Translating Receptor Pharmacology to Advance the Management of Bipolar Depression

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Faculty

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Faculty Disclosure

Disclosure

• The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).
  – The off-label and investigational use of mood stabilizers (lithium, valproate, and lamotrigine), antidepressants (SSRIs, SNRIs, and MAOIs), aripiprazole, asenapine, brexipiprazole, cariprazine, bright light, transcranial direct current stimulation, ketamine, and minocycline for the treatment of bipolar depression will be discussed.

• Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.
• This activity has been independently reviewed for balance.
Learning Objectives

• Discuss current clinical challenges in the management of bipolar depression in terms of its pervasiveness, patient impact, and response to traditional bipolar disorder pharmacotherapies
• Apply insights from dopamine receptor physiology and pharmacology to evaluate potential therapeutic targets in the treatment of bipolar depression
• Assess the mechanisms of action, efficacy, and safety of available and emerging pharmacotherapies for the treatment of bipolar depression
• Translate the latest clinical data and pathophysiologic understanding of bipolar depression into informed and individualized strategies for bipolar disorder management
Advances in Neurobiology and Treatment of Bipolar Depression
Mood Disorders: Introduction

- Mood disorders are a product of complex interactions between several “vulnerability” genes and environmental factors.
- Mood disorders are not only chronic and recurrent conditions, they may be progressive.
- Sustained functional changes in the brain may precipitate a change in structure.
- Mood disorders are associated with changes in endocrine, immune, and autonomic function.

Differential Diagnosis and Screening
GWAS in Mood Disorders: Disappointments, Insights, and Surprises

The largest mega-analysis yet conducted has failed to find any SNP or gene definitely associated with depression. Nonetheless, recent mathematical strategies for examining the combined effect of all available genomic SNPs suggests that approximately 30% of the risk for depression results from these multiple polymorphisms.

MDD has significant shared genetic etiology with schizophrenia ($r_{SNP} = .43$), bipolar disorder ($r_{SNP} = .47$), and ADHD ($r_{SNP} = .32$). MDD genes not enriched for those expressed primarily in the CNS.

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; BPD = borderline personality disorder; CNS = central nervous system; GWAS = genome-wide association studies; MDD = major depressive disorder; SCZ = schizophrenia; SNP = single nucleotide polymorphism.

The influence of early adversity (red) and family history on age of first symptoms of bipolar disorder (yellow).

**P**<.001. Hx = history.
Mood State at Presentation across the Life Cycle

N=889.
DSM-5 Field Trials Inter-rater Reliability

Anita

<table>
<thead>
<tr>
<th>Presentation</th>
<th>History</th>
<th>Treatment</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 32-year-old married female</td>
<td>• PCP referral for treatment of depression</td>
<td>• Patient self-reports history of several failed past treatment attempts with antidepressants</td>
<td></td>
</tr>
<tr>
<td>• On at least 2 occasions antidepressants made her “feel worse”, including an induction of mood lability</td>
<td>• She is currently employed as a teller at a community bank and has a 5-year-old daughter</td>
<td>• First depressive episode occurred after a breakup with a boyfriend during senior year in high school</td>
<td></td>
</tr>
<tr>
<td>• One of the depressive episodes occurred after childbirth 5 years ago</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
• Currently, she has complaints of:
  – Feeling sad and tired most days
  – Anhedonia; loss of interest in work and hobbies
  – Periods of insomnia, alternating with hypersomnolence
  – Even if she doesn’t sleep well, she “can still somehow make it through the day”
  – She reports “moving slowly” with difficulty at work and caring for her daughter
  – She had occasionally been “thinking about death” but had no specific plan for suicide
• Anita has a history of migraines
## Anita’s Responses to the Mood Disorder Questionnaire (MDQ)

1. Has there ever been a period of time when you were not your usual self and...

<table>
<thead>
<tr>
<th>Response</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>...you felt so good or so hyper that other people thought you were not your normal self or you were so hyper that you got into trouble?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...you were so irritable that you shouted at people or started fights or arguments?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...you felt much more self-confident than usual?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...you got much less sleep than usual and found you didn’t really miss it?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...you were much more talkative or spoke much faster than usual?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...thoughts raced through your head or you couldn’t slow your mind down?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...you were so easily distracted by things around you that you had trouble concentrating or staying on track?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...you had much more energy than usual?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...you were much more active or did many more things than usual?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...you were much more social or outgoing than usual, for example you telephoned friends in the middle of the night?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...you were much more interested in sex than usual?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...you did things that were unusual for you or that other people might have thought were excessive, foolish, or risky?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...spending money got you or your family into trouble?</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

The above is an example of a completed MDQ from a fictional patient.

Anita’s Responses to the Mood Disorder Questionnaire (MDQ) (cont’d)

2. If you checked YES to more than one of the above, have several of these ever happened during the same time period?  
   Yes □   No □

3. How much of a problem did any of these cause you – like being unable to work; having family, money, or legal troubles; getting into arguments or fights? Please circle one response only.
   - No problem
   - Minor problem
   - Moderate problem □
   - Serious problem

4. Have any of your blood relatives (ie, children, siblings, parents, grandparents, aunts, uncles) had manic-depressive illness or bipolar disorder?  
   Yes □   No □

5. Has a health professional ever told you that you have manic-depressive illness or bipolar disorder?  
   Yes □   No □

The above is an example of a completed MDQ from a fictional patient.  
Anita: Summary

**MDQ score:**
- **Question 1:** 9 “yes” responses
- **Question 2:** “yes”
- **Question 3:** “moderate”
- → Positive screen

**Other diagnostic considerations:**
- Symptoms are consistent with a past and present major depressive episode
  - Current passive suicidal ideation
  - Anita reported an “unusual” experience during college: During 1 of the periods of elevated energy she smoked some “pot” to relax. For several days afterwards she felt “paranoid” and “heard voices”
  - Responses to MDQ and self-description of history are suggestive of possible manic episode in the past
  - Self-description suggests early and sudden onset of symptoms
  - There is a positive family history of bipolar disorder
What is your diagnosis?

A. Major depressive disorder without psychosis
B. Bipolar I disorder depressive episode
C. Bipolar II disorder depressive episode
D. Major depressive disorder with mixed features
E. Dysthymia
Which is an accurate statement about depressive and manic episodes in a bipolar I disorder patient?

A. Nearly 10% of the time is spent in manic episodes; 3 × as long is spent in major depressive episodes

B. An even distribution of time is spent in asymptomatic, depressive, and manic episodes

C. Depression is the initial episode in women about 50% of the time

D. About 75% of the time is spent in manic episodes, 20% is spent in depressive episodes, and only 5% asymptomatic
Patients were incorrectly diagnosed with:

- Unipolar depression 60%
- Anxiety disorders 26%
- Schizophrenia 18%
- Borderline or antisocial PD 17%
- Alcohol or substance abuse 14%
- Schizoaffective disorder 11%

- For 35% of those with prior misdiagnosis, lapse in time from first treatment seeking to accurate diagnosis was 10 years or longer
- On average, people with bipolar disorder who were previously misdiagnosed received 3.5 misdiagnoses and consulted 4 physicians before receiving an accurate diagnosis

NDMDA = National Depressive and Manic-Depressive Association; PD = personality disorder.

Gender Differences in the Onset of Bipolar Disorder May Delay Correct Diagnosis

IQR = interquartile range.

Characteristics of Women Who Have Reproductive Cycle-Associated Bipolar Symptoms

- 77% of women reported increases in mood symptoms during perimenstrual, postnatal, or menopausal periods
- Women who had reproductive cycle-associated symptoms also experienced earlier age of onset for depressive and hypo/manic episodes and a greater likelihood of comorbid anxiety disorders, rapid cycling, and mixed mood compared to those who did not have these symptoms

Time Spent Depressed: BD-I vs BD-II

NIMH Collaborative Depression Study, 13 Years

% of Weeks

BD-I
Depression: Mania 3:1 (N=146)
- Asymptomatic: 58.8%
- Depressed: 31.9%
- Manic: 9.3%

BD-II
Depression: Hypo-Mania 37:1 (N=71)
- Asymptomatic: 48.4%
- Depressed: 50.3%
- Hypomanic: 1.3%

Higher Morbidity, Chronicity

BD-I = bipolar I disorder; BD-II = bipolar II disorder; NIMH = National Institute of Mental Health.
Consider Bipolar When Seeing Treatment-Resistant Depression

Re-evaluation of Referred Patients Who Had Failed ≥ 2 Adequate Trials of Antidepressants (N=61)

Initial Re-evaluation Using Structured Clinical Interview for DSM-IV
- 65% Major depressive disorder
- 35% Bipolar disorder

Later Re-evaluation Within 1 Year
- 41% Major depressive disorder
- 59% Bipolar disorder

**Features Differentiating Bipolar from Unipolar Depressive Episodes**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Unipolar</th>
<th>Bipolar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial episode in teenage years</td>
<td>Greater risk of hospitalization</td>
<td>Presence of psychotic features</td>
</tr>
<tr>
<td>Rapid onset and offset of depressive episodes</td>
<td>Greater risk of suicide attempts</td>
<td>Family history of bipolar disorders</td>
</tr>
<tr>
<td>Greater episode frequency</td>
<td>Greater risk of comorbid substance use disorders, anxiety disorders, and eating disorders</td>
<td>More mixed symptoms</td>
</tr>
</tbody>
</table>
| Antidepressant misadventures (poor response, syndromal shifts, induction of mood lability or rapid cycling) | Greater likelihood of seasonal pattern of depressive episodes | Higher rates of substance use                                            

*DeMuri-Maletic B, Maletic V. Scientific American Psychiatry. 2018; In press.*
**MDQ**

**How to Score**

**Positive Screen – All 3 of the following criteria must be met:**

**Question 1:** 7 out of 13 positive (yes) responses  
**Question 2:** Positive (yes) response  
**Question 3:** “Moderate” or “Serious” response  

Functional and Structural Brain Changes in Bipolar Disorder
Neurobiology of Mood Disorders

Etiology

- Genetic Epistasis
- Epigenome
- Stress
- Epigenetic Modulation

Pathophysiology

“Network” Level: Dysregulation of Neural Circuitry
- Functional changes
- Structural changes

Neuroendocrine, Autonomic, and Immune Dysregulation

Cellular and Subcellular Level Impact on
- Intracellular signaling
- Gene transcription
- Neurotrophic support

Clinical Presentation

Neuropsychiatric Symptoms
- Emotional
- Cognitive
- Behavioral
- Physical

Systemic Manifestations

Development

ELA = early life adversity.
Functional Brain Changes in Bipolar Disorder

Brain areas associated with cognitive control, which manifest reduced responsiveness, are labeled blue (dorsal ACC, DMPFC, DLPFC). By contrast, limbic and para-limbic brain areas involved in emotional regulation, associated with greater responsiveness, are labeled in red (amygdala, VLPFC, ventral ACC).

Functional Changes in Bipolar Disorder

Strong feature weights were observed in the amygdala for the negative faces condition, which were specific to unipolar depression, whereas higher amygdala features weights during the positive faces condition were observed, specific to bipolar patients. Medial prefrontal and orbitofrontal regions contributed to classifications specific to unipolar depression, whereas stronger feature weights in dorsolateral prefrontal areas contribute to classifications as bipolar. The pattern classification yielded up to 90% accuracy rates discriminating the 2 groups.

fMRI = functional magnetic resonance imaging.
DLPFC Activity is Associated with Bipolar Depression Severity

41 bipolar depressed patients and 41 matched normal controls underwent fMRI scanning while performing baseline, 1-back and 2-back versions of the n-back task. The patients showed failure to de-activate in the medial prefrontal cortex, an area corresponding to the anterior medial node of the default mode network.

HAM-D = Hamilton Rating Scale for Depression; MADRS = Montgomery-Asberg Depression Rating Scale.
Cortical Gray Matter Changes in Bipolar Depression

Anterior surface rendering illustrating (in blue) areas in which depressed bipolar participants (n=17) showed lower gray matter density relative to euthymic bipolar participants (n=16). MRI study.

Cellular and Molecular Pathophysiology of Bipolar Disorder
Stress and Inflammation in MDD

α7nAChR = α7 nicotinic acetylcholine receptor; Ach = acetylcholine; α/β-AR = α- or β-adrenoreceptor; GC = glucocorticoid; HPA = hypothalamic–pituitary–adrenal; NE = norepinephrine; NF-κβ = nuclear factor-κβ; TGF-β = transforming growth factor β; TNF-α = tumor necrosis factor α; TLR = toll-like receptor.
Bipolar Depression May Be Associated with Elevation of Inflammatory Cytokines

Interactions at the Glia–Synaptic Junction

Duration of Bipolar Disorder May Be Reflected in the Levels of TNF-α and BDNF

Early stage = within 3 years of the first diagnosis; Late stage = ≥ 10 years since diagnosis.
BDNF = brain derived neurotophic factor.

60 BD-I Patients compared with 60 Healthy Controls
Elevation of Inflammatory Cytokines in CSF May Alter 5-HT and Dopamine Metabolism

- Inflammatory cytokines and monoamine metabolites were compared in 63 suicide attempters and 47 healthy controls
- MADRS scores correlated significantly with CSF IL-6 levels
- IL-6 and TNF-a correlated with CSF 5-HIAA and HVA
- Higher cytokine levels were associated with increased suicidality

5-HT = serotonin; CSF = cerebrospinal fluid; HIAA = hydroxyindoleacetic acid; HVA = homovanillic acid; LN = natural log.
External stimuli such as stress may decrease AChE activity, thereby increasing extracellular ACh and the inhibitory effect on DA and NE activity resulting in depression (B). Other stimuli such as increased photoperiod exposure can increase TH, which is the precursor to DA and NE, potentially leading to a switch into manic behavior (C).

Ach = acetylcholine; AChE = acetylcholinesterase; DA = dopamine; DAT = DA transporter; NE = norepinephrine; TH = tyrosine hydroxylase.

Elevation in striatal $D_{2/3}$ receptor availability would lead to increased dopaminergic neurotransmission and mania, whilst increased striatal DAT levels would lead to reduced dopaminergic function and depression. Thus, it can be speculated that a failure of dopamine receptor and transporter homoeostasis might underlie the pathophysiology of this disorder.

Psychosis is Associated with Increased DA Synthesis in Striatum

Increased striatal dopamine synthesis capacity was evident in the bipolar psychosis group (n=22) relative to the control group (n=22). The color bar shows the t-statistic. The most significant increase was in the right caudate.

Relationship Between Striatal Dopamine Synthesis Capacity and Positive Psychotic Symptom Rating in the Bipolar Group Relative to the Schizophrenia Group.

PANSS = Positive and Negative Syndrome Scale.
Negative and Depressive Symptoms Correlate with D₃ Expression

Negative schizophrenic or depressive symptoms seemed to correlate with higher DRD3 levels [MADRS scores: apparent sadness ($r=.67$, $P=.012$), reduced sleep ($r=.67$, $P=.011$), lassitude ($r=.74$, $P=.004$); Brief Psychiatric Rating Scale: tension ($r=.89$, $P=.003$), depressive mood ($r=.61$, $P=.027$); Scale for the Assessment of Negative Symptoms: latency of response ($r=.71$, $P=.027$)].

*P=.023; **P=.009.
Regulation of Synaptic DA Concentration

$D_3$ presynaptic receptors provide more refined control of tonic dopamine release than $D_2$ because they are the higher affinity receptors.

## Binding Affinities of Partial D$_2$ Agonists and the Clinical Properties of the Receptors

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Aripiprazole $K_i$ (nM)</th>
<th>Brexpiprazole $K_i$ (nM)</th>
<th>Cariprazine $K_i$ (nM)</th>
<th>Therapeutic Effects</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>D$_2$</td>
<td>0.34</td>
<td>0.30</td>
<td>0.49</td>
<td>Antipsychotic</td>
<td>EPS, tardive dyskinesia, akathisia, NMS hyperprolactinemia</td>
</tr>
<tr>
<td>D$_3$</td>
<td>0.8</td>
<td>1.1</td>
<td>0.085</td>
<td>Antipsychotic (including negative symptoms), antimanic, antidepressant</td>
<td></td>
</tr>
<tr>
<td>5-HT$_1$A</td>
<td>1.7</td>
<td>0.12</td>
<td>2.6</td>
<td>Antidepressant, anxiolytic</td>
<td></td>
</tr>
<tr>
<td>5-HT$_2$A</td>
<td>3.4</td>
<td>0.47</td>
<td>18.8</td>
<td>Anti-EPS</td>
<td></td>
</tr>
<tr>
<td>5-HT$_2$C</td>
<td>15</td>
<td>34</td>
<td>134</td>
<td>Antidepressant</td>
<td></td>
</tr>
<tr>
<td>5-HT$_7$</td>
<td>29</td>
<td>3.7</td>
<td>111</td>
<td>Antidepressant</td>
<td></td>
</tr>
<tr>
<td>H$_1$</td>
<td>61</td>
<td>19</td>
<td>23.2</td>
<td>Anxiolytic, anti-insomnia</td>
<td>Weight gain sedation</td>
</tr>
<tr>
<td>M$_1$</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
<td>Opposes EPS</td>
<td>Xerostomia, constipation, blurry vision, cognitive dysfunction, falls (eg, older adults)</td>
</tr>
<tr>
<td>$\alpha_1$</td>
<td>57</td>
<td>3.8</td>
<td>155</td>
<td>Antihypertensive</td>
<td>Sedation, orthostasis</td>
</tr>
</tbody>
</table>

### Comparing the 3 partial D$_2$ agonists:
1. Aripiprazole has the greatest affinity for 5-HT$_2$C R; it has the weakest affinity for H, R. Theoretically, this suggests it may be less associated with metabolic symptoms and perhaps elevate monoamines for better antidepressant effects, therapeutically speaking. It may be the least sedating.
2. Brexpiprazole shows the greatest affinity for D$_2$ R, 5-HT$_1$A R, 5-HT$_2$A R, 5-HT$_7$R, H$_1$R, and $\alpha_1$R; it has the weakest affinity for D$_3$R. This suggests the possibility that it can both inhibit and enhance dopamine activity to a higher degree, treating either psychosis or depression. The serotonin modulation is highly suggestive of antidepressant activity.
3. Cariprazine shows the greatest affinity for D$_3$R; it is the weakest in affinity for D$_2$R, 5-HT$_1$A R, 5-HT$_2$A R, 5-HT$_7$R, and $\alpha_1$R. This may promote a fair amount of dopamine activity and act as an antidepressant. The serotonin modulation is highly suggestive of antidepressant activity.

EPS = extrapyramidal symptoms; NMS = neuroleptic malignant syndrome.

Pharmacologic Treatment
What is the Best Treatment for Bipolar Disorder?

• Treatment that results in the fewest, briefest, or mildest episodes and side effects; and does not induce switch
• Primary therapeutic objectives:
  – Treat acute mania, depression, mixed episodes to remission
  – Prevent recurrences of illness
  – Restore function
• Combination treatment often required during acute and maintenance treatment
Pharmacotherapy of Bipolar Depression

- Mood stabilizers, including lithium, valproate, and lamotrigine (risk of inefficacy and/or side effects)
- Certain atypical antipsychotics (risk of more severe side effects)
- Antidepressants, including SSRIs, SNRIs, and MAOIs (risks of inefficacy, hypo/manic switch)
- Novel treatments (risk of inefficacy)

MAOI = monoamine oxidase inhibitor; SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.
Antidepressants in Bipolar Disorders are either Bad or Neutral ...
Antidepressants Most Common Initial Treatments for Patients with Bipolar Disorder in United States in 2002–2003

N=7760.
*Anticonvulsant = 17%; Lithium = 8%.
Adjunctive Use of Antidepressants Conferred No Additional Benefit Than Mood Stabilizers Alone in Bipolar I or II Depression: 6-month primary effectiveness outcome

Bupropion, paroxetine, carbamazepine, and valproate are not FDA approved for the treatment of bipolar depression. Durable recovery = 8 weeks euthymia (no more than 2 depressive or 2 manic symptoms) over 6 months. Switch = DSM criteria for hypomania or mania or required treatment; mood stabilizer (MS) = lithium, carbamazepine, valproate, or any approved atypical; adjunctive antidepressant (AD) = bupropion or paroxetine.

Polarity Switches are Common with Adjunct Antidepressants

Patients with BD-I are More Likely to Have a Mood Switch with Adjunct Antidepressants

More Suicide Attempts during Antidepressant Monotherapy than with Mood Stabilizer

Lithium Decreases Risk of Suicide

N=339
Immune Genes Associated with Schizophrenia May Predict Poor Lithium Response in Patients with Bipolar Affective Disorder

Trends in the ORs for favorable treatment response to lithium for patients with BPAD in the low SCZ deciles (first to ninth) compared with patients in the highest SCZ PGS decile (10th), estimated at the most significant P value thresholds ($P<5 \times 10^{-2}$)(n=2586). In the cross-trait meta-GWAS, 15 genetic loci that may have overlapping effects on lithium treatment response and susceptibility to SCZ were identified. Functional pathway and network analysis of these loci point to the HLA antigen complex and inflammatory cytokines.

BPAD = bipolar affective disorder; OR = odds ratio; PGS = polygenic score; SCZ = schizophrenia.
Antidepressants in Bipolar Disorders are either Bad or Neutral ... 

Except When They are Good and Beneficial
Time to Relapse among Participants with Bipolar Disorder Who Discontinued Antidepressant Treatment Within 6 Months of Depressive Episode Remission or Continued Treatment for 6–12 Months or Beyond 12 Months

Long-Term Treatment with Antidepressants in BD-I and BD-II

Antidepressant Use in Bipolar Depression: ISBD Task Force Report

- Adjunctive use when there is a history of prior response
- Adjunctive use for maintenance if a patient relapses into depression after stopping the antidepressant
- Antidepressant monotherapy should be avoided in BD-I
- Avoided in BD-I or BD-II depression with ≥ 2 core manic symptoms
- Antidepressant should be completely avoided in manic and mixed episodes

ISBD = International Society for Bipolar Disorders.
Role of Atypical Antipsychotics in Bipolar Depression
Industry-Sponsored Acute Bipolar Depression Trials

- Monotherapy Quetiapine vs placebo 5 +
- Monotherapy Lamotrigine vs placebo 0 +
- Adjunctive Lamotrigine vs placebo 1 +
- Monotherapy Aripiprazole vs placebo 2 -/failed
- Mono/Adj Ziprasidone vs placebo 2 -/failed
- Adjunctive Armodafinil vs placebo 1 +/2 failed
- Adjunctive Levetiracetam vs placebo 1 -
- Monotherapy Olanzapine vs placebo 2 +
- Adjunctive Agomelatine vs placebo 2 -/failed
- Mono/Adj Lurasidone vs placebo 2 +/1 failed
- Monotherapy Lurasidone vs placebo (pediatric pts) 1 +
- Monotherapy Cariprazine vs placebo 2 +/1 failed/underpowered

Bipolar Depression: OFC Combination

Visit-wise Improvement from Baseline in MADRS (LOCF)

-20 -18 -16 -14 -12 -10 -8 -6 -4 -2 0 1 2 3 4 5 6 7 8

Week

PBO (n=355)
OLZ (n=351)
OFC (n=82)

*P<.05 vs PBO. †P<.05 vs OLZ.

LOCF = last observation carried forward; OLZ = olanzapine; OFC = olanzapine-fluoxetine combination; PBO = placebo.

Acute Bipolar Depression: Quetiapine BOLDER Trials

Values are least squares mean. †P<.01 vs placebo, ‡P<.001 vs placebo. QUE = quetiapine.

Bipolar Depression: Quetiapine XR
MADRS Mean Change from Baseline

Placebo (n=137)
Quetiapine XR 300 mg/day (n=133)

aP<.001 vs placebo; MITT, LOCF.
Bipolar Depression: Lurasidone Monotherapy

- 6-week trial of lurasidone or placebo
- Bipolar I depressed patients, with or without rapid cycling

Bipolar Depression: Add-on Lurasidone

6-week trial of lurasidone (20 to 120 mg/day) or placebo added to lithium or divalproex in bipolar I depression

MMRM: $P<.01$

Pediatric Patients (10 to 17 Years) with Bipolar Depression

LS Mean Change in CDRS-R Total Score

Baseline mean:

Placebo (n=170)  Lurasidone 20-80 mg/day (n=173)

Baseline mean:  58.6  59.2  ES=0.45

P<.05;  **P<.001;  ***P<.0001.

CDRS-R = Children’s Depression Rating Scale, Revised.

Bipolar I Depression: Cariprazine

ClinicalTrials.gov Identifier: NCT02670538.
Multi-site controlled trial in 571 patients suffering from bipolar depression, 141 in the placebo group and 140, 145, and 145 in the cariprazine 0.75-, 1.5-, and 3.0-mg/day groups.

CGI-S = Clinical Global Impressions severity subscale. Cariprazine 0.75 mg/day compared with placebo: *P < .05; **P < .01; ***P < .001. Cariprazine 1.5 mg/day compared with placebo: †P < .05; ††P < .01; †††P < .001. Cariprazine 3.0 mg/day compared with placebo: #P < .05; ##P < .01; ###P < .001.

Asenapine in Bipolar I Mixed Depressive Episodes

LS Mean Change from Baseline in MADRS Total Score

MADRS > 20, DSM-IV mixed state, BL MADRS = 24–26

*Error bars indicate standard error. *P<.05 vs placebo; †P<.05 vs olanzapine.
Antipsychotics: Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>ARI</th>
<th>ASE</th>
<th>CLZ</th>
<th>ILE</th>
<th>LUR</th>
<th>OLZ</th>
<th>QTP</th>
<th>RIS</th>
<th>ZIP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metabolic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight gain</td>
<td>+/0</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>+/0</td>
<td>+++</td>
<td>++</td>
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<td>Dyslipidemia</td>
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<td>Glucose dysregulation</td>
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<td>Somnolence/sedation</td>
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ARI = aripiprazole; ASE = asenapine; CLZ = clozapine; ILE = iloperidone; LUR = lurasidone; OLZ = olanzapine; QTP = quetiapine; RIS = risperidone; ZIP = ziprasidone; +/0 = minimal risk; ± = equivocal; DD = dose dependent; ISF = insufficient data.
Novel Treatments for Bipolar Depression
Bright Light as Adjunct Treatment of Bipolar Depression

- Significant difference in remission rates between the active treatment group (68.2%) and the inactive treatment group (22.2%) (OR=7.50, 95% CI=1.80, 31.28, \( P = .003 \); adjusted OR=12.64, 95% CI=2.16, 74.08, \( P = .004 \))

- Bipolar I and II depressed patients were randomly assigned to treatment with either 7000-lux bright white light or 50-lux dim red placebo light (N=23 for each group)

59 adults with BD-I or BD-II in a major depressive episode and receiving a stable pharmacologic regimen with HAM-D-17 scores > 17.

HAM-D-17 = 17-item Hamilton Depression Rating Scale.
Adjunct Ketamine Helps Anxious and Non-Anxious Bipolar Depression

36 patients with anxious (n=21) and non-anxious (n=15) treatment-resistant bipolar depression (types I and II; concurrently treated with either lithium or valproate) received a single infusion of ketamine (0.5 mg/kg) over 40 minutes. Significant drug effects (all \( P < .001 \)) suggested that both anxious and non-anxious groups had an antidepressant response to ketamine.

Observed mean reduction in symptom severity in the mITT sample (n=20). **P≤.01 associated with a paired t-test comparing MADRS score at a given time point to baseline. Change in depression symptom severity over time for treatment responders (n=10) and non-responders (n=10). The mean minocycline dose at study end was 256 mg daily (Range: 100–300 mg, SD: 71 mg).

Improvement in Cognition with Adjunct Minocycline Treatment in Bipolar I and II Depression

8-week, open-label study with adjunctive minocycline (100 mg bid).

In Conclusion

• Bipolar depression is a tremendous health burden in primary care patients
• Screening patients presenting with depressive symptoms, anxiety symptoms, insomnia symptoms, and substance/alcohol use is critical
• Both nonpharmacologic and pharmacologic treatments are recommended
• Wise treatment selection, along with thorough monitoring for efficacy and tolerability is indicated