## Treatment of Acute Bipolar Disorder - Depression

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

- 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.

Conduct comprehensive assessment and use measurement-based care as found in the Principles of Practice (review pages 4-7).

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

<table>
<thead>
<tr>
<th>Level 1A - Established efficacy*</th>
<th>Level 1B - Established efficacy, but with safety concerns*</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Quetiapine monotherapy <em>(bipolar disorder I &amp; II)</em></td>
<td>- Olanzapine + fluoxetine <em>(bipolar disorder I)</em></td>
</tr>
<tr>
<td>- Lurasidone monotherapy <em>(bipolar disorder I)</em></td>
<td><em>Note. Tolerability limitations include sedation and weight gain.</em></td>
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<tr>
<td>- Lurasidone or quetiapine adjunctive to lithium or divalproex <em>(bipolar disorder I)</em></td>
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<table>
<thead>
<tr>
<th>Level 2 - Established tolerability, but limited efficacy*</th>
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<tbody>
<tr>
<td>Consult specialist</td>
</tr>
<tr>
<td>- Lithium <em>(bipolar disorder I)</em></td>
</tr>
<tr>
<td>- Lamotrigine adjunctive to lithium <em>(bipolar disorder I)</em></td>
</tr>
<tr>
<td>- Lamotrigine <em>(bipolar disorder I)</em></td>
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<tr>
<td>- 2 drug combination of above medications</td>
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<tr>
<td><em>Note. Efficacy limitations include negative randomized controlled trials but positive meta-analyses.</em></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Level 3 - If levels 1 and 2 are ineffective or treatment not tolerated*</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Electroconvulsive therapy (ECT)</td>
</tr>
<tr>
<td><em>Note. Consideration merited due to clinical need, despite even greater efficacy/tolerability limitations than level 1 and 2 treatments.</em></td>
</tr>
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<thead>
<tr>
<th>Level 4 - If levels 1 - 3 are ineffective or treatment not tolerated</th>
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</thead>
<tbody>
<tr>
<td>- Transcranial Magnetic Stimulation (TMS)</td>
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<tr>
<td>- Antimanic therapy + (FDA approved medication for major depression)*</td>
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<tr>
<td>- Pramipexole</td>
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<tr>
<td>- Adjunctive – modafinil, thyroid, or stimulants</td>
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<tr>
<td>- 3 drug combination</td>
</tr>
<tr>
<td><em>Note. There is inadequate information (including negative trials) to recommend adjunctive antidepressants, aripiprazole, ziprasidone, levetiracetam, armodafinil, or omega-3 fatty acids for bipolar depression.</em></td>
</tr>
</tbody>
</table>
The primary goals of bipolar disorder care are remission, maintenance of response, and prevention of relapse.

- 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.

Conduct comprehensive assessment and use measurement-based care as found in the Principles of Practice (review pages 4-7).

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

**Level 1A - Established efficacy**

*Mild to moderate severity or not requiring hospitalization*
- Lithium monotherapy
- Monotherapy with aripiprazole, asenapine, divalproex, quetiapine, risperidone, or ziprasidone

*Severe or requiring hospitalization*
- Lithium or divalproex plus aripiprazole, asenapine, quetiapine, or risperidone

**Level 1B - Establish efficacy, but with safety concerns***

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

*Severe or requiring hospitalization*
- Lithium or divalproex plus haloperidol or olanzapine

*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.

**Level 2 - If level 1A and 1B are ineffective or not tolerated**

- Two-drug combination of lithium + divalproex
- Lithium or divalproex plus second generation antipsychotic (non-clozapine)
- Paliperidone
- Carbamazepine

**Level 3 - If levels 1 and 2 are ineffective or not tolerated**

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

**Level 4 - If levels 1, 2, and 3 are ineffective or not tolerated**

- A three-drug combination of level 1, 2, and 3. Drugs may include first generation antipsychotic (FSA) or second generation antipsychotics (SGA) BUT NOT 2 antipsychotics. Example: lithium + (divalproex or carbamazepine) + antipsychotic.
# Bipolar I Disorder Continuation/Maintenance Therapy

## Level 1A - Established efficacy
- Lithium monotherapy
- Quetiapine monotherapy
- Aripiprazole or long-acting injectable risperidone monotherapy
- Quetiapine or ziprasidone adjunctive to lithium or divalproex
- Lamotrigine (evidence strongest for prevention of depression, usually as an adjunct)

## Level 1B - Established efficacy, but safety concerns*
- Olanzapine monotherapy
- Olanzapine adjunctive to lithium or divalproex

*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.

## Level 2 - If level 1A and 1B are ineffective or not tolerated
- Continue effective and well-tolerated acute treatment(s) if not listed in level 1A or 1B
- Lithium and divalproex combination
- Lamotrigine monotherapy in patients without manic episode in past year
- Follow acute mania/bipolar depression guidelines to achieve remission or partial remission

## Level 3 - If level 1 and 2 are ineffective or not tolerated
- Adjunctive clozapine (not added to antipsychotics)

Note. Longer-term efficacy data limited for the following: divalproex monotherapy, carbamazepine (drug interaction risk), antidepressants, electroconvulsive therapy (inconvenience/expense).
<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>Lithium</td>
<td>In acute mania: 1200-2400 mg/day (serum level 0.8 – 1.2 mEq/L)</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 elderly, start with lower lithium dose, titrate more slowly, and require lower serum lithium levels.</td>
</tr>
<tr>
<td>Divalproex</td>
<td>In acute mania: 5-60 mg/kg/day; 1000-2500 mg/day (serum level 85 -125 µg/mL)</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) 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>
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<tr>
<td>Carbamazepine</td>
<td>In acute mania: 200 – 1600 mg/day (serum level 6-12 µg/mL)</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 Asians for HLA-B*1502 (serious rash risk indicator). Decreases serum levels of multiple other drugs.</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>In bipolar maintenance: 100 – 400 mg/day</td>
<td>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.</td>
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### Second Generation Antipsychotics & Antidepressants – Recommendations for Bipolar Disorder

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| **Second Generation Antipsychotics (SGA)** | In acute mania:  
• Aripiprazole: 15-30 mg/day  
• Asenapine: 10-20 mg/day  
• Olanzapine: 6-20 mg/day  
• Quetiapine: 400-800 mg/day  
• Risperidone: 2-6 mg/day  
• Ziprasidone: 80-160 mg/day  | Initial titration may be necessary for tolerability. Lower doses may be necessary in depressed patients (e.g. quetiapine 300 mg/day). Ziprasidone should be taken with food. Asenapine is sublingual. Monitor for side effects, including sedation (especially with quetiapine and clozapine), weight gain (especially with olanzapine and clozapine), akathisia (especially with aripiprazole and ziprasidone), and EPS (especially with risperidone). Monitor weight and BMI at each visit and laboratory metabolic indices at baseline, 3 months, and yearly thereafter. |
|                                  | In acute bipolar depression:  
• Quetiapine: 200-600 mg  
• Olanzapine/Fluoxetine:  
3 mg/12.5 mg – 12 mg/50 mg  
• Lurasidone: 40-120 mg  
• Clozapine: 50-400 mg/day  
(if treatment resistant)    |                                                                                                                                               |
| **Antidepressants**              | In acute bipolar depression:  
As dosed for major depression. (No specific dosing recommendations can be given in bipolar depression.) | 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. SNRIs and TCAs may have greater manic switch risk. Increased suicidality risk in pediatric and young adult patients. May be continued in patients who are on them and have stable mood. |

SNRI = Serotonin-norepinephrine reuptake inhibitor  
TCA = Tricyclic antidepressant
Pharmacological Treatment of Bipolar Disorder: 2013 Update Summary

Rajiv Tandon, MD
Professor of Psychiatry
University of Florida College of Medicine

INTRODUCTION

The Florida Medicaid Drug Therapy Management Program guidelines for the treatment of bipolar disorder were first published in 2005 and have since been updated on a biennial basis. This fifth update, like the previous iterations, was based on a comprehensive review of the literature and its critical evaluation by a panel of academic and community clinicians. As in previous editions, three related but separate guidelines were developed for the pharmacological treatment of acute bipolar depression, acute bipolar mania/hypomania, and continuation/maintenance treatment of bipolar disorder, respectively. Beginning with recommendations for elements of a good diagnostic assessment, treatment options were categorized at different levels based on the strength of the evidence and clinical considerations of comparative efficacy and safety.

COMPREHENSIVE ASSESSMENT AND PRINCIPLES OF TREATMENT

With the introduction of the DSM-5 in 2013, revisions in the diagnostic assessment became necessary in order to be consistent with changes made in the DSM-5 treatment of bipolar disorder. The category of major mood disorders was split into two chapters and bipolar disorder was explicitly separated from the depressive disorders. In the definition of mania/hypomania, increased emphasis was placed on the symptom of increased energy and activity, and both increased energy/activity along with heightened mood are necessary for a diagnosis of mania or hypomania. Particular care in the distinction of bipolar depression from unipolar depression is important for appropriate treatment planning and the use of the Mood Disorders Questionnaire (MDQ) was recommended for this purpose. The DSM-IV category of bipolar disorder-mixed was eliminated because of the rarity of its utilization in clinical practice and was replaced by the use of a “mixed features” specifier for both mania and depression if symptoms of depression were present in the context of mania or symptoms of mania/hypomania were present in the context of major depression, respectively. The presence of mixed features has important implications for proper treatment selection.

Since bipolar disorder is often co-morbid with addictive disorders, including smoking, these must be addressed at initial assessment and over the course of treatment. Increased mortality and morbidity due to medical illness must be addressed in this population, and therefore these need to be carefully assessed at initial presentation and on an ongoing basis. Since patients with bipolar disorder are at an increased risk for suicide and violent behavior, these need to be specifically monitored at initial presentation and during the course of treatment. Good pharmacological treatment needs to be combined with appropriate psychosocial care. Since treatment response varies across patients, careful assessment of symptomatology and side-effects is essential in the course of treatment. The use of appropriate rating scales is highly recommended.

PHARMACOLOGICAL TREATMENT OF ACUTE BIPOLAR DEPRESSION

For acute bipolar depression, one important change was the addition of lurasidone as a therapeutic agent at Level 1. Lurasidone was found to be effective and safe in the treatment of bipolar depression in two large-scale clinical trials and was consequently approved by the Food and
Pharmacological Treatment of Bipolar Disorder: 2013 Update Summary (continued)

Drug Administration (FDA) for the treatment of acute bipolar depression, both as monotherapy and as an adjunct to lithium or divalproex. It joins quetiapine as the Level 1a recommendation for bipolar I disorder, with quetiapine also recommended for bipolar II disorder. Despite its approval by the FDA for treatment of bipolar depression, the combination of [olanzapine + fluoxetine] remained as a Level 1b recommendation because of the metabolic safety concerns associated with the use of olanzapine. In the absence of an adequate response to level 1 treatment, it is recommended that a psychiatrist consultation be obtained. Level 2, level 3, and level 4 treatment recommendations were provided on the basis of declining evidence of efficacy and/or increasing risk of safety concerns or poor tolerability.

Pharmacological Treatment of Acute Bipolar Mania

For the pharmacotherapy of acute mania, updated treatment recommendations are provided, although the changes are relatively minor. Lithium is significantly underutilized in the treatment of acute mania in clinical practice and its prominent position as a level 1a recommendation, as monotherapy or in combination with certain antipsychotics, is re-emphasized. There are important distinctions between different antipsychotic agents with regards to their utility in the treatment of mania and this is explicitly reflected in the new treatment guidelines. For example, the use of olanzapine or haloperidol, in spite of their proven efficacy, is now relegated to a Level 1b recommendation because of metabolic and EPS safety concerns, respectively. Level 2, level 3, and level 4 treatment recommendations are provided on the basis of declining evidence of efficacy and/or increasing risk of safety concerns or poor tolerability.

Continuation and Maintenance Pharmacological Treatment of Bipolar Disorder

Several changes are apparent in the guidelines for maintenance treatment of bipolar disorder. Lithium remains a strong level 1a recommendation but divalproex is no longer recommended at this level since there are trials that have found it to be a less effective monotherapy maintenance treatment. Monotherapy with quetiapine, aripiprazole, long-acting injectable risperidone, and lamotrigine are recommended at level 1a, with distinctions made between the first three and lamotrigine with regards to utility in the prevention of manic episodes and depressive episodes, respectively. Despite its proven efficacy, olanzapine has been relegated to Level 1b because of metabolic safety concerns. Level 2 and level 3 treatment recommendations are provided on the basis of declining evidence of efficacy and/or increasing risk of safety concerns or poor tolerability.

References

