Is Two Better than One? Treatment of Bipolar I Acute Depressive Episodes

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Objectives
• Provide an overview of bipolar disorder
• Discuss current guideline recommendations for management of acute depressive episodes of bipolar I disorder
• Evaluate the role of combination therapy in acute bipolar I depression
• Analyze existing evidence to provide a clinical recommendation regarding combination therapy

Assessment Question #1
Which of the following represents the most common symptomatic state of bipolar disorder?

A. Mania/hypomania
B. Depression
C. Mixed episodes

Bipolar Disorder

Known as a “manic-depressive” illness
Characterized by changes in mood, energy, and activity level impacting daily functioning

Symptomology

<table>
<thead>
<tr>
<th>Mania/Hypomania</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated or irritable mood</td>
<td></td>
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<tr>
<td>Inflated self-esteem or grandiosity</td>
<td></td>
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<tr>
<td>Increased goal-directed activity or psychomotor agitation</td>
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<tr>
<td>Decreased need for sleep</td>
<td></td>
</tr>
<tr>
<td>Engaging in risky behaviors</td>
<td></td>
</tr>
<tr>
<td>Increased or pressured speech</td>
<td></td>
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<tr>
<td>Racing thoughts</td>
<td></td>
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<tr>
<td>Distraction</td>
<td></td>
</tr>
<tr>
<td>Depressed mood OR loss of interest</td>
<td></td>
</tr>
<tr>
<td>Weight changes/increased appetite</td>
<td></td>
</tr>
<tr>
<td>Sleep disturbances</td>
<td></td>
</tr>
<tr>
<td>Psychomotor agitation/retardation</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
</tr>
<tr>
<td>Guilt/worthlessness</td>
<td></td>
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<tr>
<td>Executive dysfunction</td>
<td></td>
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<tr>
<td>Suicidal ideation</td>
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</tbody>
</table>
Subtypes

Bipolar I Disorder
- Manic episodes lasting ≥7 days or severe symptoms requiring hospitalization

Bipolar II Disorder
- Pattern of hypomanic and major depressive episodes

Cyclothymic Disorder
- Symptoms lasting ≥2 years but not meeting diagnosis for hypomanic or major depressive episodes

Other Specified and Unspecified Bipolar and Related Disorders
- Bipolar symptoms that do not meet criteria described above

Epidemiology

Mean age of symptom onset
- 18 years in bipolar I disorder
- 22 years old in bipolar II disorder

Prevalence
- Similar between males and females in bipolar I disorder
- Higher in females with bipolar II disorder

Risk factors
- Genetic
- Environmental

Clinical Course

- Early signs include irritability, aggressiveness, hyperactivity, and mood swings
- Evaluation typically occurs secondary to symptoms of depression
- Symptoms suggestive of bipolar disorder rather than unipolar depression
  - Symptoms of depression occurring before age 25
  - Atypical depressive features
  - Racing thoughts preventing sleep
  - Lack of response to 3 or more antidepressant trials
  - Intolerance to steroids, antidepressants, or other medications

Suicidality in Bipolar Disorder

- 8 in 10 people with bipolar disorder contemplate suicide at least once
- 25-50% will attempt suicide at least once
- 4-15% of patients die by suicide
- >70% of suicides and suicide attempts in patients with bipolar disorder occur during the depressive phase
- Self-poisoning is the most common method

Management of Acute Depressive Episodes in Bipolar I Disorder

Treatment of Depressive Episodes

- Recommendations vary by guideline
- Mixed evidence regarding antidepressant use
- First-line pharmacotherapy options include:
  - Mood stabilizers
    - Lithium
    - Lamotrigine
    - Valproic acid (in combination with lurasidone)
  - Atypical antipsychotics
    - Lurasidone
    - Olanzapine-Fluoxetine
    - Quetiapine
Antidepressant Controversy

International Society for Bipolar Disorder (ISBD) released the following recommendations regarding antidepressant use in bipolar disorder:

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Acute Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Should be avoided in bipolar I disorder</td>
<td>• Should be avoided when there is a history of antidepressant-induced mania/hypomania, current or predominant mixed features, or recent rapid cycling</td>
</tr>
<tr>
<td>• Should be avoided in bipolar I and II depression when two or more concomitant core symptoms of mania are present</td>
<td>• May be used adjunctively with a mood stabilizer when there is a history of previous positive response</td>
</tr>
</tbody>
</table>

Lithium (Eskalith®, Lithobid®)

Use: Off-label for bipolar I acute depression

Dosing: Initially 300mg two to three times daily

Contraindications (CI):
- Significant cardiovascular disease, diuretic use, dehydration, debilitation, renal disease, sodium depletion

Adverse effects (AE):
- Nausea, diarrhea, dizziness, ataxia, tremor, weight gain, polypnea/polydipsia, acne, alopecia

Additional information:
- Avoid use with thiazides, angiotensin-converting enzyme inhibitors (ACEis), angiotensin II receptor blocker (ARBs), nonsteroidal anti-inflammatory drugs (NSAIDs)

Lithium Pearls

- Effective at treating and preventing depressive episodes
- Often used as adjunctive therapy with atypical antipsychotics or lamotrigine
- Black box warning (BBW) for toxicity at doses close to therapeutic levels
- Shown to reduce risk of suicidality

Lamotrigine (Lamictal®)

Use: Off-label for bipolar I acute depression

Dosing: Initiated using slow titration (see slide titled Appendix A)

CI:
- Hypersensitivity

AE:
- Nausea, dizziness, blurred vision, ataxia, headache, tremor, sedation, and rash

Additional information:
- Glucuronidation inhibitors (valproate) and inducers (carbamazepine, phenytoin, phenobarbital, primidone, rifampin, lopinavir/ritonavir)

Lamotrigine Pearls

- Effective at treating and preventing depressive episodes
- Used in combination with other agents due to slow titration to therapeutic dose
- BBW for potentially life-threatening rashes including Stevens-Johnson syndrome and toxic epidermal necrolysis
- Risk of increased suicidality and worsening depression in patients with bipolar disorder

Valproate (Depakote®)

Use: Off-label adjunctive therapy in bipolar I acute depression

Dosing:
- Loading dose 20mg/kg daily
- Maintenance dose 10-15mg/kg daily

CI:
- Hepatic disease or significant hepatic dysfunction, urea cycle or mitochondrial disorders, prophylaxis of migraine headaches in women of childbearing age, hypersensitivity

AE:
- Nausea, vomiting, abdominal pain, dizziness, blurred vision, headache, sedation, tremor, weight gain

Additional information:
- Conversion from immediate-release to extended-release requires 8-20% increase
Valproate Pearls

- More effective at treating manic and preventing depressive episodes
- Established therapeutic drug levels used to monitor response and adherence
- BBW for hepatotoxicity, fetal risk, and pancreatitis
- Dose reduction of lamotrigine required when used in combination

Assessment Question #2

Lamotrigine may be titrated more quickly in hospitalized patients.

A. True
B. False

Atypical Antipsychotics

- FDA-Approval Timeline
- Olanzapine-fluoxetine
- Quetiapine
- Lurasidone
- Cariprazine

Olanzapine-Fluoxetine (Symbyax®)

- Use: FDA-approved for bipolar depression
- Dosing: 6/25mg to 12/50mg daily in the evening
- CI: Concomitant use of monoamine oxidase inhibitors, pimozide, or thioridazine
- AE: Dry mouth, constipation, increased appetite, metabolic effects, orthostatic hypotension, blurred vision, fatique
- Additional information: Clearance increased by cigarette and marijuana smoke

Quetiapine (Seroquel®)

- Use: FDA-approved for bipolar depression
- Dosing: Initial 50mg at bedtime titrated to 300mg at bedtime
- CI: Hypersensitivity
- AE: Nausea, increased appetite, weight gain, dyspepsia, dry mouth, constipation, sedation, orthostatic hypotension
- Additional information: May cause false-positives for methadone and TCA

Lurasidone (Latuda®)

- Use: FDA-approved for bipolar depression (monotherapy or in combination with lithium or valproate)
- Dosing: 20-120mg daily with at least 350 calories
- CI: Strong CYP3A4 inhibitors and inducers
- Known hypersensitivity
- AE: Nausea, akathisia, dose-dependent sedation, and increased risk of metabolic effects
- Additional information: Initiated at therapeutic dose
- No warning for QT prolongation
- Low risk of significant metabolic effects
- May cause transient elevations in prolactin
Cariprazine (Vraylar®)

**Use**
FDA-approved for bipolar I depression

**Dosing**
1.5mg daily
May increase to 3mg daily on day 15

**CI**
Hypersensitivity

**AE**
Nausea, akathisia, dizziness, sedation

**Additional Information**
Partial dopamine D3 receptor agonist
Use with CYP3A4 inducers and inhibitors not recommended

Atypical Antipsychotics

Most are FDA-approved for bipolar I depression but may be used in bipolar II depression

Beneficial in patients with mixed or psychotic features

Recently approved cariprazine currently recommended as second-line therapy for bipolar I depression

Assessment Question #3

How many medications currently have FDA approval for treatment of depressive episodes in bipolar I disorder?

A. 2
B. 3
C. 4
D. 5
E. 6

Literature Review

Montgomery-Åsberg Depression Rating Scale (MADRS)
- 10-item assessment with scores totaling up to 60

Clinical Global Impressions-Bipolar Version (CGI-BP)
- 3-item assessment with scores totaling up to 7

Young Mania Rating Scale (YMRS)
- 11-item assessment with scores totaling up to 60

Quick Inventory of Depressive Symptomatology-self report version (QIDS-SR16)
- 16-item assessment with scores totaling up to 27

Efficacy and Safety of Lamotrigine as Add-On Treatment to Lithium in Bipolar Depression a Multicenter, Double-Blind, Placebo-Controlled Trial

Lamotrigine vs. Placebo

Objective
Evaluate the efficacy of lamotrigine as adjunctive therapy to lithium for bipolar depression

Design
- 8-week, double-blind, placebo-controlled
- Stratified randomization
- Multicenter

Assignment
- Lithium + placebo (N=60)
- Lithium + lamotrigine (N=64)

Eligibility

Inclusion Criteria
- Age ≥ 18 years
- Diagnosed with bipolar I or II disorder experiencing a major depressive episode
- MADRS score ≥ 18
- CGI-BP ≥ 4
- Receiving stable lithium dose ≥ 14 days with plasma level 0.6-1.2mmol/L

Exclusion Criteria
- Psychotic features
- Severe rapid cycling
- MADRS score ≥ 5 on item 10
- History of alcohol or substance use within 1 month or dependence within 12 months
- Severe personality disorder
- Antipsychotic or antidepressant use within 2 weeks

Study Endpoints

Primary Efficacy Endpoint
- Change from baseline in MADRS score

Secondary Efficacy Endpoint
- Response
- Switch into mania or hypomania

Post Hoc
- Significant differences between MADRS items
- Response and no switch to mania or hypomania

Methods

Lamotrigine titration
- Weeks 1-2: 25mg/day
- Weeks 3-4: 50mg/day
- Weeks 5-6: 100mg/day
- Weeks 7-8: 200mg/day

Mood stabilizers
- Lithium adjusted to maintain level of 0.6-1.0mEq/L

Concomitant medications
- Benzodiazepines were allowed at max of 2mg of lorazepam equivalents per day

Monitoring
- Lithium levels obtained at baseline and 8 weeks
- Symptoms assessed at 2, 4, 6, and 8 weeks

Results

Baseline characteristics
- Average age 46 years and 46% male
- 67% had a diagnosis of bipolar I disorder
- >80% of patients were receiving lithium for greater than 3 months with no significant difference in plasma levels
- Average MADRS score 28.5, CGI-BP 4.55
- 52 participants (81%) in the lamotrigine group and 50 participants (83%) in the placebo group completed the study
- No significant differences in occurrence of adverse events (including skin rash) between treatment groups
Results

Significant Measures Lamotrigine (SE) Placebo (SE) P-Value
MADRS change from baseline (primary measure) 15.38 (1.32) 11.03 (1.36) 0.024
MADRS at week 6 15.41 (1.30) 19.50 (1.34) 0.031
MADRS at week 8 12.87 (1.23) 17.79 (1.36) 0.006

Significant Measures Lamotrigine (%) Placebo (%) P-Value
MADRS reduction of ≥50% 33 (51.6) 19 (31.7) 0.030

Combined response without mood switch observed in 39 participants (60.9%) with lamotrigine and 28 (46.7%) with placebo (p=0.149)

Author’s Conclusions

Addition of lamotrigine to lithium therapy may have produced additive or enhanced effects resulting in clinically significant differences

Critical Appraisal

Strengths
• Randomized, controlled design
• Routine monitoring of lithium levels
• Followed appropriate lamotrigine titration

Weaknesses
• Changes to protocol after initial recruitment
• Short study duration
• Allowance of benzodiazepine use
• Lack of generalizability

Lurasidone as Adjunctive Therapy With Lithium or Valproate for the Treatment of Bipolar I Depression: A Randomized, Double-Blind, Placebo-Controlled Study


Lurasidone vs. Placebo

Objective
Evaluate the efficacy of lurasidone in combination with lithium or valproate for treatment of bipolar I depression

Design
• 6-week, double-blind, placebo-controlled
• Stratified randomization
• Multicenter, intention-to-treat analysis

Assignment
• Lithium/valproate + placebo (N=165)
• Lithium/valproate + lurasidone (N=183)
Eligibility

Inclusion Criteria
- Age 18-75 years
- Diagnosed with bipolar I disorder experiencing a major depressive episode without psychotic features
- History of a manic or mixed manic episode
- MADRS score ≥ 20
- YMRS ≤ 12
- Inadequate response after ≥ 28 days of lithium or valproate

Exclusion Criteria
- Decrease of ≥ 25% in MADRS between screening and baseline
- MADRS score ≥ 4 on item 10
- Hospitalized for manic or mixed manic episode within 60 days of
- Antidepressants use within 3 days
- Inadequate response to ≥ 3 antidepressants during current episode
- Alcohol or substance abuse within 3 months

Study Endpoints

Primary Efficacy Endpoint
- Change in MADRS score from baseline to week 6

Secondary Efficacy Endpoint
- Change in CGI-BP

Methods

Lurasidone titration
- Days 1-3: 20mg/day
- Days 4-6: 40mg/day
- Day 7: 60mg/day

Mood stabilization
- Valproate adjusted to maintain level of 50-125mg/mL
- Lithium adjusted to maintain level of 0.6-1.2mEq/L

Concomitant medications
- Anticholinergic medications permitted
- Benzodiazepines permitted during screening and weeks 1-3

Results

Baseline characteristics
- Average age 42 years, 52% male, 61.7% Caucasian
- Average MADRS score 30.7, CGI-BP 4.5
- 50.3% of patients in lurasidone arm were receiving lithium vs 45.6% in placebo arm
- 78.1% in the lurasidone group and 82.4% in the placebo group completed the study
- AE more frequently reported with lurasidone include nausea, somnolence, tremor, akathisia, and insomnia

Significant Measures

<table>
<thead>
<tr>
<th>Significant Measures</th>
<th>Lurasidone</th>
<th>Placebo</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MADRS change from baseline</td>
<td>-17.1</td>
<td>-13.5</td>
<td>0.005</td>
</tr>
<tr>
<td>CGI-BP change from baseline</td>
<td>-1.96</td>
<td>-1.51</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Significant Measures
Improvement in MADRS items including apparent sadness, reported sadness, reduced sleep, lassitude, inability to feel, and pessimistic thoughts observed with lurasidone
**Author’s Conclusions**

First large-scale randomized, controlled trial to demonstrate efficacy of antipsychotic in combination with mood stabilizer for acute treatment of bipolar depression

Adjunctive therapy with stable doses of lithium/valproate significantly improved depressive symptoms and anxiety

Minimal effects on weight gain, lipids, and glycemic control

Generalizability to bipolar II depression is unclear

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**Critical Appraisal**

**Strengths**
- Randomized, controlled design
- Relatively large sample size
- Multinational population

**Weaknesses**
- Short study duration
- Excluded patients with alcohol or substance abuse
- Benodiazepine use allowed during study initiation

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**Comparative Evaluation of Quetiapine Plus Lamotrigine Combination Versus Quetiapine Monotherapy in Bipolar Depression (CEQUEL): a 2 × 2 Factorial Randomised Trial**


**Lamotrigine vs. Placebo**

**Objective**
Evaluate the efficacy of lamotrigine as adjunctive therapy to quetiapine in patients with bipolar depression

**Design**
- Double-blind, placebo-controlled, parallel group
- Multicenter, modified intention-to-treat

**Assignment**
- Quetiapine + placebo ± folic acid (N=101)
- Quetiapine + lamotrigine ± folic acid (N=101)

**Eligibility**

**Inclusion Criteria**
- Age ≥ 16 years
- Diagnosed with bipolar I or II disorder
- Required new pharmacological therapy for an acute depressive episode
- Able to tolerate quetiapine dose ≥ 150mg/day

**Exclusion Criteria**
- Currently experiencing a manic or mixed episode
Study Endpoints

**Primary Efficacy Endpoint**
- QIDS-SR16 score at 12 weeks

**Secondary Efficacy Endpoint**
- Improvement in depressive symptoms at 52 weeks
- Proportion of participants in remission at 12 and 52 weeks
- Time to new intervention for depressive and manic symptoms

Methods

7-14 days run-in period with quetiapine
Assigned to lamotrigine or placebo
Separately randomized to folic acid or placebo

Methods

**Quetiapine titration**
- Days 1-2: 50mg/day
- Days 3-4: 100mg/day
- Day 5-6: 200mg/day
- Day 7+: 300mg/day

**Lamotrigine titration**
- Weeks 1-2: 25mg/day
- Weeks 3-4: 50mg/day
- Weeks 5-6: 100mg/day
- Weeks 7-8: 200mg/day

**Concomitant medications**
- Encouraged mood medications be discontinued prior to run-in phase

Monitoring
- Weeks 12, 22, and 52

Results

- Baseline characteristics
  - 74% diagnosed with bipolar I disorder, 46% male,
  - Average QIDS-SR16 score 15
  - 29% in lamotrigine group using antidepressants at randomization vs 40% in placebo group
  - 65% receiving quetiapine 300mg/day or greater
  - 19 patients unable to complete the run-in phase with quetiapine
  - 49% of participants had data available at 52 weeks

Significant Measures Lamotrigine (95% CI) P-Value

- Difference in QIDS-SR16 score (52 weeks) -2.69 [-4.89 to -0.49] 0.017

**Lamotrigine + Placebo**
- Remission at 12 weeks 26 (31) 13 (16) 0.026
- Remission at 52 weeks 20 (36) 6 (13) 0.012

**Lamotrigine + Lamotrigine**
- Difference in QIDS-SR16 score (95% CI) P-Value
- Lamotrigine + placebo -4.14 [-6.90 to -1.37] 0.004
- Lamotrigine + folic acid 0.02 (-2.58 to 2.82) 0.931
Author’s Conclusions

Addition of lamotrigine to quetiapine improved outcomes

Lamotrigine reduced risk of relapse in patients with bipolar I disorder who have predominantly depressive episodes

Folic acid may reduce effectiveness of lamotrigine and should be avoided in patients receiving lamotrigine therapy

Critical Appraisal

Strengths
- Randomized, controlled design
- Run-in period to assess adherence
- Limited exclusion criteria
- Duration of study

Weaknesses
- Protocol updates made during the trial
- Allowance of additional psychotropic medications (no breakdown provided)
- High drop-out rate by the 52-week assessment

Overall Conclusions

- Bipolar disorder is a common and disabling mental illness
- Although patients typically spend more time in the depressive than manic phase, there are limited evidence-based treatment options for management of acute bipolar depression
- Combination therapy may be considered in those with an incomplete response or symptom breakthrough while receiving optimized monotherapy
- Adjunctive therapy should be used cautiously due to increased risk of suicide by overdose

Appendix A

<table>
<thead>
<tr>
<th>Lamotrigine Titr</th>
<th>General</th>
<th>Administration w/ Glucuronidation Inhibitor</th>
<th>Administration w/ Glucuronidation Inducer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks 1-2</td>
<td>25mg daily</td>
<td>25mg every other day</td>
<td>50mg daily</td>
</tr>
<tr>
<td>Weeks 3-4</td>
<td>50mg daily</td>
<td>25mg daily</td>
<td>100mg daily*</td>
</tr>
<tr>
<td>Weeks 5</td>
<td>100mg daily</td>
<td>50mg daily</td>
<td>200mg daily*</td>
</tr>
<tr>
<td>Week 6</td>
<td>200mg daily</td>
<td>100mg daily</td>
<td>300mg daily*</td>
</tr>
<tr>
<td>Maintenance</td>
<td>200mg daily</td>
<td>100mg daily</td>
<td>400mg daily*</td>
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References

References