Bipolar Disorder

Andrew A. Nierenberg, MD
Thomas P. Hackett, MD Endowed Chair in Psychiatry at MGH
Director, Dauten Family Center for Bipolar Treatment Innovation
Associate Director, Depression Clinical and Research Program
Massachusetts General Hospital
Professor of Psychiatry, Harvard Medical School
### Andrew A. Nierenberg, MD

**Disclosure Statement**

<table>
<thead>
<tr>
<th>Employee Of</th>
<th>Massachusetts General Hospital</th>
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<tr>
<td>Consultant For</td>
<td>Abbott Laboratories, Astra Zeneca, Basilea, BrainCells Inc., Bristol-Myers Squibb, Cephalon, Clintara, Corcept, Eli Lilly &amp; Co., Forest, Genaissance, Genentech, GlaxoSmithKline, Innapharma, Janssen Pharmaceutica, Jazz Pharmaceuticals, Lundbeck, Medavante, Merck, Myriad, Novartis, PamLabs, PGx Health, Pfizer, Roche, Sepracor, Schering-Plough, Shire, Somerset, Sunovion, Takeda, Targacept, Teva</td>
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<td>Grant Support From</td>
<td>AFSP, AHRQ, Bristol-Myers Squibb, Cederroth, Cyberonics, Forest Pharmaceuticals, GlaxoSmithKline, Janssen Pharmaceutica, Lichtwer Pharma, Eli Lilly, NARSAD, NIMH, PCORI, Pfizer, Shire, Stanley Foundation, Takeda, Wyeth-Ayerst</td>
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<tr>
<td>Honoraria From</td>
<td>MGH Psychiatry Academy in the past 3 years (Prior to 3 years ago, honoraria from Bristol-Myers Squibb, Cyberonics, Forest Pharmaceuticals, GlaxoSmithKline, Eli Lilly, Shire, Wyeth-Ayerst), No speaker bureaus since 2003</td>
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<table>
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<tr>
<th>Other Income</th>
<th>MBL Publishing for past services as Editor-in-chief of CNS Spectrums; Slack Inc. for services as Associate Editor of Psychiatric Annals; Editorial Board, <em>Mind Mood Memory, Belvoir Publications</em></th>
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</tr>
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</table>
“...from the brain, and from the brain only, arise our pleasures, joy, laughter and jests, as well as our sorrows, pains, griefs, and tears.”

Hippocrates Circa 400 BCE
AN UNQUIET MIND
A MEMOIR OF MOODS AND MADNESS

Kay Redfield Jamison

"An invaluable memoir of maniac depression, at once medically knowledgeable, deeply human and beautifully written...at times poetic, at times straightforward, always unashamedly honest."

The New York Times Book Review
Bipolar Disorder Fast Facts

• Among top 10 causes of disability worldwide
  • 50% with onset before the age of 25
    • Costs $200 billion per year
Bipolar Disorder Fast Facts

• Types
  • Type I with manic episodes
  • Type II with hypomanic episodes
• 90% have other problems
  • Substance use disorders
  • Anxiety disorders
• 1.5 to 2.1 times more likely to have chronic physical conditions
• Loss of 8 – 25 years of life

Scott et al. JAMA Psychiatry 2016;73:150-158
DSM-V Bipolar I Disorder Epidemiology

• Lifetime prevalence 2.1%
  • ~4,884,000
• 12-month prevalence 1.5%
  • ~3,679,000

Blanco et al., Journal of Psychiatric Research 84 (2017) 310e317
Phenomenology
Major Depressive Episodes: Psychological Symptoms

- Depressed mood
- Irritability
- Anxiety/nervousness
- Reduced concentration
- Lack of interest/motivation
- Inability to enjoy things
- Lack of pleasure
- Hypersensitivity to rejection/criticism
- Perfectionism/Obsessiveness
- Indecisiveness
- Pessimism/hopelessness
- Feelings of helplessness
- Cognitive distortions
- Feeling stressed
- Low self-esteem/feelings of worthlessness
- Excessive guilt
- Thoughts of death or suicide
- Thoughts of hurting other people

Major Depressive Disorder: Behavioral Symptoms

- Crying spells
- Interpersonal friction/confrontation
- Anger attacks/outbursts
- Avoidance of anxiety-provoking situations
- Reduced productivity
- Social withdrawal
- Avoidance of emotional and sexual intimacy
- Reduced leisure-time activities
- Development of rituals or compulsions
- Workaholic behaviours
- Substance use/abuse
- Self-sacrifice/victimisation
- Self-cutting/mutilation
- Suicide attempts/gestures
- Violent/assaultive behaviour

Major Depressive Disorder: Common Somatic/Physical Symptoms

- Fatigue
- Leaden feelings in arms or legs
- Sleeping too little/insomnia
- Sleeping too much/hypersomnia
- Decreased appetite
- Weight loss
- Increased appetite
- Weight gain

- Reduced libido/arousal difficulties
- Erectile dysfunction
- Delayed orgasm/inability to achieve orgasm
- Headaches
- Muscle tension
- Gastrointestinal upset
- Heart palpitations
- Burning or tingling sensations

Bipolar Disorder:
Manic/Hypomanic Symptoms

- Increased energy
- Euphoria
- Grandiosity
- Irritability/Decreased frustration tolerance
- Racing thoughts
- Rapid speech
- Decreased need for sleep
- Unconcerned with consequences
- Impulsive
- Cognitive impairment

- Poor judgement
- Unrealistic optimism
- Increased libido
- Hallucinations or delusions
- Disorganized thinking
- Decreased productivity
- Increased productivity
- Sharper, clearer thinking
- Increased creativity
- Entrepreneurial
Response, Remission, Recovery, Relapse, Recurrence:
Phases of Treatment of Bipolar Disorder

Vieta et al. Nature Reviews Disease Primer 2018
b

Mania

Hypomania

Euthymia

Subthreshold depression

Major depression

Mixed features

Time

Vieta et al. Nature Reviews Disease Primer 2018
Bipolar: Real World - Highly Recurrent

- \( N = 3074 \)
- 1A all subjects
- 2B those with at least five inpatient episodes.
DSM-V Bipolar I Psychiatric Comorbid Conditions

Blanco et al., Journal of Psychiatric Research 84 (2017) 310e317
DSM-IV Bipolar I Cardiovascular Comorbid Conditions

Adjusted Odds Ratio

http://www.theguardian.com/commentisfree/2015/mar/04/bipolar-disorder-wouldnt-want-to-fix-mind
Depressive Symptoms Predominate in BPI

N=146
12.8 years of follow up

Judd et al. Arch Gen Psych 59:530-537, 2002
Depressive Symptoms Predominate in BPII

Judd et al. Arch Gen Psych 60:261-269, 2003

N=86
13.4 years of follow up
Suicide

Men: 36.6 per 100,000
Women: 21.7 per 100,000

Jimi Hendrix
Kurt Cobain
David Foster Wallace

Schaffer et al. ANZJP 49:785-802;2015
Bipolar vs Unipolar Depression

- Early age of onset
- More episodes (> 5)
- Probably Myth
  - More atypical symptoms
  - Hyperphagia and hypersomnia
- Probably True:
  - More psychosis; More frequently postpartum;
  - More psychomotor retardation

Real World Outcomes

Duration of Mood Episodes

Bipolar Disorder as a Mitochondrial Disease

Ana C. Andreaza, Angela Duong, and L. Trevor Young

GENETIC ALTERATIONS IN BD
- Changes in nuclear and mitochondrial DNA

MITOCHONDRIAL DYSFUNCTION IN BD
- Glycolysis:
  - ↑ lactate,
  - ↓ pH
- Oxidative Phosphorylation:
  - ↓ complex I subunits;
  - ↓ phosphocreatine
Bipolar Treatment
Vieta et al. Nature Reviews Disease Primer 2018
More antipsychotics, less mood stabilizers

FIGURE 1. Prescribing trends for second-generation antipsychotics (SGAs) and mood stabilizers in the treatment of bipolar disorder in office-based visits to psychiatrists, 1997–2016.

Data are from the National Ambulatory Medical Care Survey, 1997–2016.

# Anti-manic Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trials</th>
<th>Subjects</th>
<th>Mean Dose (mg/day)</th>
<th>Response (RR [95% CI])</th>
<th>Dropout (RR [95% CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>4</td>
<td>976</td>
<td>3.50 ± 0.00</td>
<td>2.66 [1.86–3.81]</td>
<td>0.60 [0.38–0.93]</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>2</td>
<td>427</td>
<td>700 ± 80.0</td>
<td>2.64 [1.60–4.30]</td>
<td>0.88 [0.51–1.56]</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>9</td>
<td>1663</td>
<td>9.45 ± 5.65</td>
<td>2.47 [1.89–3.25]</td>
<td>0.74 [0.53–1.04]</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>4</td>
<td>1198</td>
<td>7.12 ± 1.89</td>
<td>2.33 [1.56–3.53]</td>
<td>1.04 [0.63–1.73]</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>10</td>
<td>2031</td>
<td>13.4 ± 1.92</td>
<td>2.33 [1.82–3.02]</td>
<td>0.47 [0.35–0.63]</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>8</td>
<td>1982</td>
<td>22.5 ± 4.74</td>
<td>2.07 [1.56–2.77]</td>
<td>0.68 [0.48–0.96]</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>6</td>
<td>1306</td>
<td>612 ± 118</td>
<td>2.05 [1.49–2.85]</td>
<td>0.63 [0.41–0.94]</td>
</tr>
<tr>
<td>Valproate</td>
<td>7</td>
<td>1299</td>
<td>1431 ± 954</td>
<td>2.05 [1.48–2.87]</td>
<td>0.67 [0.47–0.97]</td>
</tr>
<tr>
<td>Lithium</td>
<td>14</td>
<td>1981</td>
<td>1260 ± 251</td>
<td>1.92 [1.49–2.49]</td>
<td>0.94 [0.69–1.29]</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>5</td>
<td>1157</td>
<td>7.50 ± 3.87</td>
<td>1.72 [1.08–2.74]</td>
<td>0.60 [0.33–1.06]</td>
</tr>
<tr>
<td>Asenapine</td>
<td>4</td>
<td>841</td>
<td>18.3 ± 0.14</td>
<td>1.61 [1.03–2.54]</td>
<td>0.88 [0.51–1.53]</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>4</td>
<td>839</td>
<td>124 ± 7.21</td>
<td>1.47 [1.06–2.04]</td>
<td>0.93 [0.61–1.41]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment type</th>
<th>Trials (n)</th>
<th>Response rates (%) [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotics</td>
<td>37</td>
<td>49.7 [47.0–52.5]</td>
</tr>
<tr>
<td>Lithium carbonate</td>
<td>7</td>
<td>49.1 [42.8–55.3]</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>8</td>
<td>48.4 [40.2–56.6]</td>
</tr>
<tr>
<td>All drugs</td>
<td>52</td>
<td>49.5 [47.3–51.7]</td>
</tr>
<tr>
<td>Placebo</td>
<td>60</td>
<td>31.6 [29.3–33.8]</td>
</tr>
<tr>
<td>Overall drug/placebo</td>
<td>52</td>
<td>1.57 [1.50–1.64]</td>
</tr>
</tbody>
</table>
**Figure 6**: Ranking of antimanic drugs according to primary outcomes: efficacy (as continuous outcome) and dropout rate

Red colour represents worst treatment and green represents best treatment in a qualitative approach. ARI=aripiprazole. ASE=asenapine. CBZ=carbamazepine. VAL=valproate. GBT=gabapentin. HAL=haloperidol. LAM=lamotrigine. LIT=lithium. OLZ=olanzapine. PBO=placebo. QTP=quetiapine. RIS=risperidone. TOP=topiramate. ZIP=ziprasidone.
Bipolar Antidepressant Treatments

- Olanzapine/Fluoxetine Combination (OFC)
  - Zyprexa/Prozac
- Quetiapine - Seroquel
- Lurasidone – Latuda
- Cariprazine – Vraylar
- (Lamotrigine)
- (No antidepressants approved for bipolar depression)
- Electroconvulsive therapy
- Repetitive transcranial magnetic stimulation (rTMS)?
Antidepressant prescriptions persist


Data are from the National Ambulatory Medical Care Survey, 1997–2016. AD = antidepressant; AP = antipsychotic; MS = lithium and antiepileptic mood stabilizers.

Mechanisms of Action Differentiates Effective from Non-Effective Treatments for BP Depression

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Action</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha 1</td>
<td>Antagonist</td>
<td>Increase NE</td>
</tr>
<tr>
<td>D1</td>
<td>Antagonist</td>
<td>Decrease DA</td>
</tr>
<tr>
<td>H1</td>
<td>Antagonist</td>
<td>Decrease Histamine</td>
</tr>
<tr>
<td>5HT2A</td>
<td>Antagonist</td>
<td>Increase 5HT</td>
</tr>
<tr>
<td>Muscarinic</td>
<td>Antagonist</td>
<td>Decrease Acetylcholine</td>
</tr>
<tr>
<td>D2</td>
<td>Antagonist</td>
<td>Mixed effects</td>
</tr>
<tr>
<td>D3</td>
<td>Antagonist</td>
<td>Increase DA</td>
</tr>
<tr>
<td>NE Reuptake</td>
<td>Inhibition</td>
<td>Increase NE</td>
</tr>
<tr>
<td>5HT1A</td>
<td>Agonism</td>
<td>Increase 5HT</td>
</tr>
</tbody>
</table>

Psychotherapy

- Cognitive behavioral therapy (CBT)
- Mindfulness based cognitive therapy (MBCT)
- Unified protocol for emotional regulation
- Dialectical behavioral therapy (DBT)
- Lifestyle interventions
Potential new treatments

- Ketamine
- Pioglitazone
- Bezafibrate
- Minocycline
- N-acetylcysteine
- Pramipexole
- Nicotinamide riboside
- Candesartan
Summary

• Bipolar disorder
  • Depressive and manic/hypomaniac episodes
  • Complex chronic course
  • Comorbid conditions
  • Complex pathophysiology

• Treatments
  • Antimanic
  • Antidepressant
  • Maintenance