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# Psychotherapeutic Medication Guidelines for Adults



## INTRODUCTION

The *Florida Best Practice Psychotherapeutic Medication Guidelines for Adults* has been produced biennially since 2005 by the Florida Medicaid Drug Therapy Management Program and sponsored by the Florida Agency for Health Care Administration. The guidelines contain evidence-based recommendations for prescribing psychotherapeutic medication to treat severe mental illness – bipolar disorder, major depressive disorder, and schizophrenia. The overarching goal of the guidelines is to inform and support clinicians (specifically primary care clinicians, who provide the majority of mental health care in the state) in making treatment decisions that are safe and evidence-based, and that maximize benefit and minimize harm to patients.

The *2015 Florida Best Practice Psychotherapeutic Medication Guidelines for Adults* include two new sections:

- Major depressive disorder with mixed features
- Mood disorders in pregnancy

The section on treating major depressive disorder with mixed features was added to reflect changes between the *DSM-IV* and *DSM-5* that replaced “mixed episodes” with the mixed features specifier that can be applied to episodes of major depression, mania, and hypomania. In addition, a section on treating mood disorders in pregnancy was added to help clinicians who often face practice challenges in deciding how best to treat women with psychotherapeutic medications during pregnancy because the evidence to guide decision making is often contradictory and/or limited. As in years past, we sought to produce a document that is sensitive to the realities of clinical practice, and provides care recommendations relevant to both clinicians and patients. It is our intent to support treatment decisions made by clinicians that will be based on empirical evidence and also account for individual variation and patient needs in treating complex and challenging mental health conditions.

## 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, Florida psychiatrists in private practice and/or working at community mental health centers (CMHCs), academics, pharmacists, medical directors at managed care organizations, and OB/GYN physicians.

The 2015 Florida Expert Panel met in Tampa, Florida on September 25-26, 2015 to review and update the adult guidelines last published in 2013. For each disorder, a psychiatrist who is a nationally-recognized content expert reviewed the scientific literature on treatment and made suggestions to the panel on revising the guidelines based on the state of the scientific evidence. The panel then discussed the guidelines and proposed revisions, and reached a consensus about whether to revise and adopt a particular set of guideline recommendations. 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) and expert consensus on the strength of the evidence. The names of the meeting attendees and meeting presentations are available on the program website at [www.medicaidmentalhealth.org](http://www.medicaidmentalhealth.org). Financial disclosures are available upon request.

## ORGANIZATION

The guidelines are organized by mental health disorder and also include a section at the beginning of the booklet on general principles of practice. The treatment recommendations for each section are categorized by levels that are hierarchically based on the strength of the scientific evidence for efficacy and for 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 was recently published<sup>1</sup> and are adapted here to explain the basis 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 is 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, the use of the adult 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 choices should be based on clinical judgment, and the patient's individual symptoms, needs, and preferences.

## DISCLAIMER

The *2015 Florida Best Practice Psychotherapeutic Medication Guidelines for Adults* reflect the current state of knowledge at the time of publication on effective and appropriate care, as well as 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 needed. 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 the guidelines. The authors bear no responsibility for the use of these guidelines by third parties.

## COMPREHENSIVE ASSESSMENT

- Careful, differential diagnostic evaluation
- Risk for suicide and violence
- Co-occurring mental and medical disorders
- Substance abuse disorders, including tobacco use
- Potential bipolar disorder must be assessed in patients presenting with depression
- Serious mental health conditions are chronic in nature; therefore, a long-term management plan is essential
  - ◆ Use measurement-based care to measure symptoms, side effects, and adherence
  - ◆ Select maintenance medications that have a low relative risk of weight gain and metabolic syndrome
  - ◆ Monitoring of physical health parameters and medication side effects (See Program publication *A Summary for Monitoring Physical Health and Side-Effects of Psychiatric Medications in the Severely Mentally Ill Population* available at [www.medicaidmentalhealth.org](http://www.medicaidmentalhealth.org))
  - ◆ Integrate care of psychiatrists and primary care providers
  - ◆ Incorporate collaborative/shared treatment decision-making with patients and family/caregivers
  - ◆ Perform a psychosocial assessment
  - ◆ Assess social support system (housing, family, other caregivers)
  - ◆ Evaluate threats to continuity of care (access to medication, adherence, etc.)
  - ◆ Give patients tools/support for recovery and self-management

## ADJUNCTIVE PSYCHOSOCIAL TREATMENTS (AS INDICATED)

- Individual and family psychoeducation
- Cognitive-behavioral therapy (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 pharmacogenomic testing - Limited data exists examining whether patient care that integrates pharmacogenomic test information results in better or safer treatment.*

## MEASUREMENT-BASED CARE

Questionnaires and rating scales are useful tools for diagnostic assessment and evaluation of treatment outcomes, and such instruments can be helpful in providing supplemental information to clinical judgment. The integration of measurement scales into routine clinical practice is suggested for each of the conditions covered in this document. Clinicians should use rating scales to assess symptom severity during the initial evaluation/treatment, when medication changes are implemented, and/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 - [www.medicaidmentalhealth.org](http://www.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)

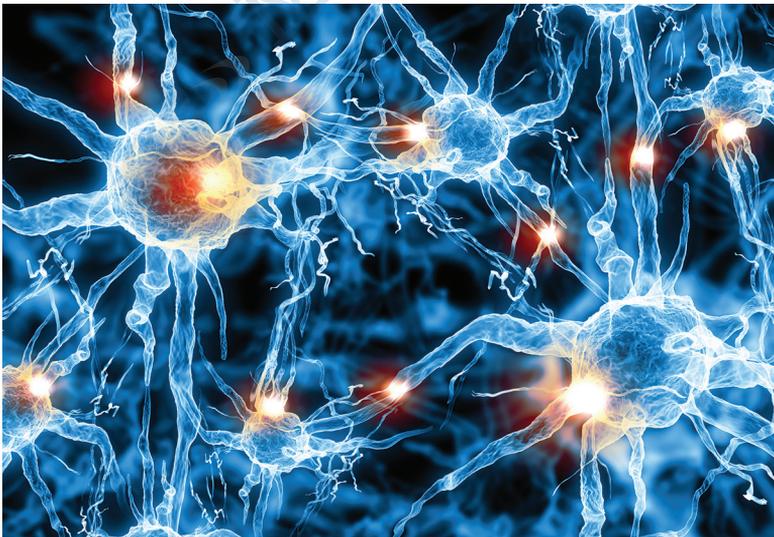
## Assessment Scales for Adult Disorders

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

## 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, and long-term treatment planning. Antipsychotics are heterogeneous or variable in efficacy:

- The risks are not insignificant.
- There is no difference in efficacy between first generation antipsychotics (FGAs) and second generation antipsychotics (SGAs).
- FGAs and 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



# Treatment of Acute Bipolar Disorder - Depression

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

The primary goals of bipolar disorder care are remission, maintenance of response, prevention of relapse, 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.

Consider psychiatric consultation, if possible, prior to psychotherapeutic treatment.

	<p><b>Level 1 Established efficacy:</b></p> <ul style="list-style-type: none"> <li>◆ Quetiapine* or lurasidone** monotherapy</li> <li>◆ Lurasidone adjunctive to lithium or divalproex (bipolar I disorder)</li> </ul> <p><i>*Only quetiapine has established efficacy for bipolar II disorder.</i>  <i>**Lurasidone has a better metabolic profile than quetiapine.</i></p>
➔	<p><b>Level 2A Established efficacy, but with safety concerns*:</b></p> <ul style="list-style-type: none"> <li>◆ Olanzapine + fluoxetine (bipolar I disorder)</li> </ul> <p><i>*Tolerability limitations include weight gain and metabolic concerns.</i></p>
	<p><b>Level 2B Better tolerability, but limited efficacy*:</b></p> <p><b>Consult specialist.</b></p> <ul style="list-style-type: none"> <li>◆ Lithium (bipolar I disorder)</li> <li>◆ Lithium adjunctive to lamotrigine (bipolar I disorder)</li> <li>◆ 2 drug combination of above medications</li> </ul> <p><i>*Efficacy limitations, relatively few positive randomized controlled trials; positive meta-analysis for lamotrigine in bipolar depression.<sup>3</sup></i></p>
➔	<p><b>Level 3 If Levels 1 and 2 are ineffective and/or not well tolerated*:</b></p> <ul style="list-style-type: none"> <li>◆ Electroconvulsive therapy (ECT)</li> </ul> <p><i>*Consideration is merited due to clinical need, despite even greater efficacy/tolerability limitations than Level 1 and 2 treatments.</i></p>
➔	<p><b>Level 4 If Levels 1 – 3 are ineffective and/or not well tolerated:</b></p> <ul style="list-style-type: none"> <li>◆ FDA approved agent for bipolar disorder + conventional antidepressant*</li> <li>◆ Pramipexole</li> <li>◆ Adjunctive – modafinil, thyroid, or stimulants</li> <li>◆ 3 drug combination</li> <li>◆ Transcranial magnetic stimulation (TMS)</li> </ul> <p><i>*There is inadequate information (including negative trials) to recommend adjunctive antidepressants, aripiprazole, ziprasidone, levetiracetam, armodafinil, or omega-3 fatty acids for bipolar depression.</i></p>

# Treatment of Acute Bipolar Disorder - Mania

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

The primary goals 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.

Consider psychiatric consultation, if possible, prior to psychotherapeutic treatment.

<p><b>Level 1A Established efficacy:</b></p> <p><i>Mild to moderate severity and/or not requiring hospitalization</i></p> <ul style="list-style-type: none"> <li>◆ Lithium monotherapy</li> <li>◆ Monotherapy with aripiprazole, asenapine, divalproex*, quetiapine, risperidone, or ziprasidone</li> </ul> <p><i>Severe and/or requiring hospitalization</i></p> <ul style="list-style-type: none"> <li>◆ Lithium or divalproex* + aripiprazole, asenapine, quetiapine, or risperidone</li> <li>◆ Electroconvulsive therapy (ECT) is recommended if medical emergency/patient welfare at risk and pharmacotherapy insufficient</li> </ul>	
<p><b>Level 1B Established efficacy, but with safety concerns**:</b></p> <p><i>Mild to moderate severity and/or not requiring hospitalization</i></p> <ul style="list-style-type: none"> <li>◆ Monotherapy with either haloperidol or olanzapine</li> </ul> <p><i>Severe and/or requiring hospitalization</i></p> <ul style="list-style-type: none"> <li>◆ Lithium or divalproex* + either haloperidol or olanzapine</li> </ul>	
	<p><b>Level 2 If Levels 1A and 1B are ineffective and/or not well tolerated:</b></p> <ul style="list-style-type: none"> <li>◆ Combination treatment with lithium + divalproex*</li> <li>◆ Combination with lithium and/or divalproex + second generation antipsychotic (SGA) other than clozapine</li> <li>◆ Paliperidone monotherapy</li> <li>◆ Carbamazepine monotherapy</li> </ul>
	<p><b>Level 3 If Levels 1 and 2 are ineffective and/or not well tolerated:</b></p> <ul style="list-style-type: none"> <li>◆ Electroconvulsive therapy (ECT)</li> <li>◆ Clozapine monotherapy</li> <li>◆ Clozapine + lithium or divalproex*</li> <li>◆ Lithium + carbamazepine</li> <li>◆ Divalproex* + carbamazepine</li> </ul>

## Treatment of Acute Bipolar Disorder - Mania (*continued*)

	<p><b>Level 4</b> If Levels 1 – 3 are ineffective and/or not well tolerated:</p> <ul style="list-style-type: none"><li>◆ A three-drug combination of Level 1, 2, and 3. Drugs may include first generation antipsychotic (FGA) or second generation antipsychotics (SGA) but <b>NOT</b> 2 antipsychotics. Example: lithium + (divalproex* or carbamazepine) + antipsychotic</li></ul>
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*\*Caution should be used when prescribing divalproex to women of reproductive age due to increased risk in pregnant women of neural tube defects and other major birth defects.*

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



# Bipolar I Disorder Continuation / Maintenance Therapy

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

	<p><b>Level 1 Established efficacy:</b></p> <ul style="list-style-type: none"> <li>◆ Periodic evaluation</li> <li>◆ Continue with effective and well-tolerated treatment</li> <li>◆ Lithium monotherapy</li> <li>◆ Quetiapine monotherapy</li> <li>◆ Aripiprazole or long-acting injectable risperidone monotherapy</li> <li>◆ Quetiapine (for recurrence prevention) or ziprasidone (for relapse prevention) adjunctive to (lithium or divalproex*)</li> <li>◆ Lamotrigine (evidence strongest for prevention of depression)</li> </ul>
	<p><b>Level 2A Established efficacy, but with safety concerns**:</b></p> <ul style="list-style-type: none"> <li>◆ Olanzapine monotherapy</li> <li>◆ Olanzapine adjunctive to lithium or divalproex*</li> </ul>
	<p><b>Level 2B If Level 1 is ineffective and/or not well tolerated:</b></p> <ul style="list-style-type: none"> <li>◆ Continue effective and well-tolerated acute treatment(s) if not listed in Level 1</li> <li>◆ Lithium and divalproex* combination</li> <li>◆ Lamotrigine monotherapy in patients without manic episode in past year</li> <li>◆ Follow acute mania/bipolar depression guidelines to achieve remission or partial remission</li> </ul>
	<p><b>Level 3 If Levels 1 and 2 are ineffective and/or not well tolerated:</b></p> <ul style="list-style-type: none"> <li>◆ Adjunctive clozapine (avoid combining with another antipsychotic)</li> <li>◆ Electroconvulsive therapy (ECT)</li> </ul>

\*Caution should be used when prescribing to women of reproductive age due to increased risk in pregnant women of neural tube defects and other major birth defects.

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

Note. Longer-term efficacy data is limited for the following: divalproex monotherapy, carbamazepine (drug interaction risk), antidepressants, electroconvulsive therapy (inconvenience/expense).

## Recommended Medications for the Treatment of Bipolar Disorder – Mood Stabilizers

Medication	Dosage	Comments
<b>Lithium</b>	<b>In acute mania:</b> 1200-2400 mg/day (serum level 0.8 – 1.2 mEq/L)	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 elderly, start with lower lithium dose, titrate more slowly, and require lower serum lithium levels.
<b>Divalproex</b>	<b>In acute mania:</b> 5-60 mg/kg/day; 1000-2500 mg/day (serum level 85 -125 µg/mL)	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) more evident above 100µg/ mL. More teratogenic than other mood stabilizers. Lower doses/levels may be necessary in non-manic compared to manic patients.
<b>Carbamazepine</b>	<b>In acute mania:</b> 200 – 1600 mg/day (serum level 6-12 µg/mL)	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*1502 (serious rash risk indicator). Decreases serum levels of multiple other drugs.
<b>Lamotrigine</b>	<b>In bipolar maintenance:</b> 100 – 400 mg/day	Initial titration to reduce risk of serious rash (Stevens-Johnson syndrome): 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.

## Recommended Medications for the Treatment of Bipolar Disorder – Second Generation Antipsychotics (SGA) and Antidepressants

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

# Pharmacological Treatment of Bipolar Disorder: 2015 Update Summary

## INTRODUCTION

Discrepancies between health outcomes achieved in the clinical ecosystem and those achieved in research settings is a disquieting and modifiable deficiency in the management of adults with bipolar disorders. The 2015 iteration of the *Florida Best Practice Psychotherapeutic Medication Guidelines for Adults* (6th update) is a critical component of decision support that attempts to narrow the foregoing gap in health outcomes by fostering precision and consistency, as well as the appropriate selection and sequencing of treatments throughout each stage of the illness. In the interest of consistency from the previous edition of the guidelines, we have retained the three algorithms for acute mania, acute bipolar depression, and bipolar continuation/maintenance with the recognition that for many individuals with bipolar disorder, the illness is highly relapse-prone, chronic in nature, and lifelong.

Since the publication of the adult guidelines fifth edition in 2013, there has been only one new U.S. Food and Drug Administration (FDA)-approved agent (i.e., cariprazine for acute bipolar mania) for any phase of bipolar disorder. Notwithstanding, there has been robust and accumulating evidence for greater attention given to clinical aspects of chronobiology, metabolic and physical health aspects, cognitive dysfunction, as well as premature mortality in this population.

## PRINCIPLES OF TREATMENT

Replicated scientific evidence indicates that the misdiagnosis of bipolar disorder occurs in a significant percentage of individuals. Thus, clinicians are encouraged to screen for bipolar disorders among adults utilizing healthcare services for affective and anxiety-related symptomatology at index visit and across repeated visits if therapeutic objectives are not achieved. Vigilance for bipolar disorder is warranted among individuals presenting in healthcare settings with depressive symptoms, as depressive episodes are often “polarity-first” as well as “polarity-predominant” in individuals with bipolar disorder. The timeliness of accurate diagnosis is underscored by convergent evidence in support of an integrated conceptual pathogenic framework indicating that bipolar disorder has both neurodevelopmental as well as neurodegenerative aspects.

In 2015, the American Heart Association consensus statement identified bipolar disorder (and major depressive disorder) as a Tier 2 risk factor for cardiovascular disease and accelerated atherosclerotic illness.<sup>4</sup> Population- and clinical-based data have consistently documented elevated rates of medical disorders (e.g. cardiometabolic) in adults with bipolar disorder. The integrated care of bipolar disorder warrants systematic and routine screening for traditional and emerging risk factors for cardiovascular disease. The foregoing recommendation is a derivative of the morbidity and mortality data directly attributable to medical disorders. As well, emerging evidence indicates that concurrent medical disorders affect the age at onset, presentation, severity of illness, and response to treatment; and therefore, are a reminder that general metabolic disorders may “metastasize” to

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

the brain. When medical disorders are present, contemporaneous management of both bipolar disorder and medical/psychiatric comorbidity is critical.

As per previous guideline iterations, all individuals with bipolar disorder must be carefully assessed for ideation/plans of harm to self and others with systematic assessment of risk for suicide. Pharmacotherapy in bipolar disorder is considered a standard of care across all phases of the illness. In addition, psychoeducation, and in some cases, manualized psychotherapy (e.g. cognitive behavioral therapy), careful attention to dietary choices, and physical activity levels, as well as sleep hygiene and chronorhythms is critical. The observation that functional outcomes in bipolar disorder are uncoupled from symptomatic outcomes has shifted attention towards other dimensions/domains of disturbance including, but not limited to, cognitive dysfunction. For multi-episode and late-stage bipolar disorder, functional remediation - which targets interpersonal and social competence, and general cognitive function - is warranted.

### PHARMACOLOGICAL TREATMENT OF ACUTE BIPOLAR DEPRESSION

Since the previous guideline publication, there have not been replicated, large randomized controlled trials and/or meta-analyses that would justify a significant alteration in the algorithmic sequence introduced in 2013. There remains a paucity of safe, well-tolerated, and effective agents for the acute phase of bipolar depression. The metabolic hazards of olanzapine justify its recommendation as a Level 2B treatment. Quetiapine, also susceptible to metabolic and weight gain hazards as well as sedation/somnolence, is the only psychotherapeutic agent with replicated evidence of efficacy in bipolar II depression. The rationale for relegating olanzapine + fluoxetine to Level 2B status (e.g., metabolic concerns) may also apply in some circumstances to quetiapine; a decision which should be made on an individual basis. Notwithstanding the introduction of the mixed features specifier, there remains an absence of controlled trial data that have evaluated therapeutic outcomes in adults with bipolar depression and mixed features specifier.

Replicated evidence indicates that armodafinil is insufficiently efficacious in adults with bipolar depression.<sup>5</sup> Results supporting the use of novel and investigational agents (e.g., ketamine, anti-inflammatory agents, and antioxidants) remains a focus of ongoing research and cannot be considered as proven effective and safe in bipolar depression. As per previous iterations, the steps of treatment modality suggested integrate both the likelihood of offering therapeutic benefit as well as safety and tolerability concerns. Data has recently emerged indicating that electroconvulsive therapy (ECT) is superior to pharmacotherapy in treatment-resistant bipolar depression.<sup>6</sup>

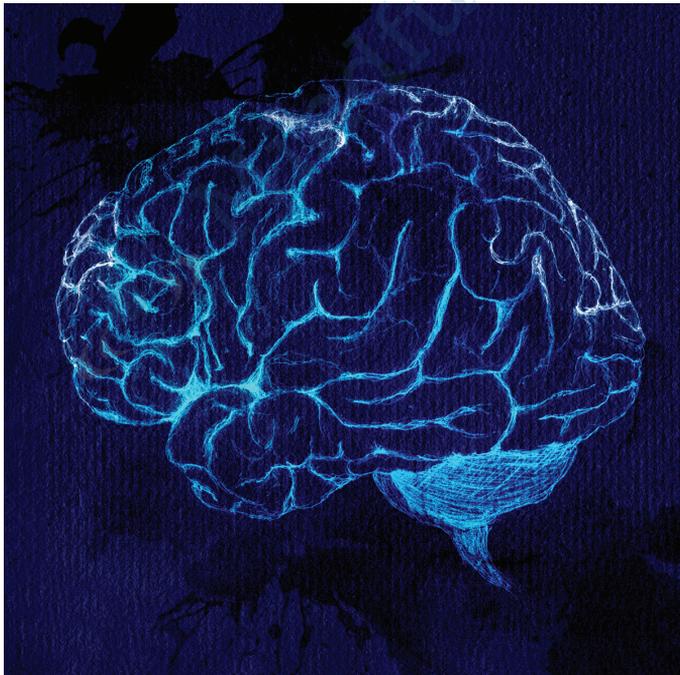
### PHARMACOLOGICAL TREATMENT OF ACUTE BIPOLAR MANIA

Mania comprises a medical emergency in adults with bipolar I disorder. The principles of safety, risk assessment, capacity determination, and timely diagnosis are critical. The scientific evidence is compelling that lithium and divalproex, as well as atypical agents offer therapeutic benefit in mania. So far, no studies have primarily enrolled individuals meeting criteria for mania with mixed features specifier. The increased risk for additive/multiplicative adverse events warrant recommendations for beginning treatment with monotherapy, recognizing that for some individuals receiving combination therapy (i.e., antipsychotic + mood stabilizer combination) may be superior.

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

### CONTINUATION & MAINTENANCE PHARMACOLOGICAL TREATMENT OF BIPOLAR DISORDER

Lithium continues to have a Level 1A recommendation in bipolar disorder as maintenance. A lack of consensus exists as to the role of continuation/maintenance adjunctive antidepressants, with a pragmatic position that they should be individualized and reserved for scenarios wherein they do not destabilize the longitudinal course and are temporally associated with symptom mitigation during therapy, as well as symptom return when discontinued. Illness progression, chronicity, and non-recovery warrant recommendations for integrated psychosocial approaches early in the illness trajectory. Careful attention to both psychiatric and medical comorbidity is paramount for assuring desired long-term health outcomes. The hazards posed by excess weight gain, directly and indirectly, on bipolar disorder pathology is a critical concern regarding treatment maintenance, as well as risk factor modification and attention given to aspects of healthy lifestyle. Where available, functional/cognitive remediation has the ability to improve outcomes for multi-episode, late-stage illness.<sup>7</sup>



# Treatment of Major Depressive Disorder

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

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

Assess for:

- Prior history of hypomania/mania
- Psychiatric and medical comorbidities (e.g. substance use disorders, anxiety disorders, obesity, diabetes)
- Presence of specifiers; notably psychosis, mixed features, suicidality
- Presence of cognitive dysfunction (e.g., memory complaints; difficulty with concentration, making decisions, and thinking clearly)

## **Level 1 Initial Treatment:**

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

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

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

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

## Treatment of Major Depressive Disorder (continued)

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

# Treatment of Major Depressive Disorder with Mixed Features

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

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

Assess for:

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

## Level 1 Initial Treatment:

- ◆ Minimal evidence for treating major depressive disorder (MDD) with mixed features specifier
- ◆ Discuss treatment options, including evidence-based psychotherapy [Cognitive-behavioral therapy (CBT), Interpersonal psychotherapy (IPT)]
- ◆ Consider second generation antipsychotic (SGA) or mood stabilizer (e.g. lithium)
- ◆ Antidepressant monotherapy 4-8 week trial at adequate dose and evaluate (antidepressant monotherapy in MDD with subsyndromal hypomania may be associated with a higher rate of suboptimal therapeutic outcomes when compared to MDD without subsyndromal hypomania):
  - ◇ Selective serotonin reuptake inhibitor (SSRI) (consider propensity for drug-drug interactions, differential risk for teratogenicity), serotonin-norepinephrine reuptake inhibitor (SNRI), or vortioxetine (if cognitive complaints)
  - ◇ Bupropion (if tolerability concerns) or mirtazapine (if insomnia a focus of clinical concern)
- ◆ For all Level 1 treatments, if partial response at 4 weeks, may continue for another 4 weeks or go to Level 2
- ◆ For all Level 1 treatments, if no response at 4 weeks, go to Level 2

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

- ◆ Reassess for hypomania/mania
- ◆ Dose optimization of medication used in Level 1
- ◆ Switch to different monotherapy SGA or mood stabilizer
- ◆ Antidepressant monotherapy from different or same class
- ◆ Combine existing antidepressant with different SGA
- ◆ Combine SGA or mood stabilizer with antidepressant

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

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

# Treatment of Major Depressive Disorder with Psychosis

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

Assess for:

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

<b>Level 1</b>	<b>Initial Treatment:</b> <ul style="list-style-type: none"><li>◆ Selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) + second generation antipsychotic (SGA)*</li><li>◆ Electroconvulsive therapy (ECT) (if patient welfare an immediate concern)</li><li>◆ Cognitive-behavioral therapy (CBT) and interpersonal psychotherapy (IPT) are not recommended as first-line modality</li></ul> <p><i>*Consider extrapyramidal symptoms (EPS) risk, weight gain, and metabolic concerns.</i></p>
	<b>Level 2</b> <b>If Level 1 is ineffective and/or not well tolerated:</b> <ul style="list-style-type: none"><li>◆ Alternative antidepressant + SGA combination</li><li>◆ ECT</li></ul>
	<b>Level 3</b> <b>If Levels 1 and 2 are ineffective and/or not well tolerated:</b> <ul style="list-style-type: none"><li>◆ Re-evaluate diagnosis</li><li>◆ Other antidepressant combinations with SGA</li><li>◆ Other antidepressant combinations with first generation antipsychotic (FGA)</li><li>◆ ECT (if not attempted earlier)</li></ul>

# Pharmacological Treatment of Major Depressive Disorder: 2015 Update Summary

## INTRODUCTION

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

## MIXED FEATURES

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

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

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

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

### NON-PSYCHOTIC MAJOR DEPRESSION

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

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

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

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

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

### PSYCHOTIC DEPRESSION

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

### TREATMENT-RESISTANT DEPRESSION

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

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

# Treatment of Schizophrenia

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

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

## Level 1 Initial Treatment:

- ◆ Monotherapy with an oral second generation antipsychotic (SGA) other than clozapine\*
- ◆ If initial trial of antipsychotic monotherapy unsuccessful, try monotherapy with another antipsychotic with low metabolic adverse effects
- ◆ If two failed trials of monotherapy, consider switching to a second generation long-acting injectable

*\*Balance efficacy, side-effects, individual vulnerabilities and preferences. Select metabolically benign medication and avoid extrapyramidal symptoms (EPS).*

## Level 2A If non-adherence to Level 1:

- ◆ Consider long-acting injectable

## Level 2B If Level 1 is ineffective:

- ◆ Consider clozapine

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

- ◆ Diagnostic review and/or consultation
- ◆ Clozapine if not tried earlier
- ◆ Antipsychotic + electroconvulsive therapy (ECT)
- ◆ Augmentation of clozapine with lamotrigine if partial or incomplete response to clozapine

*Note. There is suggestive evidence to support the use of high-potency agents.*

## Level 4 If Levels 1, 2, and 3 are ineffective and/or not well tolerated:

- ◆ Sequential augmentation of antipsychotic with N-acetyl cysteine and omega-3 fatty acid
- ◆ A trial of reserpine or other antipsychotic combination (not augmentation; if partial response with one agent)\*

*\*There is little evidence to support this approach for enhanced efficacy, but it may be useful for the treatment of side effects.*

## Recommended Medications for the Treatment of Schizophrenia

Medication	Chlorpromazine Equivalents <sup>a</sup>	Acute Therapy	Maintenance Therapy <sup>b</sup>
<b>Second Generation Antipsychotics (SGA)</b>			
Clozapine	N/A	150-600 mg/day	150-600 mg/day
Risperidone	N/A	2-8 mg/day	2-8 mg/day
Olanzapine	N/A	10-30 mg/day	10-20 mg/day
Quetiapine	N/A	300-800 mg/day	300-800 mg/day
Ziprasidone	N/A	120-240 mg/day	120-160 mg/day
Aripiprazole	N/A	10-30 mg/day	10-30 mg/day
Paliperidone	N/A	3-12 mg/day	6-12 mg/day
lloperidone	N/A	12 -24 mg/day	12-24 mg/day
Asenapine	N/A	10-20 mg/day	10-20 mg/day
Lurasidone	N/A	40-160 mg/day	40-160 mg/day
Brexipiprazole	N/A	2-4 mg/day	2-4 mg/day
Cariprazine	N/A	1.5-6 mg/day	3-6 mg/day
<b>SGA Long-Acting Injectable (LAI)</b>			
Aripiprazole Extended Release	N/A	400 mg q 4 weeks	300-400 mg q 4 weeks
Risperidone microspheres	N/A	-	25-50 mg q 2 weeks
Paliperidone palmitate	N/A	234 mg followed by 156 mg in 1 week	39-234 mg q 4 weeks
Olanzapine pamoate	N/A	-	150-300 mg q 2 weeks OR 300-405 mg q 4 weeks

## Recommended Medications for the Treatment of Schizophrenia (continued)

Medication	Chlorpromazine Equivalents <sup>a</sup>	Acute Therapy	Maintenance Therapy <sup>b</sup>
<b>First Generation Antipsychotics (FGA)</b>			
<b>Phenothiazines</b>			
Fluphenazine HCl	2	5-20 mg/day	5-15 mg/day
Trifluoperazine	5	15-50 mg/day	15-30 mg/day
Perphenazine	8	16-80 mg/day	16-64 mg/day
Chlorpromazine	100	300-1,000 mg/day	300-600 mg/day
<b>Butyrophenone</b>			
Haloperidol	2	5-20 mg/day	6-12 mg/day
<b>Others</b>			
Thiothixene	5	15-50 mg/day	15-30 mg/day
Molindone	10	30-100 mg/day	30-60 mg/day
Loxapine	10	30-100 mg/day	30-60 mg/day
<b>FGA Long-Acting Injectable (LAI)</b>			
Fluphenazine <sup>c</sup> decanoate	N/A	N/A	6.25-50 mg/2wks
Haloperidol decanoate <sup>d</sup>	NA	NA	50-200 mg/4wks

Note. Consider lower doses for 1st 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).

<sup>a</sup> Approximate dose equivalent to 100mg of chlorpromazine (relative potency); it may not be the same at lower vs. higher doses. Chlorpromazine equivalent doses are not relevant to the second generation antipsychotics and therefore are not provided for these agents.

<sup>b</sup> 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.

<sup>c</sup> Fluphenazine decanoate dosage recommendations are based on an empirical rule suggested by Kane (1996) (25 mg every 3 weeks of decanoate is equivalent to 665 chlorpromazine equivalents per day). These are theoretically determined values and should be interpreted as approximations only.<sup>12</sup>

<sup>d</sup> Haloperidol decanoate dosage recommendations are based on the following rule: 5 mg oral haloperidol (250 chlorpromazine equivalents) per day is equivalent to 50 mg haloperidol decanoate every month. Olanzapine has been found to cause more weight gain and related metabolic side effects than other SGAs.<sup>13</sup>

# Pharmacological Treatment of Schizophrenia: Antipsychotic Update and Guidance for Best Practice<sup>14-18</sup>

## 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 pharmacological treatment for schizophrenia. The 20 antipsychotics available in the United States have traditionally been classified into two major groups: 8 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 *2015 Florida Best Practice Psychotherapeutic Medication Guidelines for Adults*. Optimal individualized pharmacological treatment of schizophrenia requires an understanding of:

- The nature of schizophrenia (multiple psychopathological dimensions - positive, negative, cognitive, mood, motor, and disorganization; chronic, remitting and relapsing course);
- 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).

## 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 which 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

## Pharmacological Treatment of Schizophrenia: Antipsychotic Update and Guidance for Best Practice *(continued)*

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 a long-acting injectable formulation 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, gastro-intestinal, 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.

There is, however, no categorical distinction between FGAs and SGAs with regard to EPS and metabolic risks. The 20 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.

# Pharmacological Treatment of Schizophrenia: Antipsychotic Update and Guidance for Best Practice *(continued)*

## OPTIMIZING INDIVIDUAL OUTCOMES

Given the significant variability in drug pharmacokinetics and treatment responsiveness 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.

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 (EPSE) 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 yields 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.

# Treatment of Mood Disorders During Pregnancy

## THE PRIMARY GOALS OF TREATING MOOD DISORDERS DURING PREGNANCY

- Optimal functioning of the mother, aiming for remission of illness, with a goal of achieving or maintaining euthymia, and relapse prevention and associated risks of morbidity and mortality, including risk of suicide.
  - ◆ As women with mood disorders are generally at-risk for postpartum psychiatric illness, and illness during pregnancy predicts illness in the postpartum, treatment during pregnancy may alleviate postpartum relapse or worsening of course of illness.
- Managing risk of medication exposure to the infant.
- Individualized consideration of risk/benefit ratio for treatment options, realizing that untreated illness itself poses risks to the mother and baby. Partner with the Ob/Gyn in prenatal care, nutrition and support.

## PRINCIPLES OF PHARMACOTHERAPY DURING PREGNANCY

- Collaborative treatment decisions between the patient and her health care providers are essential, grounded on the evidence-base and guidelines that exist.
- Prioritize medications that have worked for the mother in the past.
- Minimize polypharmacy, if possible, as multiple exposures may increase risks to the fetus.
- Maximize non-pharmacologic therapies if effective, to augment pharmacotherapies. Psychotherapy is the most important effective non-medication treatment for mood disorders during pregnancy and the postpartum.
- If the patient has psychotic symptoms, antipsychotic medications are the most effective treatment and have no confirmed increase in birth defects.
- If suicide risk is significant, swift treatment is an especially high priority.

*Note. The U.S. Food and Drug Administration's (FDA) new labeling is detailed in the Pregnancy and Lactation Labeling Rule (PLLR) or "final rule" at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm>. The use of letter labeling (i.e., A, B, C, D, X) for pregnancy categories is being phased out by the FDA. This change is based on the major limitations of the letter category system. Until June 2015, when new drugs were improved by the FDA, the letter was determined based on available data at the time of approval, without a requirement for human pregnancy data. Thus, the letters were assigned primarily after review of available animal data. Also, the letters do not take into account the relative amount or quality of the body of data available for each medication, and do not take into account the risk of the untreated condition for the mother and fetus. Also, context has not historically been provided when risks are reported and any potential risks need to be compared to their occurrence in the general population, and ideally among women who suffer from the disorder for which the drug is utilized. Important in the risk/benefit discussions with patients, pregnancy itself is inherently risky, and obstetrical complications are common. The rate of birth defects in the U.S. approximately 3%.*

# Treatment of Major Depressive Disorder in Pregnancy

Refer to the treatment guidelines and dosage tables for major depressive disorder  
Begin with the lowest therapeutic dose.

<p><b>Level 1</b></p>	<p><b>Initial Treatment:</b></p> <ul style="list-style-type: none"> <li>◆ Mild to moderate depression may respond to non-pharmacological treatment alone, but severe depression should be treated with effective medication</li> <li>◆ Psychotherapy is the most evidence-based non-pharmacologic treatment for depression during pregnancy and the postpartum period</li> <li>◆ There are modest data for the use of light therapy, acupuncture, and massage, for mild depression in pregnancy. Light boxes carry the risk of triggering mania or hypomania if a patient has a bipolar disorder</li> <li>◆ Monotherapy with a selective serotonin reuptake inhibitor (SSRI) is preferred (with the exception of paroxetine, which may have an increased risk of cardiac and other malformations)*</li> <li>◆ Consider bupropion in smokers who are trying to quit/abstain during pregnancy</li> <li>◆ If only partial response to first agent, augmentation should be considered</li> </ul> <p><i>*If a woman has failed medication trials during the course of her illness, a medication that has been most helpful to her may be considered as a first-line option, even if it is not an SSRI. Data (or lack of data) should be discussed with the patient.</i></p>
<p></p>	<p><b>Level 2 If Level 1 is ineffective and/or not well tolerated:</b></p> <ul style="list-style-type: none"> <li>◆ Switch to a different SSRI</li> <li>◆ Consider monotherapy with a serotonin-norepinephrine reuptake inhibitor (SNRI) (good efficacy but less data on birth defects)</li> <li>◆ Consider augmenting with a second generation antipsychotic (SGA)</li> </ul>
<p></p>	<p><b>Level 3 If Levels 1 and 2 are ineffective and/or not well tolerated:</b></p> <ul style="list-style-type: none"> <li>◆ Consider electroconvulsive therapy (ECT): it has proven efficacy in severe depression and can be done with proper safeguards in pregnant women</li> </ul>
<p></p>	<p><b>Level 4 If Levels 1, 2 and 3 are ineffective and/or not well tolerated:</b></p> <ul style="list-style-type: none"> <li>◆ Augmentation strategies with agents other than SGAs (avoid known teratogens such as valproic acid at any time, and lithium during the first trimester)</li> <li>◆ Transcranial magnetic stimulation (TMS) is well-tolerated but has little evidence in this population</li> </ul>

*Note. Avoid benzodiazepines if possible, although the decision should be made on a case by case basis. There are inconsistent data suggesting that in the first trimester, there may be a small increased risk of oral clefts, and high doses in late pregnancy may be associated with a floppy infant syndrome at birth and withdrawal afterwards.*

*Herbal or “natural” supplements (for example, St. John’s Wort) should not necessarily be considered safe during pregnancy and warrant the same degree of study as pharmaceuticals in pregnancy. They are less regulated and there is a variable degree of quality assurance regarding manufacturing and purity, and efficacy does not require establishment before they are marketed.*

# Treatment of Bipolar Disorder in Pregnancy

Refer to the treatment guidelines and dosage tables for bipolar disorder

Begin with the lowest therapeutic dose. Treatment decisions regarding mood stabilizing medications during pregnancy are complex. For some agents, there is limited data on safety in pregnancy. Importantly, there is a lack of human pregnancy data for those agents that are currently in FDA category B. Also, some agents included in FDA categories C or D are often reasonable first-line treatment options, based on a woman's history of response, and characterization of known risks, which may be acceptable in consideration of severe past or present illness. Valproic acid remains the psychotherapeutic medication with the greatest risk of teratogenicity and long-term neurodevelopmental and cognitive deficits. It should be avoided during pregnancy.

## Level 1 Initial Treatment:

- ◆ Second generation antipsychotic (SGA) monotherapy
- ◆ Lamotrigine monotherapy\*
- ◆ Lithium monotherapy ONLY in known lithium responders (consider avoidance during the first trimester due to known association with Ebstein's anomaly)\*

*\*Both lithium and lamotrigine are metabolized during the second half of pregnancy at higher than non-pregnant rates, and declines in blood levels are typical. Many women will need to have doses increased in latter pregnancy.*

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

- ◆ Lithium monotherapy\*
- ◆ Two drug combination – SGA + SGA, or SGA + mood stabilizer\*\*

*\*Weigh benefits vs risks; has positive evidence of risk.*

*\*\*Although monotherapy is preferred in pregnancy, patient with bipolar are usually treated with more than one medication. Risks and benefits of polypharmacy should include consideration of what has helped stabilize the patient in the past, balanced with what is known about each medication's risks and benefits.*

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

- ◆ Consider electroconvulsive therapy (ECT) if symptom severity is warranted
- ◆ Carbamazepine\*
- ◆ First generation antipsychotic (FGA)

*\*Weigh benefits vs risks; has positive evidence of risk.*

*Note. Lithium is associated with a known risk of cardiac malformations in the first trimester, but the background rate is so low that even the increased risk means the overall rate is still low. Fetal echocardiogram is recommended when there has been lithium exposure in the first trimester.*

*Carbamazepine in the first trimester has been associated with fetal carbamazepine syndrome – dysmorphic features and major malformations.*

## Mood Disorders in the Postpartum Period

The new mother is at higher risk for mood episodes or psychosis in the immediate postpartum period, especially if her illness was untreated during pregnancy. Other risk factors include prior episodes, family history, and sleep loss. Close monitoring is advised. A history of bipolar disorder increases the risk of postpartum psychosis. If women stopped mood stabilizers for pregnancy, they should be reinitiated during the third trimester or immediately after delivery for prophylaxis of postpartum illness. Lithium is especially sensitive to the fluid shifts at delivery and should be monitored closely in the mother.

Interconception counseling regarding contraceptive options should occur during the course of pregnancy and at the first post-partum appointment and should include consideration of the use of a long acting reversible contraceptive (LARC) or another form of contraception to avoid an early unintended pregnancy post-partum.

### MEDICATIONS AND LACTATION

Breastfeeding is an important topic for women with mood disorders, as is sleep. Maternal mental health should be prioritized over breastfeeding. If a woman is exclusively breastfeeding, she is the only one that can feed the baby, and therefore her sleep will be greatly affected. Sleep deprivation is a major trigger for the relapse of mood episodes, particularly in bipolar disorder. It is strongly encouraged that women consider at least supplementing with bottles.

Most medications can cross into breast milk but their levels vary.

- Lithium is the medication most incompatible with breast feeding, due to relatively high levels found in neonates, and multiple adverse event reports.
- Carbamazepine has relatively higher levels in breast milk, with measurable levels in the infant.
- Clozapine also has relatively high levels in breast milk and may affect the infant's complete blood count (CBC)—since weekly blood draws are difficult in neonates, breastfeeding is not recommended in mothers on clozapine.

Formula feeding is an alternative that can allow the mother to use whichever medication works best for her.

Although some antidepressants are better studied in breastfeeding, or may have demonstrated lower levels in breast milk or infant blood levels, if a woman has responded especially well to an antidepressant in the past, it should be considered a reasonable option. Also, a woman should not switch from one antidepressant in pregnancy to another in the postpartum due to breastfeeding concerns. Staying on the same antidepressant limits the exposure that the baby has had to only one agent rather than two, and switching carries a risk of relapse.

*Note. There is little benefit for "pump and dump" which significantly increases the new mother's stress levels and time spent feeding, decreases compliance with treatment, reduces the infant's drug exposure only slightly, and is not supported by clinical studies.*

# Pharmacological Treatment of Mood Disorders During Pregnancy: 2015 Update Summary

## INTRODUCTION

Treatment decisions during pregnancy should be as collaborative as possible between health care providers and patients, and take into account the individualized risks and benefits of treatment options. In addition to the reproductive safety of psychopharmacologic treatments, the past course of illness and treatment responses should be strongly considered. Specifically, the potential risks of medications must be assessed along with the risks of untreated psychiatric disorders across pregnancy and the postpartum. In assessing the risks and benefits, it is important to keep in mind that the baseline rate of congenital malformations (birth defects) is approximately 3% of all pregnancies in the U.S.<sup>19</sup> In most cases, causes are unknown. Decision making around treatments for psychiatric disorders in pregnancy requires consideration of what is known about the medications in pregnancy, the course and severity of the woman's disorder being treated, and exposures to the baby of both untreated maternal illness and medication. Psychiatric mood and anxiety symptom burden during pregnancy is a major risk factor for serious postpartum illness.

Unplanned pregnancies are common, and the reproductive safety of treatments should be kept in consideration when treating women of reproductive potential. General recommendations for healthy pregnancies should be included in the treatment plan, as some elements are particularly relevant for individuals with mood disorders. These include getting regular exercise, abstaining from tobacco, alcohol, and illicit substances, and maintaining a healthy diet and weight.<sup>20</sup>

## MAJOR DEPRESSIVE DISORDER (MDD)

Women are not protected from new onset or recurrence of mood disorders during pregnancy. The risk of relapse appears to be highest when effective maintenance medications are discontinued. Women with histories of postpartum depression and recurrent MDD are at elevated risk for postpartum depression, and women with bipolar disorder are at risk in the postpartum for mood episodes.<sup>21-22</sup> Women with bipolar disorder are also an at-risk group for postpartum psychosis.<sup>23</sup>

Consistent with guidelines from the American Psychiatric Association and the American College of Obstetricians and Gynecologists, psychotherapy is considered a first-line treatment in mild depression.<sup>24</sup> It is also an important part of the treatment plan for women with more severe illness, and the most evidence based non-pharmacologic treatment for depression in pregnancy. A modest amount of evidence supports other non-medication interventions, including acupuncture, massage therapy, and light therapy (which may trigger mania in individuals with bipolar disorder).

The U.S. Food and Drug Administration (FDA) has recently revised labeling for pregnancy and lactation.<sup>25</sup> The letter categories are being discontinued (new drugs will no longer have that categorization and older drugs will have the letter phased out of their labels). This reflects the major limitations of these labels, in which systematic human data are often not available. For example, medications without human data have received Category B labeling, while older drugs with

## Pharmacological Treatment of Mood Disorders During Pregnancy: 2015 Update Summary *(continued)*

substantial data regarding pregnancy use typically have had a C or D category label. It is essential for a provider to know the specific safety and efficacy data for a particular medication, rather than use the letter categories for medication selection.

Antidepressants are considered first-line for moderate to severe MDD.<sup>24</sup> Selective serotonin reuptake inhibitors (SSRIs) have received a substantial amount of study in pregnancy regarding safety outcomes. Most studies do not show any increased risk of birth defects with SSRIs, although some studies have shown rare and inconsistent reports of malformations.<sup>26-27</sup> Data have been more inconsistent with paroxetine than other antidepressants, with some studies showing an increased risk of cardiovascular malformations. However, this risk has been seen inconsistently.

The most consistent risk seen in studies of SSRIs in pregnancy is poor neonatal adaptation or “withdrawal”, which is reported to affect 20-30% of babies whose mothers used antidepressants in latter pregnancy.<sup>24,28</sup> Symptoms commonly include jitteriness and fussiness, and other medical symptoms and/or more careful observation after delivery. Generally, these symptoms are mild and transient. While medication labels suggest women should consider stopping antidepressants in the third trimester due to this risk, medication discontinuation in women at-risk for serious postpartum illness may carry grave consequences for women and their newborns.

While SSRI antidepressants are best known in pregnancy, and limited information is available regarding SNRIs, the individuality of treatment responses is paramount. If a woman has had multiple past medication trials, then a woman who has had a good previous response to a lesser known antidepressant in pregnancy may be best treated with that agent to avoid multiple medication trials during pregnancy and to provide optimal benefits. Also, bupropion may be considered in women who are having difficulty with smoking cessation and/or are at risk for relapse of smoking. Antidepressant monotherapy is preferred when possible, although augmentation may be considered with partial treatment responses. Electroconvulsive therapy (ECT) may be considered with severe and/or refractory illness.

Antidepressants are generally considered reasonable for use during breastfeeding when clinically warranted, and SSRIs in particular are one of the best studied classes of medications during breastfeeding.<sup>29</sup> If a new antidepressant is needed, sertraline is often preferred, due to the amount of study in the breastfeeding context and demonstrated low levels of exposure as quantified in breast milk and infant blood levels.<sup>30</sup> If a woman has responded best to a different antidepressant, it should be strongly considered for her treatment in the postpartum.

### **BIPOLAR DISORDER**

Studies have consistently demonstrated that the risk of relapse for bipolar disorder mood episodes in women is at least as common during pregnancy as in the non-pregnant state, and that discontinuation of medications increases the risk of relapse during pregnancy.<sup>22</sup> The majority of women who stop taking mood stabilizers during pregnancy do experience relapse. Discontinuation of a mood stabilizer, especially abruptly during pregnancy, carries a high risk for mood episodes.<sup>22</sup> Risk of relapse is especially high in the postpartum, and if women have stopped medication for pregnancy, it is attenuated by prophylactic mood stabilizer treatment starting in late

## Pharmacological Treatment of Mood Disorders During Pregnancy: 2015 Update Summary *(continued)*

pregnancy or immediately postpartum. Regardless of patient choice of treatment, close monitoring is warranted during pregnancy and the postpartum.

The anticonvulsant valproic acid carries a much higher risk of teratogenesis compared with most medications commonly used in psychiatry, with rates of neural tube defects ranging from 1 to 12%.<sup>31</sup> Longer-term neurocognitive deficits with valproate have also been observed after in utero exposure. Because very early pregnancy exposure can contribute to neural tube defects, it is highly recommended to avoid use in women of reproductive age (as many pregnancies are unplanned). Carbamazepine may also increase the risk of neural tube defects, although the risk appears lower than with valproic acid.<sup>32</sup>

The risk of teratogenicity with lithium appears much lower than was once historically thought.<sup>33</sup> While lithium is associated with a rare cardiovascular defect, Ebstein's anomaly, the absolute risk is low, reported as 0.05 - 0.1% risk with first trimester exposure. This is much lower than the risk of neural tube defects observed with valproate. Lithium clearance is increased during pregnancy, and for some women, dose increases may be required later in pregnancy to maintain therapeutic benefits.

Most studies do not show an increased risk of malformations after first trimester exposure to lamotrigine. While there has been a small and inconsistently reported risk of oral clefts with lamotrigine in the first trimester, the largest and newest reports from pregnancy registries did not find any association between oral clefts and lamotrigine.<sup>31</sup> A recent prospective study of children who were exposed to anticonvulsants in utero did not find any neurocognitive problems among those exposed to lamotrigine, with those exposed to lamotrigine having testing scores similar to the general population at ages 3 and 6 years old.<sup>34</sup> There are pharmacokinetic changes of lamotrigine metabolism during pregnancy – lamotrigine is cleared more rapidly during pregnancy, and some women will require higher doses in later pregnancy to maintain therapeutic benefits.

Regarding atypical antipsychotics as a class, there have been several prospective studies to inform safety during pregnancy.<sup>35-36</sup> Prospective studies have generally not shown an increased risk of major congenital malformations among babies whose mothers took atypicals during pregnancy, compared to controls. In one study, there were no differences in outcome between mothers who took atypicals compared to mothers who took older "typical" antipsychotics, although there was a small increased risk of cardiovascular malformations compared to healthy controls. At this time, we have limited data for each individual antipsychotic medication, with those that are newest having the least amount of information about use during pregnancy.

For women with bipolar disorder, breastfeeding is a complex issue. Mood stabilizers such as lithium are associated with adverse events in nursed infants, and atypical antipsychotics are not well studied in breastfeeding.<sup>37</sup> Lamotrigine has been studied, and demonstrated to yield higher blood levels in infants than are seen with SSRIs, but publications generally do not show clinical adverse effects in babies when breastfed while mothers were treated with lamotrigine.<sup>38</sup> Although valproic acid has received some study in breastfeeding women, it is strongly discouraged to start a woman of reproductive potential on valproic acid.

## Pharmacological Treatment of Mood Disorders During Pregnancy: 2015 Update Summary *(continued)*

Sleep deprivation is destabilizing for those with bipolar disorder and may trigger a relapse during this vulnerable time. Thus for women with bipolar disorder, it is desirable that somebody else assist with the nighttime feedings in order to protect the mother's sleep and to promote euthymia. For mothers who choose to breastfeed while using medications with incomplete safety profiles during lactation, the baby should be monitored closely for signs of toxicity.

### POSTPARTUM PSYCHOSIS

The rate of postpartum psychosis is relatively rare, occurring in about 1 out of 1,000 births. However, the risk is much higher in women who have histories of bipolar disorder or a previous history of postpartum psychosis.<sup>39</sup> Previous psychiatric hospitalization is associated with an increased risk of postpartum psychosis. Postpartum psychosis must be considered an acute emergent condition. The mother and her baby are at risk of harm, as well as others in the family. Postpartum psychosis can include many symptoms of psychosis, including delusions, hallucinations, and paranoia. Women with postpartum psychosis are often agitated, and have many symptoms consistent with mania, such as decreased sleep, irritability, increased activity, and thought disorder.

Strategies for prevention and early intervention include psychoeducation of patient and family about postpartum psychosis. If mood stabilizers or antipsychotics were discontinued for pregnancy, they should be restarted immediately after delivery or during the third trimester. Because postpartum psychosis can occur very early in the postpartum, re-initiation of mood stabilizing medication may be too late after delivery, although there have not been adequate studies to advise exact timing of re-initiation.





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