Advances in Diagnosis, Neurobiology, and Treatment of Mood Disorders

June 13 - 14, 2016
Field House Coral Gables
University of Miami
Coral Gables, FL
Optimal Treatment of Bipolar Disorder

Mark A. Frye MD
Professor & Chair, Department of Psychiatry & Psychology
Director, Mayo Clinic Depression Center
Rochester, MN
Mark A. Frye M.D.

Disclosures

- **Grant Support:** Janssen Research & Development, Mayo Foundation, Myriad, National Institute of Alcohol Abuse and Alcoholism (NIAAA), National Institute of Mental Health (NIMH), Pfizer

- **Consultant:** (Mayo) Janssen Research & Development, Mitsubishi Tanabe Pharma Corporation, Myriad Genetics, Sunovion, Supernus Pharmaceuticals, Teva Pharmaceuticals, Neuralstem Inc

- **Mayo Clinic:** Mayo Clinic has a financial interest in AssureRX and the technology referenced in this publication/presentation
Learning Objectives

- Review the diagnosis and clinical management of mania in bipolar disorder.
- Differentiate bipolar depression from unipolar depression.
- Integrate the evidence-based, best-practice options for the pharmacological and non-pharmacological management of patients with bipolar disorder.
How confident are you in using the latest evidence in treating patients with bipolar disorders?

A. Extremely confident
B. Confident
C. Somewhat confident
D. Not confident at all
In the treatment of bipolar depression, which is the most commonly prescribed medication?

A. Antidepressants
B. Divalproex
C. Atypical antipsychotics
D. Stimulants
Optimal Treatment

- Diagnosis & Epidemiology of Bipolar Disorder
- Mania
- Depression
- Maintenance
- Conclusion
## Epidemiology of Bipolar Disorder

<table>
<thead>
<tr>
<th>Bipolar Disorder</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bipolar I (M / D)</td>
<td>1% of US population</td>
</tr>
<tr>
<td>Bipolar II (m / D)</td>
<td>1-2% of US population</td>
</tr>
<tr>
<td>Sex</td>
<td>Equal distribution</td>
</tr>
<tr>
<td>Onset (average)</td>
<td></td>
</tr>
<tr>
<td>First impairment (age 15-19)</td>
<td></td>
</tr>
<tr>
<td>First treatment (age 20-24)</td>
<td></td>
</tr>
<tr>
<td>First hospitalization (age 25)</td>
<td></td>
</tr>
<tr>
<td>Recurrence</td>
<td>Average 2.7-9 years</td>
</tr>
<tr>
<td>Suicide</td>
<td>~35% attempt, ~9% succeed</td>
</tr>
<tr>
<td>Predominant phase of illness</td>
<td>Depression</td>
</tr>
</tbody>
</table>


M = mania
M = hypomania
D = depression
Bipolar Diagnosis Across the Age Spectrum

Young and Bipolar

*Time* 2002, August 19.
Disruptive Mood Dysregulation Disorder (DMDD)

Inside the Volatile World of the Young and Bipolar

Why are so many kids being diagnosed with the disorder once known as manic depression?
FDA Indications: Acute Mania

- Aripiprazole, Asenapine, Olanzapine, Risperidone Quetiapine, Ziprasidone, Cariprazine (dopamine D2/D3 receptor partial agonist), Chlorpromazine all FDA approved for mania
- Carbamazepine ER and Divalproex Sodium all FDA approved for mania
- Lithium FDA approved for mania
- Inhaled loxapine is approved for acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults
Mania Matters: Episodes Associated With Neuroanatomic Change?

NAA-/Cr = N-acetylaspartate / creatine

Jail / Prison Have Replaced State Hospitals

[Bar chart showing the comparison between state hospital patients and mentally ill prisoners from 1969 to 1994.]

Mania Discharge and Subsequent Arrest
Los Angeles Community Hospitals

Mania and the Law in California: Understanding the Criminalization of the Mentally Ill

“History seems to be repeating itself. There are again a substantial number of mentally ill individuals behind bars.”

Mania is an EMERGENCY

- Need rapid, safe stabilization
  - Reduction of behavioral agitation
  - Sleep restoration
  - Management of withdrawal from drugs & alcohol

- Antimanic treatment based on
  - Manic episode (euphoric or mixed specifier)
  - Rapid cycling
  - Psychotic symptoms
  - Medication history
  - Medical comorbidities
  - Patient expectations or shared decision making
Acute Management of Agitated Patient

- Agitation mild to moderate, cooperative, non-psychotic
  - Oral lorazepam* 1-2 mg, repeat 1-2 mg Q 30-60 min until calm (or max dose 10-15 mg)

- Agitation mild to moderate, cooperative, (+) evidence of psychosis*
  - Oral olanzapine (SOT or ODO) 5-10 mg
  - Oral risperidone* 0.5-2.0 mg
  - Oral quetiapine* 25-100 mg
  - Oral haloperidol 1-5 mg (anticholinergic is antipsychotic-naïve or EPS sensitive)

* Not FDA approved for agitation; SOD = standard olanzapine-coated tablet; ODO = orally disintegrating olanzapine
* Use lorazepam if suspected catatonia, NMS, or significant EPS.

Acute Management of Agitated Patient

- Agitation moderate to severe, uncooperative, with or without psychosis
  - Haloperidol 5-10 mg IM + lorazepam 1-2 mg IM (anticholinergic if neuroleptic naïve or EPS sensitive)
  - Ziprasidone 10-20 mg IM (repeat Q 2-4 hours as needed until calm, or max dose 40 mg/24 hours)
  - Olanzapine 10 mg IM (repeat after 2 hours until calm, or max dose 30 mg/day)
  - Aripiprazole 9.75 mg IM (repeat after 2 hours until calm, or max dose 30 mg/day)

## Short-acting Injectable Antipsychotic Drugs: Comparative Safety and Efficacy in Treating Agitation

Pooled analysis of 9 RCT, effect sizes reported as NNT (vs. PLC) for positive response to treatment; no direct head-to-head comparisons

<table>
<thead>
<tr>
<th>Medication</th>
<th>Number needed to treat (NNT) vs. PLC</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ziprasidone IM, 10-20 mg</td>
<td>3</td>
<td>2 to 4</td>
</tr>
<tr>
<td>Olanzapine IM, 10 mg</td>
<td>3</td>
<td>2 to 3</td>
</tr>
<tr>
<td>Aripiprazole IM, 9.75 mg</td>
<td>5</td>
<td>4 to 8</td>
</tr>
</tbody>
</table>

Orally Inhaled Loxapine Powder

- **Dosing**: 10 mg single inhaled dose (1/24 hrs)
- **Pooled analysis** of two Phase III randomized trials (one study in patients with schizophrenia, one study in patients with BP-I)

- **NNT (vs. PLC) for positive response**:
  - Loxapine 5 mg, NNT 4
  - Loxapine 10 mg, NNT 3

- **NNT (vs. PLC) for requiring only one dose of study drug without rescue medication**:
  - Loxapine 5 mg, NNT – n.s.
  - Loxapine 10 mg, NNT 7


Approved by the FDA 2012
Double-Blind Comparison of Clonazepam* vs Lorazepam* in Acute Mania

Double-blind comparison of clonazepam and lorazepam monotherapy (14 days) in 24 patients with acute mania

- **Lorazepam** N=13 (Mean dose 12 ± 4.1 mg)
- **Clonazepam** N=11 (Mean dose 11.3 ± 4.1 mg)

- **7-day Response**
  - CGI Improvement 1 or 2: 46% (p < 0.10)
  - CGI Improvement 1 or 2: 9% (p < 0.10)

- **14-day Remission**
  - CGI Improvement 1 or 2: 61% (p < 0.05)
  - CGI Improvement 1 or 2: 18%

- **Remission**
  - CGI Improvement 1 or 2: 39%
  - CGI Improvement 1 or 2: 0%

## FDA Approved Bipolar Disorder Treatments*

<table>
<thead>
<tr>
<th>Agent</th>
<th>Manic</th>
<th>Mixed</th>
<th>Depression</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Asenapine</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Olanzapine/Fluoxetine</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Quetiapine/XR</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Risperidone (Oral / IM)</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+ (IM)</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Carbamazepine ER</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Divalproex DR/ER</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Lithium</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
</tbody>
</table>

---

*Asenapine, Olanzapine, Quetiapine, Risperidone indication as monotherapy and adjunct to Li or DVPX and with / without psychosis.
Comparative Efficacy and Acceptability of Antimanic Drugs in Acute Mania: A Multiple-Treatments Meta-Analysis

- Data are from a systematic review of 68 randomized trials of pharmacotherapy for acute mania in adults (16,073 patients)
- Any-cause early discontinuation is proxy for “acceptability”
- Multiple treatments meta-analysis (accounts for direct and indirect comparisons)

Cariprazine for Acute Mania Associated With Bipolar I Disorder

- Randomized, DB, PLC-controlled trial (2010-2011); cariprazine 3-6 mg/d vs. cariprazine 6-12 mg/d vs. PLC over 3 weeks; 497 patients with BP-I manic or mixed episodes; primary endpoint – change YMRS total score; secondary endpoints – response, remission

Lithium in Acute Mania

- Gold standard – benchmark
- Lithium non-response differs from other mood stabilizers
- Clinical predictors account for <50% of variance, suggesting genetic factors
- Prophylactic response familial
- Numerous side effects, narrow therapeutic index
- Believed to reduce suicide rates via unknown mechanism


*Not FDA approved for acute mania
## Variable Lithium Response Rate

### Based on Bipolar Subtype

<table>
<thead>
<tr>
<th>Poor Response 30%</th>
<th>Rapid Cycling</th>
<th>Mixed Mania</th>
<th>Substance Abuse</th>
<th>(-) Family History</th>
<th>&gt;3 Episodes</th>
<th>DMI Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>D</td>
</tr>
<tr>
<td>Good Response 70%</td>
<td>Nonrapid Cycling</td>
<td>Euphoric Mania</td>
<td>No Substance Abuse</td>
<td>(+) Family History</td>
<td>Few Lifetime Episodes</td>
<td>MDI Pattern</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>M D</td>
</tr>
</tbody>
</table>

**DMI** = Depression mania euthymic interval; **MDI** = Mania depression euthymic interval

National Institute of Mental Health (NIMH)
International Group for The Study of Lithium Treated Patients (IGSLI)

- 4 linked SNPs chromosome 21 associated with lithium response
  - (rs79663003, p=1.37 × 10^{-8}; rs78015114, p=1.31 × 10^{-8};
    rs74795342, p=3.31 × 10^{-9}; and rs75222709, p=3.50 × 10^{-9})

- Replicated prospective study (n=73) lithium monotherapy X 2 years
  - (p=0.03268, hazard ratio 3.8, 95% CI 1.1-13.0)

- Response-associated region-2 genes for long, non-coding RNAs (lncRNAs) increasingly recognized regulators of gene expression
  - AL157359.3 and AL157359

TSH and with Depressive Relapse in Lithium Maintained Bipolar Patients


<table>
<thead>
<tr>
<th>Intervention</th>
<th>Mean TSH (µU/ml)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>2.4 ± 0.4</td>
<td>40</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>1.4 ± 0.1</td>
<td>54</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.5 ± 0.1</td>
<td>39</td>
</tr>
</tbody>
</table>

* P < 0.05 Intervention vs. No intervention
Free T4 & Depressive Severity in Lithium Maintenance

$P < 0.01$; Beck Depression Inventory 10-16 = mild depression

Maintenance Treatment of Bipolar Disorder: Differential Response to Lithium and Carbamazepine*


Patients Remaining Well (%)

<table>
<thead>
<tr>
<th>Months</th>
<th>Lithium</th>
<th>Carbamazepine</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>12</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>18</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>24</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>30</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

Classical
BP I, no mood-incongruent delusions/comorbidity

Nonclassical
BP II, BP NOS, mood-incongruent delusions, comorbidity

P<0.006
n=67

P<0.08
n=104

BP I=bipolar I disorder; BP II=bipolar II disorder; BP NOS=bipolar disorder not otherwise specified.

*Not FDA approved for bipolar disorder
Lifetime Prevalence of Alcohol Use Disorders*

*Use = abuse or dependence; OR = Odds ratio

Why Do Patients Drink?

- Treat insomnia
- Impulsivity
- Maintain euphoria
- Disinhibition

- Self-medicating
- Induce numbness
- Anxiolytic
- Blunt trauma

Valproate for Mania: Dose-Response Effect

Prospective study of 374 patients with acute mania stratified into 6 groups based on VPA serum level ranges (lowest level ≤ 55.0 mcg/mL)

Results

- Linear relationship between VPA serum level and therapeutic response
- Efficacy significantly > PLC beginning at 71.4-85.0 mcg/mL
- Efficacy was associated with highest VPA serum levels (>94 mcg/mL)

Carbamazepine* Levels: Correlation with Improvement

- Anticonvulsant serum levels (4-12 mcg/mL)
- Mood stabilization serum levels unclear
  - Plasma carbamazepine (n=10, r=0.21, ns)
  - Plasma-10, 11 epoxide (n=10, r=0.62, p<0.06)
  - CSF carbamazepine (n=10, r=0.23, ns)
  - CSF-10, 11 epoxide (n=10, r=0.67, p<0.01)
- Induction of CYP450 3A3/4
  - Decreases serum concentrations of many medications
  - Autoinduction 3-5 weeks (ie after hospital discharge) with need to adjust dose


*Not FDA approved for bipolar disorder
Divalproex & Carbamazepine* in Acute Mania

Pros
● Effective in manic and mixed episodes
● Effective in alcohol withdrawal & relapse prevention
● Several effective in migraine prevention

Cons
● Ineffective in acute mania (LTG, TPX, GBP)
● P450 3A/4 heteroinduction
● Weight gain & endocrine disturbances (VAL)
● Teratogenicity (VAL, CBZ)
● Rash risk

CBZ = carbamazepine; VAL = valproate; LTG = lamotrigine; GBP = gabapentin; OLZ = olanzapine.
DVPX = divalproex; TPX = topiramate


*Not FDA approved for bipolar disorder
Other Anticonvulsant Drugs

- **Oxcarbazepine** *
  - One negative randomized, DB, PLC-controlled trial
  - No PLC-controlled studies in adults

- **Lamotrigine**
  - Two unpublished negative trials

- **Gabapentin** *
  - Negative PLC-controlled add-on study (LI, VPA)

- **Topiramate** *
  - Four negative PLC-controlled trials


*Not FDA approved for mania bipolar disorder
Typical Antipsychotics in Acute Mania

**Pros**
- Efficacious for acute mania
- Haloperidol* may be more rapidly efficacious than olanzapine, quetiapine, ziprasidone

**Cons/adverse effects**
- Acute EPS, tardive dyskinesia, akathisia, neuroleptic malignant syndrome

**Negative impact on course of illness**
- ↑ post-mania depressive symptom severity
- ↑ frequency of major depressive episodes


*Not FDA approved for bipolar disorder
Atypical Antipsychotics in Acute Mania

- **Pros**
  - As a class, effective in acute mania and mixed episodes
  - Rapid control of acute mania/mixed, rapid cycling, psychosis/no psychosis
  - Sustained improvement of symptoms

- **Cons**
  - Tardive dyskinesia, neuroleptic malignant syndrome
  - Weight gain, related dysmetabolic effects

TD = tardive dyskinesia; EPS = extrapyramidal symptoms

ECT for Acute Mania

- Electroconvulsive therapy (ECT) is a mood stabilizer
- 2 controlled studies of acute mania
  - ECT vs lithium
  - ECT vs lithium + haloperidol,
- ECT reported significant benefits for acute mania

# Target Dose Range for Acute Mania

<table>
<thead>
<tr>
<th>Agent</th>
<th>Monotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>0.8 – 1.2 mmol/L</td>
</tr>
<tr>
<td>Divalproex</td>
<td>90 – 125 mg/L</td>
</tr>
<tr>
<td>Carbamazepine*</td>
<td>4-12 mcg/ml vs. 800 mcg</td>
</tr>
<tr>
<td>Asenapine</td>
<td>10 mg bid sublingual</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>10 – 20 mg/d</td>
</tr>
<tr>
<td>Risperidone</td>
<td>4 – 5 mg/d</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>600 – 800 mg/d</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>80 – 120 mg/d</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>15 – 30 mg/d</td>
</tr>
<tr>
<td>Clozapine*</td>
<td>150 – 450 mg</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>3 – 6 mg/d</td>
</tr>
</tbody>
</table>


*Not FDA approved for bipolar disorder*
# Mood Stabilizer Safety and Tolerability Concerns

<table>
<thead>
<tr>
<th>Mood Stabilizer</th>
<th>Safety and Tolerability Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>Gastrointestinal, Weight gain, Neurotoxicity, Renal toxicity, Thyroid toxicity, Hair Loss, Cardiac toxicity, Acne, Psoriasis, Teratogen, Suicidality (?)</td>
</tr>
<tr>
<td>Valproate</td>
<td>Gastrointestinal, Weight gain, Tremor, Hepatotoxicity, Thrombocytopenia, Hair Loss, Pancreatitis, PCOS, Teratogen, Suicidality (?)</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Gastrointestinal, Weight gain, Rash, Neurotoxicity, Hepatotoxicity, Thyroid changes, Blood dyscrasias, Cardiac toxicity, Hyponatremia, Teratogen, Suicidality (?)</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Gastrointestinal, Rash, Neurotoxicity, Headache, Hepatotoxicity, Dizziness, Pruritis, Dream abnormality, Teratogen, Suicidality (?)</td>
</tr>
</tbody>
</table>

All Mood Stabilizers Have at Least One Boxed Warning

# Antipsychotic Safety and Tolerability Concerns

## First-Generation
- Depression
- Akathisia
- Acute dystonia
- Tardive dyskinesia<br>Commonly linked to First-generation antipsychotics

## Second-Generation
- Weight gain
- Sedation
- Hyperglycemia, Diabetes<br>Commonly linked to Second-generation antipsychotics
- Suicidality in age ≤ 24
- Akathisia
- Hyperprolactinemia
- Cerebrovascular in elderly

## Warnings
- Boxed warnings are given to highlight specific risks or concerns.

### Cardiac/pneumonia in older adults

#### First-Generation
- Cardiac/pneumonia in older adults<br>Commonly linked to First-generation antipsychotics

#### Second-Generation
- Cardiac/pneumonia in older adults<br>Commonly linked to Second-generation antipsychotics

---

**Warnings** - boxed; <sup>a</sup> antipsychotic class warning; <sup>b</sup> Second generation antipsychotic class warning; <sup>c</sup> aripiprazole, quetiapine, olanzapine + fluoxetine combination (antidepressant class warning); <sup>d</sup> risperidone, olanzapine, aripiprazole

---

# All Antipsychotics Have at Least One Boxed Warning

Bipolar Disorder — A Focus on Depression

Mark A. Frye, M.D.

This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

A 26-year-old businesswoman seeks evaluation for a pattern of “hibernating away” each winter; this pattern began when she was in high school. Her current symptoms include excessive sleeping, a 20-lb (9-kg) weight gain related to an increased intake of sweets and excessive alcohol use, anhedonia, lack of motivation, negative ruminations, and decreased productivity at work. She reports a history of several-week periods in college when she had less need for sleep, with associated increases in mood, energy, and libido. During the last episode, she exceeded her credit-card limit and was evaluated at an emergency department for alcohol intoxication. How should she be evaluated and treated?
Bipolar Depression: Best Practices

- FDA approved
  - Olanzapine Fluoxetine (OFC)
  - Quetiapine monotherapy
  - Lurasidone mono & adjunct therapy
- Maximize the mood stabilizer
- Antidepressants FDA off-label*
  - Do they work? Are they safe?
- Psychotherapy
- Novel Treatment

*FDA off-label – antidepressants are not indicated for treatment of bipolar depression
Epidemiology Bipolar Disorder – Focus Depression

- **Lifetime prevalence rate 4.5 %**
  - 1% for BPI, 1.1% BPII, 2.4% subthreshold

- **Suicide**
  - 25% attempt, 15% succeed (5% never hospitalized)

- **Comorbid anxiety and substance use disorders**
  - Greater risk suicidality and treatment emergent mania

- **Work days lost/ ill worker/ year**
  - BP > UP, driven by depression, not mania

- **Subsyndromal depression**
  - Functional disability & subsequent relapse

**Antipsychotics**

- **OLZ/OFC**
  - 10 mg / 7.5 mg
  - 40 mg

- **Quetiapine**
  - 300 and 600 mg
  - ~17 mg

- **Aripiprazole**
  - ~17 mg

- **Ziprasidone**
  - ~90 mg

**OFC = olanzapine/fluoxetine combination.** *P* < .05; †*P* < .001 vs. placebo.


*Not FDA approved for bipolar depression*
PREVAIL 2 Trial

6-week randomized double-blind trial of lurasidone monotherapy for acute bipolar I depression

- N = 505
- Bipolar I depression
- MADRS ≥ 20

Lurasidone
20-60 mg/day
n = 166

Lurasidone
80-120 mg/day
n = 169

Placebo
n = 170

PREVAIL 2: Results

Compared with placebo, lurasidone associated with statistically significant reductions in MADRS scores from baseline to week 6 (primary endpoint).

Response Rates*  
NNT = 5  

NNT = 5

NNH = 17

NNH = 15

*Response: ≥ 50% MADRS decrease.
Meta-Analysis Lamotrigine* in Acute BP Depression

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk Ratio (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCA2001</td>
<td>1.71 (1.08,2.69)</td>
<td>8.3</td>
</tr>
<tr>
<td>SCA2010</td>
<td>1.11 (0.83,1.48)</td>
<td>20.6</td>
</tr>
<tr>
<td>SCA40910</td>
<td>1.09 (0.81,1.48)</td>
<td>21.7</td>
</tr>
<tr>
<td>SCA30924</td>
<td>1.24 (0.91,1.70)</td>
<td>19.9</td>
</tr>
<tr>
<td>SCA10022</td>
<td>1.26 (0.95,1.67)</td>
<td>20.7</td>
</tr>
<tr>
<td>LAMLIT</td>
<td>1.63 (1.05,2.53)</td>
<td>8.8</td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td>1.26 (1.10,1.44)</td>
<td></td>
</tr>
</tbody>
</table>

0.371223 Risk Ratio 2.6938

Favors Placebo

Favors Drug


*Not FDA approved for bipolar depression
Meta-Analysis Divalproex* in Acute BP Depression

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Divalproex n/N</th>
<th>Placebo n/N</th>
<th>RR (random)</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sachs</td>
<td>14/21</td>
<td>10/22</td>
<td>1.47 [0.85, 2.54]</td>
<td>67.72</td>
<td></td>
</tr>
<tr>
<td>Davis</td>
<td>6/13</td>
<td>3/12</td>
<td>1.85 [0.59, 5.79]</td>
<td>15.62</td>
<td></td>
</tr>
<tr>
<td>Ghaemi</td>
<td>2/9</td>
<td>1/8</td>
<td>1.78 [0.20, 16.10]</td>
<td>4.20</td>
<td></td>
</tr>
<tr>
<td>Muzina</td>
<td>6/26</td>
<td>3/28</td>
<td>2.15 [0.60, 7.74]</td>
<td>12.46</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>69</td>
<td>70</td>
<td>1.61 [1.02, 2.53]</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 28 (Divalproex), 17 (Placebo)

Test for heterogeneity: Chi² = 0.40, df = 3 (P = 0.94), I² = 0%  
Test for overall effect: Z = 2.06 (P = 0.04)

Relative risk of remission in patients treated with divalproex vs. placebo.


*Not FDA approved for bipolar depression
Maximize the Mood Stabilizer Lithium* & BP Depression

**Mean Change in HAM-D Score**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Lithium&lt;sub&gt;+&lt;/sub&gt; &lt; 0.8 mEq/L</th>
<th>Lithium&lt;sub&gt;+&lt;/sub&gt; ≥ 0.8 mEq/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li + PAR</td>
<td>N = 19</td>
<td>N = 14</td>
</tr>
<tr>
<td>Li + IMI</td>
<td>N = 19</td>
<td>N = 17</td>
</tr>
<tr>
<td>Li Only</td>
<td>N = 21</td>
<td>N = 22</td>
</tr>
</tbody>
</table>


**Li** = lithium, **IMI** = imipramine, **PAR** = paroxetine


*Not FDA approved for bipolar depression*
Antidepressants Most Common Initial Treatment for Bipolar Disorder Patients in US in 2002-2003

Antidepressants (AD) Not Effective for Bipolar Depression

- Meta-analysis 16 studies acute AD Rx vs. placebo or active comparator in BPI / II depressed patients (n = 3113)
- The pooled treatment estimates
  - Clinical response ([RR] = 1.17, 95% CI, 0.88-1.57; p = 0.28)
  - Clinical remission (RR = 1.14, 95% CI, 0.90-1.45; p = 0.28)
- Pooled treatment estimates for 1000 patients
  - No increase risk of switch
- In smaller analysis
  - 43% TCA, 15% venlafaxine, 7% SSRI, 5% bupropion

Depressive Episode Relapse with Antidepressant Discontinuation

Cox regression analyses log rank = 10.09, \( P = .006 \)

Meta-Analysis of Antidepressant Induced Mania (AIM+)

SSRI = fluoxetine, fluvoxamine, paroxetine, or sertraline

Risk Factors for Switch

- Mixed Depression
- Tricyclic antidepressants (TCA) vs. SSRI/SNRI
- History of antidepressant-induced mania (AIM)
- Absence of antimanic mood stabilizer
  - First 3 months associated with greatest liability
- Low thyroid stimulating hormone (with TCAs)
- Polymorphism (s/s or s/l) at 5-HTTLPR
- Hyperthymic temperament
- Comorbid alcoholism
- Female gender and comorbid anxiety disorder
- Age (peripubertal > adolescents)
- BP I > BP II

Baseline Mixed Depression Associated with Treatment Emergent Mania (TEM)

- Prior to antidepressant treatment
- 3 YMRS items significantly higher in TEM
  - ↑ motor-energy
  - speech
  - thought content
- Factor analysis to identify clusters of YMRS items that covaried and analysis of variance only identified motor/verbal activation ($F(2,169) = 3.99, p = .02$)

YMRS = Young Mania Rating Scale, TEM = Treatment Emergent Mania
Recurrent “Unipolar”

BP-IV
Hyperthymia + Depression

Depressive Mixed State

DSM-5 Mixed Specifier

Mayo Clinic Individualized Medicine Biobank for Bipolar Disorder (BP)

SLC6A4 polymorphism & Antidepressant Induced Mania
SLC6A4 S Allele and AIM: Meta-Analysis Results

Meta-analysis marginally significant evidence of association between S allele and AIM+ ($p = 0.059$)

Pharmacogenomic Haplotype Analysis: L-A-Protective

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>Freq.</th>
<th>Score</th>
<th>Sim p</th>
<th>Max stat sim p</th>
<th>Global sim p</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-A-10</td>
<td>0.344</td>
<td>-2.448</td>
<td>0.012</td>
<td>0.047</td>
<td>0.020</td>
</tr>
<tr>
<td>L-G-12</td>
<td>0.027</td>
<td>-1.555</td>
<td>0.14</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>S-A-10</td>
<td>0.214</td>
<td>0.144</td>
<td>0.86</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>L-A-12</td>
<td>0.136</td>
<td>0.965</td>
<td>0.31</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>S-A-12</td>
<td>0.225</td>
<td>1.034</td>
<td>0.28</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

Cases N = 113; Controls N = 182

Haplotype analysis suggests an association between AIM and haplotypes composed of the 5HTTLPR, rs25531, and the intron 2 VNTR in the SLC6A4 gene, with the L-A-10 haplotype being associated with reduced risk of AIM.

6-Week, Randomized Placebo-Controlled Evaluation of Adjunctive Modafinil* for Bipolar Depression

- N = 85
- Bipolar I/II depression
- Inadequate response to mood stabilizers ± AD Rx

**Mean Baseline to Endpoint Change in IDS-C Score**

<table>
<thead>
<tr>
<th></th>
<th>Modafinil</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Endpoint (adjusted for baseline)</td>
</tr>
<tr>
<td><strong>IDS-30</strong></td>
<td>30</td>
<td>35</td>
</tr>
<tr>
<td><strong>IDS-4 Fatigue and Energy Subset</strong></td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

- Modafinil well tolerated; headache most common AE
- No difference (modafinil vs placebo) in weight gain or treatment-emergent mania

*Not FDA approved for bipolar depression*

---


---

*a hypersomnia, energy level, cognitive slowing, and leaden paralysis.
AD: antidepressant; IDS-C: Inventory for Depressive Symptomatology–Clinician.
8-Week Randomized Double-Blind Adjunctive Armodafinil* in Acute Bipolar I Depression: Results

Response Rates:
- Armodafinil: 46.2%
- Placebo: 34.2%
- NNT = 9
- \( P = .015 \)

AE Discontinuation:
- Armodafinil: 5.6%
- Placebo: 3.5%
- NNH = 50

≥7% Weight Gain:
- Armodafinil: 1.6%
- Placebo: 4.4%
- NNH = -37

\(^a\) Response: ≥50% IDS-C30 decrease


*Not FDA approved for bipolar depression*
ECT Bipolar Depression

- 6-week, 6-site, randomized trial of 3X/week RUL ECT vs algorithm based pharmacological treatment (n = 73)
  - Response rate 74% (17/23) vs. 35% (7/20, p .01)

- Bitemporal generally acknowledge to have greater efficacy and side effects

Meta-analysis of 19 TMS studies in bipolar depression (n = 181)
- Stimulation targets: left, right, bilateral DLPFC
- High vs Low or sequential stimulation frequency
- Response: TMS 44% (47/106) vs Sham 25% (19/75, $p < 0.01$)

Bilateral sequential (1 Hz rDLPFC $\rightarrow$ 10 Hz lDLPFC) vs sham rTMS for 4 weeks (n = 49)
- No significant difference in baseline to end point change, response or remission rates

Substantial clinical trial design heterogeneity
- Stimulation target
- Laterality
- High (10hz) vs low (1 Hz) stimulation

Archival Report

A Randomized Sham-Controlled Trial of Deep Brain Stimulation of the Ventral Capsule/Ventral Striatum for Chronic Treatment-Resistant Depression


ABSTRACT
BACKGROUND: Multiple open-label trials of deep brain stimulation (DBS) for treatment-resistant depression (TRD), including those targeting the ventral capsule/ventral striatum target, have shown encouraging response rates. However, no randomized controlled trials of DBS for TRD have been published.

METHODS: Thirty patients with TRD participated in a sham-controlled trial of DBS at the ventral capsule/ventral striatum target for TRD. Patients were randomized to active versus sham DBS treatment in a blinded fashion for 16 weeks, followed by an open-label continuation phase. The primary outcome measure was response, defined as a 50% or greater improvement on the Montgomery-Åsberg Depression Rating Scale from baseline.

RESULTS: There was no significant difference in response rates between the active (3 of 15 subjects; 20%) and control (2 of 14 subjects; 14.3%) treatment arms and no significant difference between change in Montgomery-Åsberg Depression Rating Scale scores as a continuous measure upon completion of the 16-week controlled phase of the trial. The response rates at 12, 18, and 24 months during the open-label continuation phase were 20%, 26.7%, and 23.3%, respectively.

CONCLUSION: The results of this first randomized controlled study of DBS for the treatment of TRD did not demonstrate a significant difference in response rates between the active and control groups at the end of the 16-week controlled phase. However, a range of 20% to 26.7% of patients did achieve response at any time during the open-label continuation phase. Future studies, perhaps utilizing alternative study designs and stimulation parameters, are needed.

Keywords: Deep brain stimulation, DBS, Treatment resistant depression, TRD, Major depression, Ventral capsule/ventral striatum
Ketamine* for Treatment Resistant Bipolar Depression- Replication

- Ketamine noncompetitive NMDA antagonist
- FDA approved as a general anesthetic
- 0.5 mg/kg over 40 minutes vs one infusion of saline placebo.
- Almost immediate reductions in depression rating scores.


*Not FDA approved for bipolar depression
(Pooled) 6-week Randomized Double-Blind Adjunctive Pramipexole* in Acute Bipolar Depression

**p = 0.0016 vs. PBO

Response Rates:
- **Pramipexole vs. Placebo**: 63.6% vs. 14.3%
- NNT: 3

Switch Rates:
- **Pramipexole vs. Placebo**: NNH: -231

15 BPI, 28 BPII on
- Li (N = 18, 0.7 mEq/L)
- DVPX (N = 18, 77 ug/mL)
- LTG (N = 6)
- GBP (N = 3)
- CBZ (N = 2)

Response: ≥ 50% HDRS/MADRS decrease


*Not FDA approved for bipolar depression.
Adjunctive Levothyroxine in Bipolar Depression

Total study group (n = 62)

*\( p < 0.05 \) vs placebo (ITT; LOCF)

Adjunctive levothyroxine (300 \( \mu \)g/day) or placebo in patients with bipolar I or II disorder

HAM-D, Hamilton rating scale for depression


*Not FDA approved for bipolar depression*
Intensive Psychotherapies Improve Bipolar Depression

- N = 293 bipolar depressed outpatients
- Protocol meds + 9 mos:
  - FFT (family-focused therapy)
  - IPSRT (interpersonal and social rhythm therapy)
  - CBT (cognitive behavior therapy)
  - CC (collaborative care)
- Intensive psychotherapies
  - Higher recovery rate
  - Shorter time to recovery
  - 1.6x more likely to be clinically well during any study month

Maintenance of Antidepressant Response After Group IPSRT Group for Bipolar Disorder

P < .05, N = 6, YMRS (Young Mania Rating Scale); IDS-C (Inventory of Depressive Symptomatology- Clinician Rated); BDI-II (Beck Depression Inventory-II)

FDA Language of Maintenance

- **Lithium** - “... prevents or diminishes the intensity of subsequent episodes”
- **Lamotrigine** - “to delay the time to occurrence of mood episodes in patients treated for an acute mood episode with standard therapy”
- **Olanzapine** - “maintaining monotherapy after achieving a responder status for an average of 2 weeks”
- **Aripiprazole** - “recent manic or mixed episode that had been stabilized and then maintained for at least 6 weeks”
- **Quetiapine** - “maintenance of bipolar I disorder as adjunct therapy to lithium or valproate”
- **Risperidone long acting injectable** - “as monotherapy or adjunct therapy to lithium or valproate for maintenance treatment of bipolar I disorder“
- **Ziprasidone** - “adjunct to lithium or valproate for maintenance

* Physicians’ Desk Reference. 2016. Website: http://pdr.net*
Maintenance Trial Design

Screening

BPI recent episode

Open-label stabilization of investigational agent

Stabilization Criteria
YMRS
MADRS

Durational Criteria
Consecutive ratings

6-18 weeks

Enriched Double-blind maintenance

Investigational Agent
OR
Placebo

26 – 72 weeks

Goals of Maintenance Treatment in Bipolar Disorder

- Prevent recurrent mood episodes
- Decrease frequency and intensity of recurrent episodes
- Abolish/reduce interepisode/subsyndromal symptoms
- Prevent Suicide
- Manage comorbidity
- Enhance/normalize functioning
Mania Matters

- Treat the illness
  - Short term high dose benzodiazepine, sleep restoration, containment
- Individualize treatment
  - Right medication to the right patient
- Improved psychoeducation
- Enhanced treatment adherence and minimize side effect burden
Conclusions

- Evidence-based options
  - OFC, Quetiapine, Lamotrigine, Lurasidone
- Maximize the mood stabilizer
- Evidence-base + Comorbidity
  - Psychotic depression or psychotic illness – AAP
  - Weight neutrality – ARI, LUR, ZIP, LTG
  - Migraine – valproate
  - Smoking cessation – bupropion (with MS)
  - Antisuicidal or classic illness- Lithium
- Antidepressants in BP depression
  - Evidence base does not support monotherapy use
  - Switch rate is not 0%
How has this presentation improved your confidence in using the latest evidence in treating patients with bipolar disorders?

A. Extremely confident
B. More confident
C. Somewhat confident
D. Not confident at all
In the treatment of bipolar depression, which is the most commonly prescribed medication?

A. Antidepressants
B. Divalproex
C. Atypical antidepressants
D. Stimulants
Funding for this work was provided by the Marriott Foundation.

Thank you to the bipolar patients and their families who have contributed to the development and richness of this clinical resource.