary effects on both morbidity and mortality outcomes. Moreover, by improving precision, consistency, and appropriateness of treatment selection, decision support with evidence informed guidelines have demonstrated to reduce both individual and societal costs attributable to bipolar disorder.

The update of the 2017-2018 Florida Best Practice Psychotherapeutic Medication Guidelines for Adults represents the most up-to-date treatment recommendations and decision support for multiple stakeholders involved with, and who provide care for, individuals diagnosed with bipolar disorder. This current iteration provides a further refinement, in some cases differential emphasis, from the previous published version (Ostacher, Tandon, and Suppes 2016). In contradistinction from most treatment guidelines in bipolar disorder, the 2017-2018 Florida Best Practice Psychotherapeutic Medication Guidelines for Adults represents a synthesis of evidence and multi-disciplinary opinion from multiple stakeholders, including, but not limited to academicians, clinicians, and experts in private and public healthcare policy. The current portrait sketched of bipolar disorder as a common, complex, and lifelong disorder that significantly curtails human capital invites the need for multi-disciplinary consensus on pragmatic and scalable interventions. The updated version of the 2017-2018 Florida Best Practice Psychotherapeutic Medication Guidelines for Adults provides an update of pharmacologic, psychosocial, and neurostimulatory treatment approaches for symptom management.

PRINCIPLES OF TREATMENT

There are several guiding principles of treatment that are emphasized in the 2017-2018 guidelines. A particular emphasis is made on the importance of timely and accurate diagnosis. It remains a modifiable deficiency in bipolar disorder that the majority of affected individuals continue to be misdiagnosed and/or diagnosed long after observable characteristics and service utilization related to bipolar disorder have appeared. Safety assessment continues to be a priority and guiding principle in bipolar disorder, with emphasis not only on suicide and risk reduction, but also an urgency given to risk factor modification for common and chronic non-communicable comorbid physical health conditions (e.g., cardiovascular disease, metabolic syndrome). A third guiding principle is the importance of careful calculus of benefit of treatment expected compared to the holistic appraisal of treatment-related side effects and safety concerns. It is the view of the
authorship of the guideline, that collective treatments for acute-based management (i.e., acute mania, acute bipolar depression) need to anticipate both short- and long-term side effects and safety concerns (e.g., weight gain). Priority is always given to safe, well-tolerated treatments that are supported by rigorous, randomized, double-blind, placebo-controlled trials.

Moreover, the guiding principle of integrating multimodality treatments in bipolar disorder is emphasized in light of the evidence supporting and the rationale for considering manualized-based psychosocial treatments (e.g., cognitive behavioral therapy, interpersonal social rhythm therapy). The 2017-2018 guideline further presses the principle on the importance of giving equal priority to somatic health (e.g., cardiovascular disease) as is given to conventional treatment targets in bipolar disorder (e.g., mania, sleep, cognitive impairment). Finally, patient health management, locus of care (e.g., medical home), and the importance of functional recovery and positive mental health and resiliency, are emphasized.

Pharmacological Treatment of Acute Bipolar Depression

Bipolar depression is the predominant therapeutic target in bipolar disorder in most early and later phases of the illness. Furthermore, depressive symptoms as part of bipolar disorder are often chronic, and highly associated with risk, comorbidity (e.g., cardiovascular disease), functional impairment, and suicidality. The United States Food and Drug Administration (FDA) has approved three psychotherapeutic agents of bipolar depression (i.e., lurasidone, quetiapine, and olanzapine-fluoxetine combination). The expert panel for the Florida Guidelines consensually agree to also list lamotrigine as a possible first-line treatment strategy in bipolar depression. The expert panel recognizes that lamotrigine has not received regulatory approval for marketing in bipolar depression. Notwithstanding, results conducted in large academic centers, as well as meta-analyses, indicate that lamotrigine is an effective agent for both acute and recurrence prevention of bipolar depression (lamotrigine is currently FDA-approved for recurrence prevention in bipolar disorder). Cariprazine, a D3 preferring D2/D3 partial agonist is currently approved for mania and mixed states in bipolar disorder, but not for bipolar depression. At the time of completing the 2017-2018 Florida Guidelines, results from two pivotal registration trials in adults with bipolar I depression indicate that cariprazine is efficacious in the acute treatment of bipolar I depression. The 2017-2018 guidelines re-emphasize the ubiquity and hazards posed by mixed features in bipolar disorder. Hitherto, no safe and reliable treatment is unequivocally established and efficacious in mixed bipolar depression (McIntyre, 2017). Notwithstanding, select atypical antipsychotics are likely the initial treatments of choice for many individuals with bipolar depression and mixed features. Select second generation antipsychotics are also recommended as first-line treatment for mania with mixed features.

Antidepressant utilization remains an understudied and controversial issue in bipolar disorder. No single antidepressant or class of antidepressants are approved for bipolar disorder. It is recognized by the Florida Expert Panel that antidepressants continue to be utilized at a high rate in adults with bipolar disorder. The guiding principle of utilizing antidepressants in bipolar disorder is that they should not be prioritized over better established and FDA-approved treatment, and should be utilized as adjunctive treatment strategies. The use of antidepressant monotherapy is highly discouraged in bipolar I disorder, while the safe and effective use of antidepressants in bipolar II disorder remains a possibility, but still requires replicated empirical evidence. Psychosocial treatments, like pharmacotherapeutic treatments for bipolar disorder, are recognized to be more effective earlier in the illness course. For treatment-resistant bipolar depression, electroconvulsive
Pharmacological Treatment of Bipolar Disorder: 2017-2018 Update Summary (continued)

therapy (ECT) remains the recommended treatment option, with evidence also supporting alternate neurostimulatory approaches (e.g., rTMS).

Pharmacological Treatment of Acute Bipolar Mania

The expert panel recognizes that mania is not only a defining feature of bipolar I disorder, but is a medical emergency requiring urgent detection, establishment of safety, appropriate setting assignment for care, and evidence-based treatments. No substantive changes were made to the acute mania guidelines when compared to the 2015 iteration, with an ongoing emphasis on FDA-approved second-generation antipsychotics, lithium, and divalproex, as the most commonly recommended first-line strategies.

Continuation and Maintenance Pharmacological Treatment of Bipolar Disorder

Bipolar disorder is a highly progressive condition, as evidenced by greater episode frequency, duration, and complexity, as well as diminished treatment response across the illness trajectory. It is also recognized in bipolar disorder that best practices utilizing integrated multimodality therapies reduce and forestall risk of recurrence, and speculatively, neurobiological progression and cumulative illness load. Since the publication of the 2015 guidelines, the FDA has approved aripiprazole long-acting injectable (LAI) as a recurrence prevention treatment in bipolar disorder. The FDA has also approved aripiprazole proteus (Abilify MyCite®), which may be extrapolated to the bipolar population. Aripiprazole proteus (Abilify MyCite®) is a combination product comprised of oral aripiprazole embedded with an ingestible digital sensor to record and communicate medication ingestion events. Whether digital sensory detection improves compliance and health outcomes in bipolar disorder, however, is not well known. As per the previous guidelines, key therapeutic targets during long-term treatment of bipolar include subsyndromal depression, affective instability, cognitive impairment, sleep disturbance, comorbidity (e.g., substance use disorder, anxiety disorder, cardiovascular disease, obesity), as well as interpersonal, social and workplace dysfunction (Miskowiak et al., 2017). Multimodality interventions incorporating pharmacotherapy, psychosocial treatment, cognitive remediation, lifestyle modification (e.g., exercise), are critical components of long term care. As with major depressive disorder (MDD), it is also recommended by the expert panel that advocacy, for example, the Depression and Bipolar Support Alliance (DBSA), can play a critical role in education support service access and illness/treatment literacy and should be considered an integral component of care for any person affected by bipolar disorder.

References:


DSM-5 Diagnosis: Major Depressive Disorder

**Major Depressive Episode:**

- Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. 
  
  **Note:** Do not include symptoms that are clearly attributable to another medical condition.

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

- The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- The episode is not attributable to the physiological effects of a substance or to another medical condition. 
  
  **Note:** The above criteria represent a major depressive episode.

- The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.
- There has never been a manic episode or a hypomanic episode. 
  
  **Note:** This exclusion does not apply if all of the manic-like or hypomanic-like episodes are substance-induced or are attributable to the physiological effects of another medical condition.
Treatment of Major Depressive Disorder

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

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

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

Assess for:

- Prior history of hypomania/mania*
- Psychiatric and medical comorbidities (e.g., substance-related disorders, anxiety disorders, obesity, diabetes)
- Presence of specifiers, notably: psychosis, mixed features, suicidality
- Presence of cognitive dysfunction (e.g., memory complaints; difficulty with concentration, making decisions, and thinking clearly)
- Assess for recurrence vulnerability factors (e.g., symptom severity, age of onset, number of depressive episodes)

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

Level 1 Initial Treatment:

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

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

- Monotherapy 4-8 week trial at adequate dose and evaluate*:
  - Selective serotonin reuptake inhibitor (SSRI)**, serotonin-norepinephrine reuptake inhibitor (SNRI), or vortioxetine
  - Bupropion or mirtazapine

- If partial response at 4 weeks, may continue for another 2 to 4 weeks or go to Level 2.

- If no response at 4 weeks, ensure dose optimization and go to Level 2.

Notes:

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

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

Initiate combination therapy for individuals with recurrent depression, persistent depressive disorder, and history of trauma.
Treatment of Major Depressive Disorder (continued)

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

- 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:
  - Evidence-based psychotherapy (e.g., CBT, IPT)
  - Second-generation antipsychotic FDA-approved for augmentation therapy for major depressive disorder (MDD) (i.e., aripiprazole or brexipiprazole)
  - An antidepressant (do not combine SSRI and SNRI)

*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.

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

- Evaluate adherence
- Seek psychiatric consultation
- (SSRI or SNRI) + quetiapine (tolerability concerns)
- (SSRI or SNRI) + (lithium or T3)
- (SSRI or SNRI) + (L-methylfolate or S-adenosylmethionine)
- Tricyclic antidepressant (TCA)
- Monoamine oxidase inhibitor (MAOI)
- Electroconvulsive therapy (ECT)
- Transcranial magnetic stimulation (TMS)*

*Note: TMS only has Level 1 evidence for acute treatment.

Level 4  If Levels 1 – 3 are ineffective and/or not well tolerated:

- Re-evaluate diagnosis if patient has failed to respond to 2 or more treatments
- Monoamine oxidase inhibitor (MAOI) augmentation (AVOID CONTRAINDIATED COMBINATIONS)
- L-methylfolate augmentation
- Triple drug combination (little evidence exists supporting or refuting this strategy)
  - (SSRI or SNRI) + mirtazapine + bupropion
  - (SSRI or SNRI) + mirtazapine + lithium*
  - (SSRI or SNRI) + bupropion + second generation antipsychotic (SGA)
- Other neuromodulatory approaches [e.g., vagus nerve stimulation (VNS)]
- Intravenous ketamine (at specialized centers only and in accordance with best practices)

*Note: Caution should be used when prescribing lithium due to increased risk to the fetus with use during pregnancy (i.e., Ebstein’s anomaly).
Treatment of Major Depressive Disorder with Mixed Features

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

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

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

Assess for:

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

### Level 1  Initial Treatment:

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

**Note:** Antidepressant monotherapy in MDD with subsyndromal hypomania may be associated with a higher rate of suboptimal therapeutic outcomes when compared to MDD without subsyndromal hypomania.
  - Bupropion (if tolerability concerns) or mirtazapine

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

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

- Reassess for hypomania/mania
- Ensure dose optimization of medication used in Level 1.
- Switch to different monotherapy SGA** or mood stabilizer*.
- Antidepressant monotherapy from different or same class
- Combine existing antidepressant with different SGA**.
- Combine SGA** or mood stabilizer with antidepressant.
Level 3  If Levels 1 and 2 are ineffective and/or not well tolerated:
- Consider electroconvulsive therapy (ECT) or transcranial magnetic stimulation (TMS)
- Alternative antidepressants, including tricyclic antidepressant (TCA), monoamine oxidase inhibitor (MAOI), or first generation antipsychotic (FGA)**

Notes:
* Caution should be used when prescribing lithium, lamotrigine, divalproex or carbamazepine to women of reproductive age due to increased risks to the fetus with use during pregnancy, including neural tube and other major birth defects. Please see Florida Best Practice Recommendations for Women of Reproductive Age with Serious Mental Illness and Comorbid Substance Use Disorders and online guideline on the Pharmacological Treatment of Mood Disorders During Pregnancy.
**Side-effect concerns with these agents include weight gain, metabolic syndrome, and extrapyramidal symptoms (EPS). Side-effects warrant vigilance and close monitoring on the part of the clinician.

Florida Clozapine Hotline available to give guidance:
1-727-562-6762
Rhemsath@aol.com
Treatment of Major Depressive Disorder with Psychotic Features

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

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

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

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

### Level 1 Initial Treatment:
- Treatment with Level 1 antidepressant for major depressive disorder without psychotic features. Selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) + second generation antipsychotic (SGA)*
- Electroconvulsive therapy (ECT) (if patient welfare is an immediate concern)
- Cognitive-behavioral therapy (CBT) and interpersonal psychotherapy (IPT) are not recommended as first-line modality.

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

### Level 2 If Level 1 is ineffective and/or not well tolerated:
- Alternative antidepressant + SGA combination
- ECT

### Level 3 If Levels 1 and 2 are ineffective and/or not well tolerated:
- Re-evaluate diagnosis
- Other antidepressant combinations with SGA
- Other antidepressant combinations with first generation antipsychotic (FGA)
- ECT (if not attempted earlier)
Pharmacological Treatment of Major Depressive Disorder: 2017-2018 Update Summary

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Head, Mood Disorders Psychopharmacology Unit (MDPU), University Health Network
Chairman and Executive Director, Brain and Cognition Discovery Foundation (BCDF)
Director, Depression and Bipolar Support Alliance (DBSA)

INTRODUCTION

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

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

PRINCIPLES OF TREATMENT

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

During the past ten years, extant evidence indicates that individuals with MDD and higher levels of pre-treatment function have higher response rates to conventional antidepressant treatment. The bidirectional association between symptoms and function in MDD raises a myriad of conceptual questions and hypotheses, as well as clinical implications. An axiomatic clinical implication derived
from the foregoing observation is that augmenting patient function contemporaneously with symptom targeting in MDD provides a greater probability to therapeutic success and acceptability.

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

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

### Major Depressive Disorder without Mixed Features

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

### Major Depressive Disorder with Mixed Features

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

### Major Depressive Disorder with Psychosis

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

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

REFERENCES:


Florida Medicaid Drug Therapy Management Program for Behavioral Health

Working with Medicaid providers to:

- Improve behavioral health prescribing practices
- Improve patient adherence to medication
- Reduce clinical risks and medication side effects
- Improve behavioral and physical health outcomes

The following treatment guidelines are available on our website at medicaidmentalhealth.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

The Florida Clozapine Hotline and The Florida Pediatric Psychiatry Hotline are free services that provide consultation about medication management.

Florida Clozapine Hotline
1-727-562-6762
Florida Pediatric Psychiatry Hotline
1-866-487-9507

If you would like hard copies of any of our guidelines mailed to you, please contact Sabrina Singh at sabrinasingh@usf.edu.

For more information, visit us at medicaidmentalhealth.org.
DSM-5 Criteria: Schizophrenia

Box 4.

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 be 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

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

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.*

<table>
<thead>
<tr>
<th>Level 1</th>
<th>Initial Treatment:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Monotherapy with an oral antipsychotic (SGA) other than clozapine*</td>
</tr>
<tr>
<td></td>
<td>If initial trial of antipsychotic monotherapy unsuccessful, try monotherapy with another antipsychotic with low metabolic adverse effects.</td>
</tr>
<tr>
<td></td>
<td>If two failed adequate trials of monotherapy, consider switching to a long-acting injectable antipsychotic medication (LAI) or clozapine.</td>
</tr>
</tbody>
</table>

*Note: Balance efficacy, side-effects, individual vulnerabilities and preferences. Select a medication with lower metabolic risk and lower risk of extrapyramidal symptoms (EPS).*

<table>
<thead>
<tr>
<th>Level 2A</th>
<th>If non-adherence to Level 1:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Consider long-acting injectable antipsychotic medication (LAI)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level 2B</th>
<th>If Level 1 is ineffective and/or not well tolerated:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Consider clozapine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level 3</th>
<th>If Levels 1 and 2 are ineffective and/or not well tolerated:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diagnostic review and/or consultation</td>
</tr>
<tr>
<td></td>
<td>Clozapine if not tried earlier</td>
</tr>
<tr>
<td></td>
<td>Antipsychotic + electroconvulsive therapy (ECT)</td>
</tr>
<tr>
<td></td>
<td>Augmentation of clozapine with lamotrigine if partial or incomplete response to clozapine</td>
</tr>
</tbody>
</table>
Table 4. Recommended Medications for the Treatment of Schizophrenia: Oral Antipsychotics

<table>
<thead>
<tr>
<th>Medication</th>
<th>Chlorpromazine Equivalents(^a)</th>
<th>Acute Therapy</th>
<th>Maintenance Therapy(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First Generation Antipsychotics (FGAs)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>100</td>
<td>300-1,000 mg/day</td>
<td>300-800 mg/day</td>
</tr>
<tr>
<td>Fluphenazine HCl</td>
<td>2</td>
<td>5-20 mg/day</td>
<td>5-15 mg/day</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>2</td>
<td>5-20 mg/day</td>
<td>6-12 mg/day</td>
</tr>
<tr>
<td>Loxapine</td>
<td>10</td>
<td>30-100 mg/day</td>
<td>30-60 mg/day</td>
</tr>
<tr>
<td>Molindone</td>
<td>10</td>
<td>30-100 mg/day</td>
<td>30-60 mg/day</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>8</td>
<td>16-80 mg/day</td>
<td>16-64 mg/day</td>
</tr>
<tr>
<td>Thiothixene</td>
<td>5</td>
<td>15-50 mg/day</td>
<td>15-30 mg/day</td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>5</td>
<td>15-50 mg/day</td>
<td>15-30 mg/day</td>
</tr>
<tr>
<td><strong>Second Generation Antipsychotics (SGAs)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>N/A</td>
<td>10-30 mg/day</td>
<td>10-30 mg/day</td>
</tr>
<tr>
<td>Asenapine</td>
<td>N/A</td>
<td>10-20 mg/day</td>
<td>10-20 mg/day</td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>N/A</td>
<td>2-4 mg/day</td>
<td>2-4 mg/day</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>N/A</td>
<td>1.5-6 mg/day</td>
<td>3-6 mg/day</td>
</tr>
<tr>
<td>Clozapine</td>
<td>N/A</td>
<td>150-600 mg/day</td>
<td>150-600 mg/day</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>N/A</td>
<td>12-24 mg/day</td>
<td>12-24 mg/day</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>N/A</td>
<td>40-160 mg/day</td>
<td>40-160 mg/day</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>N/A</td>
<td>10-30 mg/day</td>
<td>10-20 mg/day</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>N/A</td>
<td>3-12 mg/day</td>
<td>3-12 mg/day</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>N/A</td>
<td>300-800 mg/day</td>
<td>300-800 mg/day</td>
</tr>
<tr>
<td>Risperidone</td>
<td>N/A</td>
<td>2-8 mg/day</td>
<td>2-8 mg/day</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>N/A</td>
<td>80-240 mg/day</td>
<td>80-160 mg/day</td>
</tr>
</tbody>
</table>

Notes:
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).

\(^a\)Approximate 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.

\(^b\)Drug-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.
INTRODUCTION

The primary objectives in the treatment of schizophrenia are to reduce the frequency and severity of psychotic exacerbation, ameliorate a broad range of symptoms, and improve functional capacity and quality of life. Treatment for schizophrenia includes medication and a range of psychosocial interventions. Antipsychotics are the cornerstone of the pharmacological treatment for schizophrenia. The 21 antipsychotics available in the United States have traditionally been classified into two major groups: 9 first-generation (conventional) agents (FGAs) and 12 second-generation (atypical) agents (SGAs). Whereas the efficacy of these antipsychotic agents in the treatment of schizophrenia is broadly similar (with the exception of clozapine’s greater efficacy in otherwise treatment-refractory patients), there are significant differences in their side-effect profiles. This article summarizes our current understanding of the pharmacotherapy of schizophrenia and is the basis for the 2017-2018 Florida Best Practice Psychotherapeutic Medication Guidelines for Adults. Optimal individualized pharmacological treatment of schizophrenia requires an understanding of:

- The clinical and biological nature of schizophrenia in order to identify targets of treatment and define specific treatment goals;
- How available treatments compare (similarities and differences in terms of efficacy, safety/tolerability, costs, ease of use, and pharmacokinetics and pharmacodynamics); and
- How to use available treatments optimally (targeted, measurement-based, and individualized).

NATURE OF SCHIZOPHRENIA AND DEFINITION OF TREATMENT TARGETS AND TREATMENT GOALS

Schizophrenia is a chronic, remitting and relapsing illness with onset in late adolescence or early adulthood. It is characterized by multiple psychopathological dimensions (positive, negative, cognitive, mood, motor, and disorganization) each of which have distinct neurobiological underpinnings, clinical profiles, and patterns of treatment response. Each of these symptom domains contribute to functional impairment and adversely impact quality of life. Objectives of treatment therefore include maximal reduction in severity of each of these symptom domains and prevention of relapse. Since different patients exhibit varying admixtures of these symptoms, individualized tailoring of treatment is essential.

WHAT DO ANTIPSYCHOTIC MEDICATIONS DO?

Antipsychotic medications are the mainstay in the pharmacological treatment of schizophrenia. They are effective in treating acute psychotic relapses and reducing the likelihood of such relapses. All antipsychotics are effective in reducing positive symptoms (i.e., hallucinations, delusions, and paranoia) and disorganization, but are only minimally effective for negative and cognitive symptoms that significantly contribute to the disability associated with schizophrenia. They can...
ameliorate mood and motor symptoms, but can also make them worse (e.g., neuroleptic dysphoria and neuroleptic malignant syndrome). They are associated with a range of adverse effects (e.g., motor, metabolic, and other disturbances) and differ substantially in their side-effect profiles.

**HOW DO ANTIPSYCHOTIC MEDICATIONS COMPARE?**

**Efficacy**

With the exception of clozapine, all antipsychotic medications are about equally effective in treating positive symptoms and disorganization. Clozapine is more effective than other antipsychotics in treating positive symptoms in otherwise treatment-refractory patients and reducing suicidality in schizophrenia. The relatively minor differences in efficacy observed among the other antipsychotic agents principally relate to dosing and different degrees of ease of use. Response over the first 2-4 weeks of antipsychotic therapy is highly predictive of long-term response. The maximum effect, however, may not be achieved for several months, and trajectories of response vary considerably across patients. Responsiveness to antipsychotics also varies as a function of stage of illness, with first-episode patients responding faster and at a higher rate than those at later stages of the illness. Antipsychotics are equally ineffective in treating primary negative and cognitive symptoms while differing in their effects on secondary symptoms [when agents cause extrapyramidal side effects (EPS), they worsen secondary negative and cognitive symptoms].

Antipsychotic medications substantially decrease the likelihood of relapse in schizophrenia, without any consistent differences among agents. Since medication nonadherence is common in schizophrenia, long-acting injectable antipsychotics may have an advantage over oral treatment in reducing relapse rates. Six agents (aripiprazole, fluphenazine, haloperidol, olanzapine, paliperidone, and risperidone) are available in long-acting injectable formulations requiring injections at intervals ranging from 2 weeks to 3 months.

**Safety and Tolerability**

Antipsychotic medications cause a range of side-effects including neurological, metabolic, cardiovascular, gastrointestinal, hematological, genitourinary, musculoskeletal, endocrine, and other side-effects. In contrast to their broadly similar efficacy, antipsychotics differ markedly in their adverse effect profiles. Compared with the FGAs, it is generally believed that the SGAs have a lower risk of EPS but a higher risk of metabolic adverse effects. However, due to differences in pharmacological profiles within the FGA and SGA classes, there is substantial variation within both classes in their propensity to cause EPS and metabolic adverse effects. Increased risk of EPS has been associated with neurotoxicity, however, leading to the panel’s recommendation to preferentially use SGAs rather than FGAs in the initial treatment of schizophrenia. Because of the adverse sequelae of EPS and its treatment (e.g., secondary negative symptoms, secondary depression, secondary cognitive impairment, and tardive dyskinesia), EPS must be avoided. Similarly, because of the increased mortality associated with metabolic side-effects (e.g., hyperlipidemia and diabetes mellitus), these must be minimized.

The 21 antipsychotic medications available in the United States also differ in their propensity to cause other side-effects, such as sedation, hypotension, cardiac arrhythmias, prolactin elevation and
related sexual dysfunction, and anticholinergic effects, with substantial variation within both the FGAs and the SGAs for each of these effects, without any definitive categorical separation between the two classes.

Patients with schizophrenia also vary in their vulnerability to develop various adverse effects with different agents. The likelihood that a patient will develop a particular side effect thus depends on the agent selected, how that agent is used (e.g., dose, titration method, and in combination with what other agents), and the patient’s vulnerability.

**Optimizing Individual Outcomes**

Given the significant variability in drug pharmacokinetics and treatment responsivity in individual patients, it should be emphasized that broadly equivalent efficacy across patient groups does not translate into equal efficacy in individual patients. Despite exciting recent developments in pharmacogenetics, it is still not currently possible to predict which antipsychotic may be optimal for a given patient. There is also no best agent or best dose for all patients, although dose ranges for optimal effectiveness do exist. Decisions about antipsychotic therapy, therefore often entail a trial and error process involving careful monitoring of response and adverse effects, an ongoing risk-benefit assessment, and judicious switching if necessary.

Because of the marked inter-individual variability in both efficacy and safety/tolerability, careful measurement of both the beneficial and adverse effects in every patient during the course of antipsychotic treatment is essential. In the DSM-5 (section 3), a simple and reliable 5-point 8-item scale is available to measure response of different symptom dimensions in schizophrenia (and other psychotic disorders). The use of this scale is strongly recommended. It is easy to use and can be administered in a few minutes. Similarly, EPS, metabolic disturbances, and other side-effects should be closely monitored and appropriately addressed.

In order to make informed treatment decisions, measurement of the severity of each of the six symptom domains in the course of treatment is necessary. Since antipsychotic agents are primarily effective in the treatment of positive symptoms and disorganization, persistence of these symptoms should prompt consideration of a different antipsychotic regimen including use of clozapine or a long-acting antipsychotic agent. If positive symptoms have improved but depressive symptoms persist, use of an antidepressant should be considered. If positive symptoms improve but negative symptoms worsen, the possibility of EPS should be effectively addressed. In this manner, measurement-based pharmacological treatment enables optimal individualization of treatment in persons with schizophrenia.

To achieve optimal therapy for schizophrenia, clinicians must balance efficacy benefits and side-effect costs of treatment in a way that is customized for the needs and vulnerabilities of the individual patient. The meticulous application of this approach can reduce the significant gap between what we know about best practices and the therapy that is actually provided for patients with schizophrenia.
Clinical Guidance

Schizophrenia is characterized by positive, negative, cognitive, disorganization, and mood symptoms. Antipsychotics are the mainstay of the pharmacological treatment of schizophrenia. Findings concerning efficacy for positive symptoms and disorganization suggest no consistent differences among available antipsychotics, with the exception of clozapine’s superior efficacy for treatment-resistant schizophrenia. Efficacy for negative, depressive, and cognitive symptoms appears to be determined by: 1) The extent to which reduction in positive symptoms brings about improvement in these other domains; and 2) The extent to which extrapyramidal side effects and anticholinergic effects (of the antipsychotic and of agents used to treat EPS) exacerbate them. Thus, the ability of antipsychotics to produce a potent antipsychotic effect without EPS and need for concomitant anticholinergic therapy yield multiple therapeutic benefits. In contrast to their broadly similar efficacy, antipsychotics differ markedly in their propensity to cause various adverse effects. Choice of antipsychotic medication should be based on individual preference, prior treatment response and side-effect experience, medical history and risk factors, and adherence history, with side-effect profile a major determinant of antipsychotic choice. Systematic measurement of efficacy and adverse effects is essential and can guide optimal individualization of antipsychotic treatment.

References

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

Conduct a comprehensive assessment and use measurement-based care as found in the Principles of Practice.

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.**

---

### Level 1  Initial Treatment:

- After stabilization or obtaining a sufficient evidence for efficacy and tolerability, offer any of the following LAIs. Base the selection on past efficacy and tolerability patterns to specific oral or LAI antipsychotics, 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

- If initial trial of LAI is unsuccessful, try monotherapy with another LAI from the above group

---

### 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)
- Clozapine + ECT

---

*Note: Balance efficacy, side-effects, individual vulnerabilities and preferences. Select medication with lower propensity for metabolic and extrapyramidal side-effects.
## Table 5. Recommended Medications for the Treatment of Schizophrenia: Long-Acting Injectable Antipsychotics

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose Interval</th>
<th>Dosage Strengths/Forms</th>
<th>Starting Dose</th>
<th>Maintenance Dose</th>
<th>Oral Supplementation</th>
<th>Time to Peak</th>
<th>Steady State</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-Generation Long-Acting Injectable Antipsychotics</strong>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluphenazine decanoate</td>
<td>Varies</td>
<td>25 and 100 mg/mL ampoules/vials/syringes</td>
<td>Varies, 12.5 mg</td>
<td>Varies, 12.5 to 100 mg</td>
<td>No</td>
<td>2 to 4 days</td>
<td>2 to 3 months</td>
</tr>
<tr>
<td>Haloperidol decanoate</td>
<td>4 weeks</td>
<td>50 and 100 mg/mL ampoules</td>
<td>Varies, 50 mg</td>
<td>Varies, 300 mg</td>
<td>No</td>
<td>6 to 7 days</td>
<td>2 to 3 months</td>
</tr>
<tr>
<td><strong>Second-Generation Long-Acting Injectable Antipsychotics</strong>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aripiprazole monohydrate (Abilify Maintena®)</td>
<td>Monthly</td>
<td>300, 400 mg vial kits and dual-chamber syringe</td>
<td>400 mg</td>
<td>400 mg (300 to 400 mg)</td>
<td>2 weeks</td>
<td>5 to 7 days</td>
<td>400 mg: 4 to 8 months 300 mg: 3 to 4 months</td>
</tr>
<tr>
<td>Aripiprazole lauroxil (Aristada®)</td>
<td>Monthly</td>
<td>441, 662, 882 mg prefilled syringes</td>
<td>Varies, 441 to 882 mg</td>
<td>Varies, 441 to 882 mg</td>
<td>3 weeks</td>
<td>4 days</td>
<td>4 to 6 months</td>
</tr>
<tr>
<td>Olanzapine pamoate‡ (Zyprexa Relprevv®)</td>
<td>2 or 4 weeks</td>
<td>210, 300, 405 mg vial kits</td>
<td>Varies, up to 300 mg every 2 weeks</td>
<td>Varies, up to 300 mg every 2 weeks</td>
<td>No</td>
<td>4 days</td>
<td>3 months</td>
</tr>
<tr>
<td>Paliperidone palmitate (Invega Sustenna®)</td>
<td>Monthly</td>
<td>38, 117, 156, 234 mg prefilled syringes</td>
<td>234 mg (day 1) + 156 mg (day 8)</td>
<td>117 mg (38 to 234 mg)</td>
<td>No</td>
<td>13 days</td>
<td>7 to 11 months</td>
</tr>
<tr>
<td>Paliperidone palmitate (Invega Trinza®)</td>
<td>Once every 3 months</td>
<td>273, 410, 546, 819 mg prefilled syringes</td>
<td>Depends on once-monthly dose</td>
<td>Varies, 273 to 819 mg</td>
<td>No</td>
<td>30 to 33 days</td>
<td>Continues steady state at equivalent dose</td>
</tr>
<tr>
<td>Medication</td>
<td>Dose Interval</td>
<td>Dosage Strengths/Forms</td>
<td>Starting Dose</td>
<td>Maintenance Dose</td>
<td>Oral Supplementation</td>
<td>Time to Peak</td>
<td>Steady State</td>
</tr>
<tr>
<td>----------------------------------</td>
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<td>-----------------------</td>
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<td>--------------</td>
</tr>
<tr>
<td>Risperidone Microspheres</td>
<td>2 weeks</td>
<td>25, 37.5, 50 mg vial kits</td>
<td>25 mg</td>
<td>25 mg (25 to 50 mg)</td>
<td>3 weeks</td>
<td>4 to 6 weeks</td>
<td>1.5 to 2 months</td>
</tr>
<tr>
<td>(Risperdal Consta®)</td>
<td></td>
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</tr>
</tbody>
</table>


Notes:
*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.

‡Olanzapine pamoate (Zyplarx 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.
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

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., 2017) 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.
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; Correll et al., 2016).

- 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
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.).

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).

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).
REFERENCES:


List of Abbreviations

AHCA: Florida Agency for Healthcare Administration
BD: Bipolar Disorders
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 Medication
MADRS: Montgomery-Asberg Depression Rating Scale
MAOI: Monoamine Oxidase Inhibitor
List of Abbreviations (continued)

MDD: Major Depressive Disorder
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
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
QIDS: Quick Inventory of Depression Symptomatology
RCT: Randomized Controlled Trial
rTMS: Repetitive Transcranial Magnetic Stimulation
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
μg/mL: micrograms per milliliter
VNS: Vagus Nerve Stimulation
YMRS: Young Mania Rating Scale
References

References for Bipolar Disorder:


**References for Major Depressive Disorder:**


References for Schizophrenia:

Adell A. Lu-Aa21004, a multimodal serotonergic agent, for the potential treatment of depression and anxiety. IDrugs. 2010;13(12):900-10


Kales HC and DeQuardo JR. Combined electroconvulsive therapy and clozapine in treatment-resistant schizophrenia. Prog Neuropsychopharm Biol Psychiatry. 1999;23: 547-56.


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