A MIXED BAG:
MANAGING BIPOLAR DEPRESSION

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Learning Objectives

• Screen for mixed features in all patients presenting with mood episodes

• Implement treatment strategies for patients with depressive episodes with mixed features
Reliability of MDD Diagnosis Is Poor

<table>
<thead>
<tr>
<th>Interclass kappa range</th>
<th>Reliability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.60-0.79</td>
<td>Very good</td>
</tr>
<tr>
<td>0.40-0.59</td>
<td>Good</td>
</tr>
<tr>
<td>0.20-0.39</td>
<td>Questionable</td>
</tr>
<tr>
<td>&lt;0.20</td>
<td>Poor</td>
</tr>
</tbody>
</table>

Limitation of cross-sectional diagnosis can be mitigated by assessing:
- Longitudinal factors
  - Age of onset
  - Course of illness
- Response to treatment
- Family history

GAD, generalized anxiety disorder.
Mixed Features Very Common: Look for the Four ‘A’s: Anxiety, Agitation, Anger, Attentional (Disturbance)

Core symptoms
manic depressive

Elevated mood
>3 <5

Elevated mood +
depressed mood or loss of interest
>3 >5

Depressed mood or loss of interest
<3 >5

DSM-IV-TR
Manic
Mixed
Depressive

DSM-5
Manic
Manic with mixed features
Depressive with mixed features
Depressive

Core symptoms
manic depressive

Elevated mood + energy
>3 <5

Elevated mood + energy
>3 >5

Depressed mood or loss of interest
>3 >5

Depressed mood or loss of interest
<3 >5
Mixed features specifier (MFS) was operationalized as a score ≥1 on 3 or more select items on the Young Mania Rating Scale (YMRS) or ≥1 on 3 select items of the Montgomery-Åsberg Depression Rating Scale (MADRS) or Hamilton Depression Rating Scale (HAMD-17) during an index major depressive episode (MDE) or hypo/manic episode, respectively.

*Data from a post hoc analysis of participants who met criteria for a current mood episode as part of MDD (n=506) or BD (BD-I: n=216, BD-II: n=130)

Can Inducible Pluripotent Stem Cells Guide Research Into Causes and Cures?

Cumulative Effect of Previous Bipolar Manic Episodes on Neurocognition

Increasing number of manic episodes associated with poorer neurocognition
Differences in Global Cognition in BD-I and BD-II

Bora E. J Affect Disord. 2018;229:125-134.
Differences in Global Cognition in PBD and NPBD

<table>
<thead>
<tr>
<th>Studies</th>
<th>Estimate (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoff 2013</td>
<td>0.210 (0.604, 0.504)</td>
</tr>
<tr>
<td>Ancin 2013</td>
<td>0.180 (0.159, 0.813)</td>
</tr>
<tr>
<td>Simonsen 2011</td>
<td>0.430 (0.077, 0.783)</td>
</tr>
<tr>
<td>Molina 2015</td>
<td>-0.160 (-0.453, 0.253)</td>
</tr>
<tr>
<td>Nitburg 2016</td>
<td>0.200 (-0.192, 0.592)</td>
</tr>
<tr>
<td>Szoke 2008</td>
<td>0.070 (-0.352, 0.462)</td>
</tr>
<tr>
<td>Demnko 2016</td>
<td>0.010 (-0.441, 0.461)</td>
</tr>
<tr>
<td>Lahera 2008</td>
<td>-0.160 (-0.581, 0.311)</td>
</tr>
<tr>
<td>Brissos 2011</td>
<td>0.230 (-0.269, 0.790)</td>
</tr>
<tr>
<td>Glahn 2007</td>
<td>0.220 (-0.250, 0.690)</td>
</tr>
<tr>
<td>Martinez-Aran 2008</td>
<td>0.370 (-0.129, 0.860)</td>
</tr>
<tr>
<td>Bora 2007</td>
<td>0.190 (-0.360, 0.710)</td>
</tr>
<tr>
<td>Lu 2002</td>
<td>0.210 (-0.300, 0.720)</td>
</tr>
<tr>
<td>Savitz 2009</td>
<td>0.270 (-0.239, 0.808)</td>
</tr>
<tr>
<td>Thaler 2013</td>
<td>0.400 (-0.183, 0.988)</td>
</tr>
<tr>
<td>Allen 2010</td>
<td>0.150 (-0.433, 0.738)</td>
</tr>
<tr>
<td>Lee 2013</td>
<td>0.070 (-0.657, 0.697)</td>
</tr>
<tr>
<td>Selva 2007</td>
<td>0.340 (-0.346, 1.026)</td>
</tr>
<tr>
<td>Glahn 2006</td>
<td>0.650 (-0.154, 1.454)</td>
</tr>
<tr>
<td>Garcia 2015</td>
<td>0.220 (-0.629, 1.063)</td>
</tr>
<tr>
<td>Jimenez Lopez 2017</td>
<td>0.230 (-0.102, 0.662)</td>
</tr>
</tbody>
</table>

Overall (I²=0 %, P=0.961) 0.169 (0.090, 0.268)

Bora E. J Affect Disord. 2018;229:125-134.
ADHD in Adults with Bipolar Disorder and Major Depressive Disorder: Results From the International Mood Disorders Collaborative Project

Percentage of cases meeting criteria for lifetime comorbid ADHD

Diagnosed Mood Disorder

MDD

BDI/II

Is antidepressant resistance a predictor of bipolar disorder?

Change in diagnosis from MDD to BP with stratified responses to antidepressants during an 8-year follow-up (n = 1,485)

Rates of diagnosis change from MDD to bipolar disorder

MDD = major depressive disorder

High Prevalence of Inflammation in Depression

- Cytokines = non-antibody proteins released by cells on contact with antigens
- Cytokines induce depressive symptoms and HPA axis activation
- Depressed patients have high levels of cytokines


**Meta-analysis of cytokine levels in MDD**

- IL-1β (14 / 1000)
- TNF-α (31 / 2476)
- CRP (20 / 1425)
- IL-6 (13 / 2022)
Mood Disorders, Accelerated Aging, and Inflammation: Is the Link Hidden in Telomeres?

Obesity and Mental Illness Result in Premature Brain Aging

Functional Connections Showing Significant Differences Between Neonates Born From Normal & High BMI Mothers

Expression of Insulin and Dopamine Genes in the Prefrontal Cortex Altered in Individuals Who Are Obese: Implications for Cognition and Reward

Fig. 1. Gene Expression in the Dorsolateral Prefrontal Cortex. Mean standardized expression values of insulin and dopamine signaling genes in the dorsolateral prefrontal cortex, according to group (HC vs. MI) and BMI. For illustration purposes, BMI was dichotomized as obesity (BMI ≥ 30 kg/m²) and non-obesity (BMI < 30 kg/m²). HC: healthy controls; MI: mental illness.

Premature Aging in Bipolar Disorder Moderated by BMI: Evidence Gathered From Immune Cells

C-Reactive Peptide is Elevated in Bipolar Disorder: A Meta-Analysis


Figure 2. Meta-Analysis of C-Reactive Protein Levels in Bipolar Disorder

<table>
<thead>
<tr>
<th>Study</th>
<th>Bipolar Disorder</th>
<th>Control</th>
<th>SMD</th>
<th>95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Aksoy et al, 2010</td>
<td>30</td>
<td>3.74000</td>
<td>2.70000</td>
<td>30</td>
<td>2.43000</td>
</tr>
<tr>
<td>Cunha et al, 2008</td>
<td>80</td>
<td>5.81000</td>
<td>8.99000</td>
<td>32</td>
<td>1.60000</td>
</tr>
<tr>
<td>Dickerson et al, 2007</td>
<td>122</td>
<td>4.80000</td>
<td>6.97000</td>
<td>165</td>
<td>4.40000</td>
</tr>
<tr>
<td>Dickerson et al, 2013</td>
<td>192</td>
<td>1.32000</td>
<td>1.80000</td>
<td>228</td>
<td>0.99100</td>
</tr>
<tr>
<td>Fontoura et al, 2012</td>
<td>28</td>
<td>0.35700</td>
<td>0.46000</td>
<td>12</td>
<td>0.10000</td>
</tr>
<tr>
<td>Hope et al, 2011</td>
<td>112</td>
<td>1.20000</td>
<td>2.50000</td>
<td>239</td>
<td>0.80000</td>
</tr>
<tr>
<td>Huang et al, 2007</td>
<td>13</td>
<td>5.80000</td>
<td>9.60000</td>
<td>31</td>
<td>1.50000</td>
</tr>
<tr>
<td>Hung et al, 2007</td>
<td>15</td>
<td>0.50000</td>
<td>0.70000</td>
<td>14</td>
<td>0.38200</td>
</tr>
<tr>
<td>Tsai et al, 2012</td>
<td>33</td>
<td>0.00358</td>
<td>0.00298</td>
<td>33</td>
<td>0.00140</td>
</tr>
<tr>
<td>Vuksan-Cusa et al, 2013</td>
<td>60</td>
<td>4.24000</td>
<td>4.09000</td>
<td>59</td>
<td>2.59000</td>
</tr>
<tr>
<td>Wadee et al, 2002</td>
<td>45</td>
<td>11.42200</td>
<td>18.24000</td>
<td>45</td>
<td>4.67800</td>
</tr>
</tbody>
</table>

Overall effect                | 730              | 888           | 0.39  | 0.24 to 0.55     | 100%   |

P = .0001
Heterogeneity: $I^2 = 47.6\%$
$\tau^2 = 0.0291$, $P = .0394$

Abbreviations: CI = confidence interval, SD = standard deviation, SMD = standardized mean difference.
Insulin: Endogenous Monoamine Oxidase Inhibitor and Brain Trophic Factor

Change in Course of Bipolar Illness in Six Patients Before & After Development of Comorbid Insulin Resistance

Step 1: Risk stratification by disease process (Table 11-2).
Step 2: Assess all CV risk factors. If there are ≥2 comorbidities, move tier II patient to tier I for subsequent management.
Step 3: Tier-specific treatment goals/cut point defined.
Step 4: Initial therapy: For tier I, initial management is therapeutic lifestyle change PLUS disease specific management (Table 11-3).
Step 5: For tier II, if goals are not met, consider medication per risk factor specific recommendations in these guidelines.


CV Risk Factors/Comorbidities
- Family history of early CVD in expanded first-degree pedigree (male ≤55 y; female ≤65 y)
- Fasting lipid profile
- Smoking history
- BP, 3 separate occasions, interpreted for age/sex/height percentile
- FG
- Diet, physical activity/exercise history

Tier I: High Risk
- BMI ≤85th percentile for age/sex
- BP ≤90th percentile for age/sec/height
- Lipids (mg/dL): LDL-C ≤100, TG <90, non-HDL <120
- FG <100 mg/dL, HbA1c <7%

Tier II: Moderate Risk
- BMI ≤90th percentile for age/sex
- BP ≤95th percentile for age/sec/height
- Lipids (mg/dL): LDL-C ≤130, TG <130, non-HDL-C <140
- FG ≤10 mg/dL, HbA1c <7%

Tier I: High Risk
- Diabetes mellitus, type 1 and type 2
- Chronic kidney disease/end-stage renal disease/post-kidney
- Post-heart transplant
- Kawasaki disease with current coronary artery aneurysms

Tier II: Moderate Risk
- Kawasaki disease with regressed coronary aneurysms
- Chronic inflammatory disease
- HIV
- Nephritic syndrome
- Major depressive disorder or bipolar disorder

MDD and BD Are Independent Risk Factors for Heart Disease
Better Treatment of BD Depression and Avoidance of Metabolic Adverse Events Identified By Patients As Greatest Unmet Need

- Better treatment of depression
- Lower risk of weight gain
- Prevention of relapse in depression
- Improved functionality/quality of life
- Lower risk of sleeping difficulties
- Lower risk of suicidal thoughts
- Lower risk of diabetes
- Lower risk of muscle stiffness
- Lower risk of sedation

# Bipolar I Disorder: FDA-Approved Treatments

<table>
<thead>
<tr>
<th>Year</th>
<th>Agent</th>
<th>Year</th>
<th>Agent</th>
<th>Year</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1973</td>
<td>Chlorpromazine</td>
<td>2006</td>
<td>Quetiapine (XR; 2008)</td>
<td>2003</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>1994</td>
<td>Divalproex (ER; 2005)</td>
<td>2013</td>
<td>Lurasidone*</td>
<td>2004</td>
<td>Olanzapine</td>
</tr>
<tr>
<td>2000</td>
<td>Olanzapine*</td>
<td>2003</td>
<td>Risperidone*</td>
<td>2005</td>
<td>Aripiprazole*</td>
</tr>
<tr>
<td>2003</td>
<td>Risperidone*</td>
<td>2004</td>
<td>Quetiapine (XR; 2008)*</td>
<td>2009</td>
<td>Risperidone LAI*</td>
</tr>
<tr>
<td>2004</td>
<td>Ziprasidone</td>
<td>2004</td>
<td>Aripiprazole*</td>
<td>2009</td>
<td>Ziprasidone (adjunct)</td>
</tr>
<tr>
<td>2004</td>
<td>Carbamazepine ER</td>
<td>2009</td>
<td>Asenapine*</td>
<td>2017</td>
<td>Asenapine</td>
</tr>
<tr>
<td>2009</td>
<td>Asenapine*</td>
<td>2015</td>
<td>Cariprazine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adjunctive and monotherapy
LAI: long-acting injectable formulation

Figure 1. Clinical Response (A), Remission (B), and Switch (C) in Randomized Controlled Trials Comparing Antidepressant Versus Placebo for Bipolar Depression

A. Clinical Response

<table>
<thead>
<tr>
<th>Study/Subcategory</th>
<th>Antidepressant, n/N</th>
<th>Placebo, n/N</th>
<th>Relative Risk (fixed), 95% CI</th>
<th>Weight, %</th>
<th>Relative Risk (fixed), 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohn et al (1989)</td>
<td>30/59</td>
<td>5/27</td>
<td></td>
<td>5.13</td>
<td>2.75 (1.20–6.30)</td>
</tr>
<tr>
<td>Shelton and Stahl (2004)</td>
<td>5/20</td>
<td>3/10</td>
<td></td>
<td>2.99</td>
<td>0.83 (0.25–2.80)</td>
</tr>
<tr>
<td>Tohen et al (2003)</td>
<td>46/82</td>
<td>137/351</td>
<td></td>
<td>38.77</td>
<td>1.44 (1.14–1.81)</td>
</tr>
<tr>
<td>Amsterdam et al (2005)</td>
<td>3/17</td>
<td>1/8</td>
<td></td>
<td>1.02</td>
<td>1.41 (0.17–11.54)</td>
</tr>
<tr>
<td>Sachs et al (2007)</td>
<td>58/163</td>
<td>71/169</td>
<td></td>
<td>52.09</td>
<td>0.85 (0.65–1.11)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>341</td>
<td>565</td>
<td></td>
<td>100.00</td>
<td>1.18 (0.99–1.40)</td>
</tr>
</tbody>
</table>

Total events: 142 (antidepressant), 217 (placebo)
Test for heterogeneity: $\chi^2 = 12.81$ ($P = .01$), $I^2 = 68.8\%$
Test for overall effect: $Z = 1.86$ ($P = .06$)

Antidepressants are not recommended as monotherapy treatment in bipolar depression

Lurasidone Versus Placebo

Mean dose = 36.2 mg/day

Montgomery-Åsberg Depression Rating Scale Total Score

- LS Mean in Change From Baseline
- Baseline, Week 1, Week 2, Week 3, Week 4, Week 5, Week 6

- Lurasidone (N=108)
- Placebo (N=100)

ES, effect size; LS, least squares

Lurasidone Efficacious in Bipolar Depression with Subsyndromal Hypomania


**MADRS responder rate (LOCF-endpoint) (%)**

- **Subsyndromal hypomania group 1**
  - Lurasidone: 51.1%
  - Placebo: 32.2%

- **Subsyndromal hypomania group 2**
  - Lurasidone: 51.1%
  - Placebo: 31.1%

- **No subsyndromal hypomania**
  - Lurasidone: 53.2%
  - Placebo: 27.8%

**P < .01.**

C-Reactive Protein and Response to Lurasidone in Patients With Bipolar Depression

Fig. 1. Baseline C-Reactive Protein Level and Week 6 Change in Montgomery-Asberg Depression Rating Scale (MADRS) Score and Clinical Global Impression Bipolar Version, Severity of Illness (CGI-BP-S) Score (Depression) Associated with Lurasidone (vs. Placebo) Treatment. p-values were estimated based on MMRM model adjusted for baseline MADRS score and study site; p < 0.01 for both the log-transformed and stratified CRP-by-lurasidone (vs. placebo) interaction effect on week 6 change in MADRS score, p < 0.01 for both the log-transformed and stratified CRP-by-lurasidone (vs. placebo) interaction effect on week 6 change in CGI-BP-S score (Depression). Least squares mean change in MADRS and CGI-BP-S scores for lurasidone (20-60 mg/d or 80-120 mg/d) comparisons with placebo at week 6 when study participants were stratified into low, medium and high pre-treatment wr-CRP groups. Lurasidone, lurasidone 20-60 mg/d or 80-120 mg/d; CGI-BP-S Score (Depression), Clinical Global Impression Bipolar Version, Severity of Illness score (Depression); wr-CRP, wide-range c-reactive protein; BMI, body mass index; d, effect size (lurasidone vs. placebo).
Log(CRP)-Treatment interaction $P < 0.05$.

- **Lurasidone**
- **Placebo**

### Baseline CRP Levels

- **$\leq 2$ mg/L**
- **2.1 - 5.0 mg/L**
- **$> 5$ mg/L**

<table>
<thead>
<tr>
<th>Baseline CRP Levels</th>
<th>Lurasidone (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\leq 2$ mg/L</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>2.1 - 5.0 mg/L</td>
<td>55</td>
<td>45</td>
</tr>
<tr>
<td>$&gt; 5$ mg/L</td>
<td>60</td>
<td>40</td>
</tr>
</tbody>
</table>

**NNT** = 3.8

**NNT** = 2.6

***

Fig. 2. Baseline wr-CRP and Week 6 Response Rate Associated with Lurasidone (vs. Placebo) Treatment.

Both cariprazine dosages significantly reduced MADRS total scores from baseline to Week 6 compared to placebo.

MADRS=Montgomery-Åsberg Depression Rating Scale; LSMD=least-squares mean difference; CI=confidence interval; LS=least squares.

A Mixed-effects model for repeated measures was used for LS mean.

*P<0.05 for cariprazine 1.5 mg/d compared with placebo; **P<0.05 for cariprazine 3.0 mg/d compared with placebo (unadjusted)
Cariprazine for Acute Bipolar Depression:

RGH-MD-56 Study Design: Positive Study

A. MADRS total score

B. CGI-S score

### Psychostimulants: Antidepressant Effect Size Low Without Mood Destabilization


<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Treatment Total Events</th>
<th>Placebo Events</th>
<th>Placebo Total Events</th>
<th>Treatment Weight</th>
<th>Placebo Weight</th>
<th>Treatment Odds Ratio M-H, Random, 95% CI</th>
<th>Placebo Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3.2.1 MDD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abolfazil 2011</td>
<td>8</td>
<td>22</td>
<td>0</td>
<td>22</td>
<td>0.9%</td>
<td></td>
<td>26.38 [1.41, 492.81]</td>
<td></td>
</tr>
<tr>
<td>Fava 2005</td>
<td>68</td>
<td>156</td>
<td>55</td>
<td>152</td>
<td>23.1%</td>
<td></td>
<td>1.36 [0.86, 2.15]</td>
<td></td>
</tr>
<tr>
<td>Lavretsky 2015</td>
<td>29</td>
<td>48</td>
<td>20</td>
<td>48</td>
<td>9.5%</td>
<td></td>
<td>2.14 [0.95, 4.83]</td>
<td></td>
</tr>
<tr>
<td>Michelson 2007</td>
<td>29</td>
<td>72</td>
<td>28</td>
<td>74</td>
<td>13.4%</td>
<td></td>
<td>1.11 [0.57, 2.15]</td>
<td></td>
</tr>
<tr>
<td>Patkar 2006</td>
<td>4</td>
<td>30</td>
<td>1</td>
<td>30</td>
<td>1.4%</td>
<td></td>
<td>4.46 [0.47, 42.51]</td>
<td></td>
</tr>
<tr>
<td>Trivedi 2013</td>
<td>37</td>
<td>88</td>
<td>33</td>
<td>85</td>
<td>15.4%</td>
<td></td>
<td>1.14 [0.62, 2.10]</td>
<td></td>
</tr>
<tr>
<td>Weintraub 2010</td>
<td>3</td>
<td>28</td>
<td>0</td>
<td>27</td>
<td>0.8%</td>
<td></td>
<td>7.55 [0.37, 153.42]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>444</strong></td>
<td><strong>438</strong></td>
<td></td>
<td></td>
<td><strong>64.5%</strong></td>
<td></td>
<td><strong>1.50 [1.02, 2.21]</strong></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>178</td>
<td></td>
<td>137</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau^2 = 0.07; Chi^2 = 8.16, df = 6 (p = 0.23), I^2 = 27%
Test for overall effect: Z = 2.06 (P = 0.04)

| 3.2.2              |                |                       |               |                     |                 |              |                                          |                                          |
| Calabrese 2010     | 13             | 124                   | 8             | 123                 | 7.7%            |              | 1.68 [0.67, 4.22]                        |                                          |
| Calabrese 2014     | 46             | 228                   | 34            | 196                 | 21.0%           |              | 1.20 [0.74, 1.97]                        |                                          |
| Frye 2007          | 16             | 41                    | 8             | 44                  | 6.8%            |              | 2.88 [1.07, 7.75]                        |                                          |
| **Subtotal (95% CI)** | **393**      | **363**               |               |                     | **35.5%**       |              | **1.55 [0.96, 2.48]**                    |                                          |
| Total events       | 75             |                       | 50            |                     |                 |              |                                          |                                          |

Heterogeneity: Tau^2 = 0.04; Chi^2 = 2.49, df = 2 (p = 0.29), I^2 = 20%
Test for overall effect: Z = 1.80 (P = 0.07)

**Total (95% CI)**

<table>
<thead>
<tr>
<th></th>
<th>Treatment Events</th>
<th>Treatment Total Events</th>
<th>Placebo Events</th>
<th>Placebo Total Events</th>
<th>Treatment Weight</th>
<th>Placebo Weight</th>
<th>Treatment Odds Ratio M-H, Random, 95% CI</th>
<th>Placebo Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>837</strong></td>
<td><strong>801</strong></td>
<td><strong>100.00%</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>253</td>
<td></td>
<td>50</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau^2 = 0.03; Chi^2 = 10.63, df = 9 (p = 0.30), I^2 = 15%
Test for overall effect: Z = 2.85 (P = 0.004)

Test for subgroup differences: Chi^2 = 0.01, df = 1 (P = 0.93), I^2 = 0%
### Psychostimulants: Antidepressant Effect Size Low Without Mood Destabilization (Cont.)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment</th>
<th>Placebo</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>2.2.1 Atomoxetine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Michelson 2007</td>
<td>29</td>
<td>72</td>
<td>28</td>
<td>74</td>
</tr>
<tr>
<td>Weintraub 2010</td>
<td>3</td>
<td>28</td>
<td>0</td>
<td>27</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>32</td>
<td>100</td>
<td>28</td>
<td>101</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.64; Chi² = 1.51, df = 1 (p = 0.22), I² = 34%
Test for overall effect: Z = 0.63 (P = 0.53)

| 2.2.4 Methylphenidate |           |         |            |            |        |                     |                     |
| Lavieltsky 2015       | 29        | 48      | 20         | 48         | 9.5%   | 2.14 [0.95, 4.83]   |                     |
| Patkar 2006           | 4         | 30      | 1          | 30         | 1.4%   | 4.46 [0.47, 42.51]  |                     |
| Subtotal (95% CI)     |           |         |            |            |        | 2.33 [1.08, 5.01]   |                     |
| Total events          | 33        | 78      | 21         |            |        |                     |                     |

Heterogeneity: Tau² = 0.00; Chi² = 0.36, df = 1 (p = 0.55), I² = 0%
Test for overall effect: Z = 2.16 (P = 0.03)

| 2.2.5 Modafinil or Armodafinil |           |         |            |            |        |                     |                     |
| Abolfazli 2011         | 8         | 22      | 0          | 22         | 0.9%   | 26.38 [1.41, 492.81] |                     |
| Calabrese 2010         | 13        | 124     | 8          | 123        | 7.7%   | 1.68 [0.67, 4.22]   |                     |
| Calabrese 2014         | 46        | 228     | 34         | 196        | 21.0%  | 1.20 [0.74, 1.97]   |                     |
| Fava 2005              | 68        | 156     | 55         | 152        | 23.1%  | 1.36 [0.86, 2.15]   |                     |
| Frye 2007              | 16        | 41      | 8          | 44         | 6.8%   | 2.88 [1.07, 7.75]   |                     |
| Subtotal (95% CI)      | 8          | 571     | 105        | 537        | 59.5%  | 1.60 [1.04, 2.47]   |                     |
| Total events           | 151       |         |            |            |        |                     |                     |

Heterogeneity: Tau² = 0.08; Chi² = 6.42, df = 4 (p = 0.17), I² = 38%
Test for overall effect: Z = 2.16 (P = 0.03)

Total (95% CI) 837 801 100.00% 1.48 [1.13, 1.95]
MPH Did Not Increase Proxy For Mania in Patients On Mood Stabilizing Medication

Ketamine in Bipolar Depression

18 patients with treatment-resistant BP depression receiving Li or VPA

Randomized, placebo-controlled, double-blind, crossover trial

Dose = 0.5 mg/kg

Primary outcome was change in MADRS score

Significant improvement at 40 minutes; most improvement at 2 days

71% response to ketamine, 6% to placebo

Ketamine was well tolerated; most common adverse effect dissociative symptoms (at 40 minutes)

GLP-1 Receptor Agonists for Antipsychotic Associated Cardio-Metabolic Risk Factors: Individual Participant Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Mean difference GLP-1RA vs. control</th>
<th>SE</th>
<th>Treatment effect</th>
<th>Study effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F value</td>
<td>p-value</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>168</td>
<td>-3.71</td>
<td>0.65</td>
<td>33.19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>167</td>
<td>-3.00</td>
<td>0.68</td>
<td>19.24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>168</td>
<td>-1.19</td>
<td>0.22</td>
<td>30.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c (IFCC)</td>
<td>166</td>
<td>-3.25</td>
<td>0.66</td>
<td>24.54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FPG (mmol/L)</td>
<td>166</td>
<td>-0.45</td>
<td>0.09</td>
<td>24.89</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>166</td>
<td>-0.01</td>
<td>0.02</td>
<td>0.33</td>
<td>0.566</td>
</tr>
<tr>
<td>LDL (mmol/L)</td>
<td>162</td>
<td>-0.17</td>
<td>0.08</td>
<td>4.82</td>
<td>0.030</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>166</td>
<td>-0.24</td>
<td>0.12</td>
<td>3.73</td>
<td>0.055</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>160</td>
<td>-1.89</td>
<td>1.61</td>
<td>1.39</td>
<td>0.241</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>160</td>
<td>-1.91</td>
<td>1.17</td>
<td>2.68</td>
<td>0.104</td>
</tr>
<tr>
<td>HoMA</td>
<td>163</td>
<td>-0.58</td>
<td>0.59</td>
<td>0.96</td>
<td>0.328</td>
</tr>
<tr>
<td>Insulin (pmol/L)</td>
<td>163</td>
<td>4.59</td>
<td>12.93</td>
<td>0.13</td>
<td>0.723</td>
</tr>
<tr>
<td>Android/gynoid ratio</td>
<td>131</td>
<td>-0.006</td>
<td>0.014</td>
<td>0.16</td>
<td>0.692</td>
</tr>
<tr>
<td>Visceral fat (gm)</td>
<td>97</td>
<td>-177.51</td>
<td>68.71</td>
<td>6.67</td>
<td>0.011</td>
</tr>
</tbody>
</table>

Liraglutide Improves Cognitive Function and Neuronal Markers of Viability In Bipolar Disorder

Evaluating the Effect of Coenzyme Q10 Augmentation on Treatment of Bipolar Depression: A Double-Blind, Controlled Clinical Trial

**FIGURE 2.** The MADRS scores between and within the 2 groups, and over time. Montgomery-Asberg Depression Rating Scale (MADRS) scores decreased over time, but more so in the CoQ10 condition, compared to the control condition. Points are means and bars are standard deviations.
Forest Plot of Pooled Effect Sizes of Adjunctive Anti-inflammatory Agents for Bipolar Depression

O3FA = omega-3 fatty acids; NSAID = nonsteroidal anti-inflammatory drug; NAC = N-acetylcysteine.

Statins, Calcium Channel Blockers, and Metformin Decrease Psychiatric Hospitalizations and Self-harm in Bipolar Disorder and Schizophrenia

Hayes JF et al. JAMA Psychiatry. 2019; Epub ahead of print.
Infliximab is Superior to Placebo at Mitigating Depressive Symptoms in Adults With BD Reporting Physical and Sexual Abuse

ECT for Treatment-Resistant Bipolar Depression

- Response rates at 6 weeks:
  - Algorithm-based therapy 35.0%
  - ECT 73.9% (p=0.01)

- Remission rates at 6 weeks:
  - Algorithm-based therapy 30.0%
  - ECT 34.8% (p=0.74)

- AEs possibly related to ECT:
  - Failing memory (n=2)
  - Tension or inner unrest (n=1)
  - Increased sweating (n=3)
  - Diminished sexual desire (n=2)
  - Headache (n=1)
  - Tooth damage (n=1)

Psychosocial Treatments

- Cognitive behavioral therapy
- Family-focused therapy
- Interpersonal therapy
- Social rhythm therapy
- Psychoeducation
- Healthy lifestyle choices
  - Appropriate food
  - Exercise
  - Sleep hygiene

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

- Selection of acute treatment should take maintenance treatment goals into account
- Be aware of safety and tolerability concerns, evidence for maintenance use, and acute efficacy

**Level 1 Estimated efficacy:**
Quetiapine* or lurasidone** monotherapy
*Only quetiapine has been established for bipolar II disorder; **Lurasidone has a better metabolic profile than quetiapine

**Level 2A Established efficacy, but with safety concerns***:
- Olanzapine + fluoxetine (bipolar I disorder)
*Tolerability limitations include weight gain and metabolic concerns

**Level 2B Better tolerability, but limited efficacy***:
Consult specialist:
- Lithium (bipolar I disorder)
- Lithium adjunctive to lamotrigine (bipolar I disorder)
- 2 drug combination of above medications
*Efficacy limitations, relatively few positive randomized controlled trials; positive meta-analysis for lamotrigine in bipolar depression

### Treatment of Acute Bipolar Disorder – Depression (Cont.)

#### Level 3 If Levels 1 and 2 are ineffective and/or not well tolerated*:
- Electroconvulsive therapy (ECT)
*Consideration is merited due to clinical need, despite even greater efficacy/tolerability limitations than Level 1 and 2 treatments

#### Level 4 If Levels 1-3 are ineffective and/or not well tolerated:
- FDA approved agent for bipolar disorder + conventional antidepressant*
- Pramipexole
- Adjunctive – modafinil, thyroid, or stimulants
- 3 drug combination
- Transcranial magnetic stimulation (TMS)
*There is inadequate information (including negative trails) to recommend adjunctive antidepressants, aripiprazole, siprasidone, levetiracetam, armodafinil, or omega-3 fatty acids for bipolar depression

Posttest Question

Of the two Level 1 monotherapy treatments for bipolar disorder/depression, which has a better metabolic profile?

1. Lurasidone
2. Quetiapine
3. They have the same metabolic profile