Solving Clinical Challenges in Bipolar Disorder

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Faculty Disclosure

• **Dr. Goldberg**: Consultant—Lundbeck, Sunovion, Otsuka, WebMD; Royalties—American Psychiatric Publishing, Inc.; Speaker—Allergan, Neurocrine, Otsuka, Sunovion, Takeda-Lundbeck.
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 use of antidepressant monotherapy for the treatment of bipolar disorder 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

• Describe challenges in diagnostic screening, differential diagnosis, comorbidity, and diagnostic accuracy in bipolar disorder

• Discuss the evidence base for antidepressants, lamotrigine, and complex combination pharmacotherapy regimens for bipolar disorder

• Identify strategies to overcome obstacles to side effect management during pharmacotherapy for bipolar disorder

• Describe the evidence base for phototherapy and other nonpharmacologic treatments for bipolar disorder
All questions/cases in this presentation were submitted by clinicians within the Psych Congress database which includes conference attendees, newsletters subscribers, and more.
Part I: Diagnostic Nosology, Accuracy, and Screening
Many patients diagnosed with bipolar II disorder appear to have borderline personality disorder and/or complex PTSD. 

*How do you navigate this challenging diagnostic territory?*
• Focus on the non-overlapping features (eg, sleep/energy changes from normal)
• Distinguish identifiable episodes from persistent trait characteristics
• Patterns of “mood instability” may differ across diagnoses
• Notion of mood “reactivity” and interpersonal or environmental “triggers”
• History of trauma may lead to more complex course across all diagnoses
• Recognize comorbidities vs differential diagnoses
Disorders Most Difficult-to-Differentiate from Bipolar I Disorder

Online survey of 154 psychiatrists at www.psychiatrist.com

Bipolar Disorder Comorbidity with PTSD

Patients With Co-Occurring Bipolar Disorder And Posttraumatic Stress Disorder: A Rapid Review of the Literature

Joseph M. Cerimele, MD, MPH\textsuperscript{4,*}; Amy M. Bauer, MD, MS\textsuperscript{3}; John C. Fortney, PhD\textsuperscript{3,*}; and Mark S. Bauer, MD\textsuperscript{2}

ABSTRACT

**Objective:** To summarize the current literature on epidemiology, clinical correlates, and treatment of individuals with co-occurring bipolar disorder and posttraumatic stress disorder (PTSD).

**Data Sources:** We conducted a focused, time-sensitive review called “rapid review” in November 2015, using keyword searches (including keywords bipolar disorder, post-traumatic stress disorder, PTSD, and others) in PubMed for studies of adults with co-occurring bipolar disorder and PTSD.

**Study Selection:** Results were sorted and systematically searched. An article was excluded if it did not describe adult patients with co-occurring PTSD and bipolar disorder or did not report original data on epidemiology, clinical correlates, or treatment.

**Data Extraction:** Information on study characteristics including population studied and key findings were extracted onto a data collection tool.

**Key Points:**

- 4\% to 40\% of patients with BD manifest signs of PTSD
  - Higher prevalence in women and in BD-I > BD-II
- Incidence in National Comorbidity Survey: 24\%
- Shorter durations of euthymia
- Higher risk for mood episode relapses
- Greater depressive symptom burden
- Lower quality of life
- Earlier age at bipolar onset
- More comorbid substance use disorders

Bipolar Disorder and Borderline Personality Disorder

Comorbid Prevalence: 17%–29%


Diagram showing overlapping symptoms and characteristics of Bipolar Disorder and Borderline Personality Disorder.
Different Patterns of Affective Instability in Bipolar II Disorder vs Borderline Personality Disorder

BPD = borderline personality disorder.

Bipolar
More depression and elation ($P<.05$)

BPD
More anger ($P=.002$)
Different Patterns of Affective Instability in Bipolar II Disorder vs Borderline Personality Disorder

*P<.05.

ALS = Affective Lability Scale.
Borderline Personality Disorder and Bipolar Disorder: 4-Year Prospective Follow-up

196 patients with BPD and 433 with other personality disorders

Co-occurrence of BPD + BD

P = .001

New Onset BD in Existing BPD or Other PDs

P = .007

Comorbidity in Bipolar Disorder is Common

N=288 BD Participants in Stanley Bipolar Cohort

# of Comorbid Psychiatric Disorders

N=656 BD Participants in STEP-BD

# of Comorbid Psychiatric Disorders

STEP-BD = Systematic Treatment Enhancement Program for Bipolar Disorder.
Comparison of Bipolar II Disorder Depression with Major Depressive Disorder–Borderline Personality Disorder

<table>
<thead>
<tr>
<th></th>
<th>BD-II Depressed (%) (n=62)</th>
<th>MDD + BPD (%) (n=206)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTSD</td>
<td>10</td>
<td>30</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Substance use disorders</td>
<td>10</td>
<td>25</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Somatoform disorders</td>
<td>7</td>
<td>17</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Expressed anger*</td>
<td>1.2</td>
<td>2.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Somatic anxiety*</td>
<td>2.0</td>
<td>2.7</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Paranoid thinking*</td>
<td>1.2</td>
<td>1.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Somatization*</td>
<td>0.4</td>
<td>1.4</td>
<td>&lt;.01</td>
</tr>
<tr>
<td># Suicide attempts</td>
<td>0.6</td>
<td>1.6</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

Personality Disorder Comorbidity in Bipolar II Disorder vs Major Depressive Disorder–Borderline Personality Disorder

<table>
<thead>
<tr>
<th>Personality Disorder</th>
<th>BD-II (%)</th>
<th>MDD + BPD (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paranoid</td>
<td>2.6</td>
<td>19.2</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Schizoid</td>
<td>0.0</td>
<td>0.8</td>
<td>NS</td>
</tr>
<tr>
<td>Schizotypal</td>
<td>0.0</td>
<td>2.5</td>
<td>NS</td>
</tr>
<tr>
<td>Antisocial</td>
<td>2.6</td>
<td>8.3</td>
<td>NS</td>
</tr>
<tr>
<td>Histrionic</td>
<td>2.6</td>
<td>1.7</td>
<td>NS</td>
</tr>
<tr>
<td>Narcissistic</td>
<td>2.6</td>
<td>5.0</td>
<td>NS</td>
</tr>
<tr>
<td>Avoidant</td>
<td>23.1</td>
<td>28.3</td>
<td>NS</td>
</tr>
<tr>
<td>Dependent</td>
<td>5.1</td>
<td>10.0</td>
<td>NS</td>
</tr>
<tr>
<td>Obsessive-Compulsive</td>
<td>5.1</td>
<td>10.0</td>
<td>NS</td>
</tr>
<tr>
<td>ANY PD</td>
<td>38.5</td>
<td>56.7</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>
Question

What scales and screeners do you recommend using for bipolar disorder?
• Screens should cast a wide/overinclusive net – not a proxy for actual Dx
• Screens have *poor* PPV, *good* NPV
• **Screening tool limitations**: Poor patient insight, diagnostic contaminants (eg, substance intoxication/withdrawal), nonspecific/nonpathognomonic symptoms, wide differential Dx
• **Mood Disorder Questionnaire** (MDQ): Functions better as a semi-structured interview; not designed to capture BD-II, cyclothymic disorder, or subthreshold bipolar conditions (unspecified/NOS)
• The Dx best screen is probably to assess **DIGFAST** questions in every patient with mood disorders
• **Bipolar Inventory of Symptoms Scale** (BISS) provides a good semi-structured interview for tracking symptoms

*NOS = not otherwise specified; NPV = negative predictive value; PPV = positive predictive value.*
DIGFAST

- Distractible
- Impulsivity/indiscretions
- Grandiosity
- Fast thoughts
- Activity increase/energy
- Sleep requirements ↓
- Talk talk talk talk talk talk
How well does the MDQ perform as a diagnostic screen?

Self-Rated vs Clinician-Reviewed MDQ in Mood Disorder Inpatient with Substance Use Disorders

<table>
<thead>
<tr>
<th>MDQ Assessment</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-rated MDQ</td>
<td>0.77</td>
<td>0.52</td>
<td>0.38</td>
<td>0.86</td>
</tr>
<tr>
<td>Clinician-reviewed MDQ</td>
<td>0.97</td>
<td>0.95</td>
<td>0.88</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Review of 20 studies

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.61</td>
<td>0.88</td>
<td>0.58</td>
<td>0.89</td>
</tr>
</tbody>
</table>

PPV = \( \frac{TP}{TP + FN} \)

Point of View

Misuse of the Mood Disorders Questionnaire as a case-finding measure and a critique of the concept of using a screening scale for bipolar disorder in psychiatric practice


Objectives: Under-recognition of bipolar disorder (BD) is common and incurs significant costs for individuals and society. Clinicians are often encouraged to use screening instruments to help them identify patients with the disorder. The Mood Disorder Questionnaire (MDQ) is the most widely studied measure for this purpose. Some studies, however, have used the MDQ as a case-finding instrument rather than a screening scale. Such inappropriate use of screening scales risks distorting perceptions about many facets of BD, from its prevalence to its consequences.

Methods: Studies using the MDQ were reviewed to identify those reports that have used the scale as a case-finding measure rather than a screening scale.

“"There is no substitute for a competent clinical interview"
Research report

Identifying hypomanic features in major depressive disorder using the hypomania checklist (HCL-32)

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Abstract

Background: Recent studies have challenged the traditional unipolar/bipolar divide with increasing support for a more dimensional view of affective disorders. We here examine the occurrence of hypomanic symptoms in individuals with a history of major depression selected to exclude indicators of underlying bipolarity.

Methods: The presence of hypomanic symptoms was assessed by the Hypomania Checklist (HCL-32) self-report questionnaire in a sample of almost 600 patients meeting DSM-IV criteria for Bipolar I disorder (BPI N=260) or Major Recurrent Depressive disorder (MDDR N=322). Subjects were recruited and assessed using consistent, robust methodology.

Results: We found that a score of 20 or more on the HCL-32 yielded the best combination of sensitivity (68%) and specificity (85%) to distinguish between BPI and MDDR. Within our highly selected and well defined MDDR sample (for which exclusion criteria included personal or family histories of bipolar or psychotic illness), 17% of MDDR subjects scored over the threshold of 20 on the HCL-32.

Conclusions: The HCL-32 identified a substantial number of patients meeting DSM-IV criteria for recurrent major depression (even when selected to exclude personal and family histories of bipolar illness) who reported bipolar symptoms at a level similar to that reported by patients meeting diagnostic criteria for bipolar disorder. This demonstrates the limitations of using DSM-IV criteria to distinguish those with and without bipolar features of illness.
Development of the Bipolar Inventory of Symptoms Scale


Objective: Most rating scales for bipolar disorders (BDs) do not encompass the spectrum of symptomatology now established as characterizing the illness. We report the rationale, format, reliability and initial validity studies of the Bipolar Inventory of Symptoms Scale (BISS), a 44-item scale designed to encompass the spectrum of behavioral disturbances in BDs.

Method: Structured video interviews of 20 patients representing four bipolar syndromal subtypes were rated by nine raters.

Results: Generally, high inter-rater reliability and internal consistency were established for the depression and mania subscales and the BISS total score. The BISS discriminated across subtypes of bipolar patients with depressed, manic/hypomanic, mixed manic or recovered status.

Conclusion: The BISS has adequate reliability, concurrent validity and is capable of discriminating between bipolar subtypes. It also provides a comprehensive scale to assess discrete behavioral components of BD.

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Key words: bipolar; assessment; rating scales; depression; mania

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Question

What are your thoughts on bipolar spectrum as a diagnostic entity?
• Depends what’s meant by “bipolar spectrum” and “diagnostic entity”
  – In the National Comorbidity Survey, 2.4% of respondents had lifetime subthreshold mania/hypomania (while BD-I was 1% and BD-II was 1.1%)
• Hard to validate constructs that if they lack operational criteria
• Risk for over-including nonspecific symptoms that cut across multiple diagnoses
• Risky/impractical to extrapolate treatment effects to ill-defined “spectrum” cases

33% of patients with MDD had

- Early onset
- “Complex temperament structure”
- High mood instability
- Irritability
- Suicidality

BD family history in 3% to 14% of patients with MDD
“…given the finite limits of how our species can react psychopathologically, it is hardly surprising that affective instability and fluctuations of mood can be found in many, if not most, other disorders. Widespread acceptance of increasingly broad definitions risks weakening or trivializing the core concept of bipolar disorder…”
On being bipolar without being bipolar

JF Goldberg  Norwalk, CT, USA

The paper in this issue by Smith and colleagues raises provocative and important issues of both theoretical and clinical relevance to the basic nosology of affective disorders. One element of their treatise involves controversies about defining the elements, which comprise the bipolar spectrum. A second involves the distinction between affective recurrence (i.e., cyclicity) versus polarity (i.e., affective switch) as most critical for distinguishing bipolar from unipolar disorders.

Increasingly in the literature, the concept of partial or form fruste manifestations of bipolar disorder has become recognised as both plausible and logical for a disease so pleomorphic as bipolar illness. From the standpoint of complex (i.e., non Mendelian) genetics, it is now generally accepted that bipolar disorder likely involves multiple genes of small effect – with incomplete penetrance. This makes the understanding of bipolar disorder complex.

As thought-provoking and scientifically important as these ideas are, there remain several clinical and theoretical implications, and dilemmas, related to the above tenets. First, the concept of a “bipolar spectrum” has been hampered by the absence of an empirically-derived operational definition, with inclusion and exclusion criteria, and established construct validity. At present, almost anything and everything related to mood may be fair game to include under this broad heading, creating a potential free-for-all with high risk for false-positive cases. Empirical efforts are needed to help “preserve the conceptual integrity” of a bipolar diagnosis (Baldessarini, 2000) and avert the potential to create even greater nosologic confusion. For example: do particular component symptoms of mania (such as the loss of need for sleep) have greater predictive value either for diagnosing a full manic syndrome or the

- Overly broad constructs such as “impulsivity,” “mood instability,” “sensation-seeking,” encompass numerous conditions

- Mood disorder complexity involves many factors other than polarity – eg, psychosis, recurrence, chronicity, melancholia, mood reactivity, personality structure, and capacity for resilience

- Drug response/non-response confers little or no diagnostic specificity
Part II: Pharmacologic Treatments
Question

Many patients with bipolar disorder are on complex polypharmacy.  

*What approaches do you have to minimize this?*
• Every player on the “roster” should have a defined role
• Deprescribe medications that are judged to be *ineffective* after an adequate trial or *inappropriate* to the current clinical state (eg, antidepressants or stimulants during mania, sleep aids in the setting of hypersomnia) or *redundant*
• Assure each drug is appropriate for its intended purpose
• Simplify when feasible with multi-purposes single drugs – eg,
  – Comorbid anxiety + insomnia + neuropathic pain =  
    **gabapentin**
  – Comorbid binge eating + migraine + alcohol abuse =  
    **topiramate**
# Prevalence of Extensive Combination Pharmacotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Extent of Complex Combination Pharmacotherapy</th>
</tr>
</thead>
</table>
| STEP-BD                                    | 18% took $\geq 4$ medications  
40% took $\geq 3$ medications  
10% took $\geq 2$ SGAs – more side effect burden than taking 1 SGA                                           |
| Butler Hospital/Brown                       | 36% received $\geq 4$ medications                                                                                         |
| Institute of Living                         | 21% received $\geq 4$ medications                                                                                         |
| UK THIN Primary Care database               | In 1995: 23% on $\geq 2$ medications;  
In 2005: 48% received $\geq 2$ medications; largest rise seen in SGA use (35% of patients in 2005) |
| Charité – University Medicine Berlin        | Nearly all patients in a cohort of 80 bipolar outpatients took a mean of 3.8 medications over 3 months            |

SGA = second-generation antipsychotic.

Complex Combination Pharmacotherapy for Bipolar Disorder: Knowing When Less Is More or More Is Better

Joseph F. Goldberg, M.D.

Combination pharmacotherapy for bipolar disorder is commonplace and often reflects the severity and complexity of the illness and the comorbid conditions frequently associated with it. Across treatment settings, about one-fifth of patients with bipolar disorder appear to receive four or more psychotropic medications. Practice patterns often outpace the evidence-based literature, insofar as few systematic studies have examined the efficacy and safety of two or more medications for any given phase of illness. Most randomized trials of combination pharmacotherapy focus on the utility of pairing a mood stabilizer with a second-generation antipsychotic for prevention of either acute mania or relapse. In real-world practice, patients with bipolar disorder often take more elaborate combinations of mood stabilizers, antipsychotics, antidepressants, anxiolytics, stimulants, and other psychotropics for indefinite periods that do not necessarily arise purposefully and logically. In this article, I identify clinical factors associated with complex combination pharmacotherapy for patients with bipolar disorder; describe approaches to ensuring that each component of a treatment regimen has a defined role; discuss the elimination of unnecessary, ineffective, or redundant drugs in a regimen; and address complementary, safe, rationale-based drug combinations that target specific domains of psychopathology for which monotherapies often provide inadequate benefit.

Focus 2019; 17:218–231; doi: 10.1176/appi.focus.20190008
Characteristics Associated with Extensive Polypharmacy in Bipolar Disorder

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Female</td>
</tr>
<tr>
<td>Race</td>
<td>White</td>
</tr>
<tr>
<td>Age</td>
<td>&gt; 50 years</td>
</tr>
<tr>
<td>Psychosis</td>
<td>Present</td>
</tr>
<tr>
<td>Medication dosage</td>
<td>Typically low</td>
</tr>
<tr>
<td>Depressive illness burden</td>
<td>High</td>
</tr>
<tr>
<td>Comorbid personality disorders</td>
<td>BPD</td>
</tr>
<tr>
<td>Comorbid other psychiatric diagnoses</td>
<td>PTSD, anxiety disorders</td>
</tr>
<tr>
<td>History of suicide attempt(s)</td>
<td>Present</td>
</tr>
<tr>
<td>Personality traits</td>
<td>Low levels of openness, extraversion, conscientiousness</td>
</tr>
</tbody>
</table>
Question

What is your opinion about the use of antidepressants without a mood stabilizer?
• In BD-II depression with no mixed features, the literature most strongly supports fluoxetine, sertraline, or venlafaxine monotherapy

• NO database to support antidepressant monotherapy in BD-I depression (although the absence of evidence does not mean evidence of absence)
Sertraline vs Lithium vs Their Combination in BD-II Depression

Comparable response rates over study period

Adding lithium to SSRI does not further improve response

No difference in switch rates

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Switch Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>19.4%</td>
</tr>
<tr>
<td>Sertraline</td>
<td>19.9%</td>
</tr>
<tr>
<td>Combo</td>
<td>13.4%</td>
</tr>
</tbody>
</table>

In non-rapid cyclers:

Better response to lithium (79%) or sertraline (78%) monotherapy than to their combination (36%) (P=.004)

SSRI = selective serotonin reuptake inhibitor.
Longer Time until Relapse in Bipolar II Disorder with Fluoxetine than Lithium

Median days to depression relapse

- Fluoxetine: 250 days
- Lithium: 150 days
- Placebo: 187 days

Depression relapse 2.5× more likely with lithium than fluoxetine

ISBD Task Force Recommendations about Antidepressant Use in Bipolar Depression

1. Adjunctive antidepressants for acute bipolar depression
   a. Permissible if history of positive antidepressant response
   b. Avoid in the presence of ≥ 2 core manic symptoms, psychomotor agitation, or rapid cycling

2. Antidepressant monotherapy for acute bipolar depression
   a. Avoid in BD-I
   b. Avoid in BD-II in the presence of ≥ 2 core manic symptoms

ISBD = International Society for Bipolar Disorders.
Do mood stabilizers “protect” against TEAEs?
What’s the evidence?

109 trials (N=114,521 participants)

TCAs riskier than SSRIs

Overall mania risk = 12.5%
• W/ no mood stabilizer = 13.8%
• W/ mood stabilizer = 15.9%

Observational/retrospective study of 158 inpatients with BD in Germany

39/158 (25%) became manic

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mood stabilizer</td>
<td>0.30</td>
<td>0.13–0.69</td>
</tr>
<tr>
<td>Tricyclic</td>
<td>3.76</td>
<td>1.56–9.05</td>
</tr>
</tbody>
</table>

Mood stabilizer use associated with lesser probability of TEAEs but nonrandomized design precludes causal inferences and ignores possible confounding by indication.

AD = antidepressant; TCA = tricyclic antidepressants; TEAE = treatment emergent adverse event.
Do you feel that lamotrigine is a good first-line choice in bipolar II disorder?
• From an evidence-based medicine standpoint: *No*
• From a subjective, impressionistic, data-unsupported stance: *Maybe*
• Inconsistent data in the manufacturers’ FDA registration trials for acute bipolar depression, drug-placebo differences were less for BD-II than BD-I depression
• A recent naturalistic study of relapse prevention in a Japanese cohort suggests better prevention of a mood episode (but not specifically against depression) in BD-II than BD-I

**Meta-Analysis of Lamotrigine Trials in Acute Bipolar Depression**

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk Ratio (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCAB2001</td>
<td>1.71 (1.08, 2.69)</td>
<td>8.3</td>
</tr>
<tr>
<td>SCAA2010</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</td>
<td>1.26 (1.10, 1.44)</td>
<td></td>
</tr>
</tbody>
</table>

Risk Factors: 0.371223 favors PBO, 2.6938 favors Drug.

Why Lamotrigine Failed to Separate from Placebo in Acute Bipolar Depression Trials

Pooled analysis of 5 lamotrigine RCTs in acute bipolar depression

<table>
<thead>
<tr>
<th></th>
<th>Moderate Baseline Severity</th>
<th>High Baseline Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamotrigine Response Rate</td>
<td>48%</td>
<td>45%</td>
</tr>
<tr>
<td>Placebo Response Rate</td>
<td>45%</td>
<td>30%</td>
</tr>
</tbody>
</table>

High baseline severity moderates response (ie, suppresses placebo response rate)

RCT = randomized controlled trial.
1-Year Lamotrigine Relapse Prevention: BD-I vs BD-II

Time to Relapse/Recurrence of a Mood Episode

Time to Relapse/Recurrence of a Depressive Episode

* Lamotrigine significantly prolonged the time to recurrence/relapse of mood episodes in bipolar II patients than in bipolar I patients ($P = .0103$).

* There was no difference between bipolar I and bipolar II patients in the time to major depressive episode.

Augmentation of lamotrigine or placebo to quetiapine in BD-I or BD-II depressed outpatients
(BD-II subgroup was not separately analyzed)

Lamotrigine: The CEQUEL Trial

<table>
<thead>
<tr>
<th>Lamotrigine</th>
<th>Placebo</th>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission @ 12 weeks</td>
<td>31%</td>
<td>16%</td>
<td>2.11 (1.09-4.07)</td>
</tr>
<tr>
<td>Remission @ 52 weeks</td>
<td>36%</td>
<td>13%</td>
<td>3.73 (1.35-10.29)</td>
</tr>
</tbody>
</table>

QTP = quetiapine.
And if your hope is to treat moment-to-moment mood instability per se …


**Change in Affective Lability Scale Total Scores**

<table>
<thead>
<tr>
<th></th>
<th>Lamotrigine (n=15)</th>
<th>Placebo (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in Scores</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>.012</td>
<td></td>
</tr>
</tbody>
</table>

**Change in Impulsivity Scores**

<table>
<thead>
<tr>
<th></th>
<th>Lamotrigine (n=15)</th>
<th>Placebo (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in Scores</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>.001</td>
<td></td>
</tr>
</tbody>
</table>
Part III:
Side Effect Management
Questions

Lithium is still one of the best drugs we have for bipolar disorder, but some patients don’t like it because of the side effects. **What are your best tips for improving tolerance of this lifesaving drug?**

*Any tips on minimizing long-term lithium induced side effects in patients with bipolar I disorder who have failed other treatments?*
Lithium Tricks

- Dose lithium once/day to minimize renal disease
- Treat urinary frequency with amiloride 5 mg PO BID (watch [K⁺])
- If upper GI complaints, consider extended-release formulation for more distal absorption; if lower GI complaints consider lithium citrate
- Treat tremor (if not indicative of high serum levels) with propranolol or primidone (but beware P450 induction)
- If NSAIDs are co-prescribed, reduce lithium dose by ~ 20% and monitor levels
- Lithium can usefully increase WBCs in patients taking clozapine (or carbamazepine) if and when concerns arise about leukopenia
- Lithium co-therapy with other mood stabilizing agents may spare the need for optimizing lithium levels and allow additive or synergistic effects with fewer adverse effects than might occur with higher dose lithium monotherapy
- Lithium’s “anti-suicide effect” refers to suicidal behaviors, not ideation – think of it as putting a “brake” on ideation by reducing impulsive action

GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug; WBC = white blood cell.
Questions

How do you educate patients about possible medication side effects? Do you provide educational handouts on side effect management?

Shared decision-making
Basic Concepts in Side Effect Management

- Differentiate hazardous from annoying adverse effects
- Beware nocebo effects
  - Suggestibility, neuroticism, phobic-obsessive traits, alexithymia, patient expectations, somatic amplification
- Beware “the Internet”
- Clarify the plausibility of suspected adverse effects from primary illness symptoms
- Recognize adverse effects that are dose-related and/or transient from persistent
- Everything is a risk–benefit analysis
- Pursue pharmacologic antidote strategies when feasible

### Management Strategies for “Annoying” Side Effects

<table>
<thead>
<tr>
<th>Annoying/Manageable</th>
<th>Antidotes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergic effects (constipation, dry mouth)</td>
<td>Bethanechol 24 mg PO TID, cevimeline 30 mg PO qDay-BID, dry mouth oral rinse, over-the-counter remedies</td>
</tr>
<tr>
<td>Bruxism</td>
<td>Cyclobenzaprine 2.5–10 mg/HS, buspirone 10 mg BID–TID, trazodone 150–200 mg/HS, hydroxyzine 10–25 mg/HS</td>
</tr>
<tr>
<td>Nausea</td>
<td>Prochlorperazine, trimethobenzamide, 300 mg q4–6° PRN, promethazine 12–25 mg BID PRN, ondansetron 4–8 mg PO q 6–8° (probably illogical for vortioxetine-associated nausea)</td>
</tr>
<tr>
<td>Sialorrhea</td>
<td>Glycopyrrolate 1 mg PO BID, biperiden 2 mg qDay or BID, metoclopramide 10–30 mg/day; atropine drops SL</td>
</tr>
<tr>
<td>Tremor</td>
<td>Propranolol 10 mg BID–TID, primidone* 50–300 mg/day, methazolamide 100–200 mg/day</td>
</tr>
<tr>
<td>SSRI discontinuation effects</td>
<td>Switch to longer t ½ drug (eg, fluoxetine, vortioxetine) if slow dosage reductions are still poorly tolerated</td>
</tr>
</tbody>
</table>

Part IV: Nonpharmacologic Treatments
Chronotherapy has good evidence to treat bipolar depression.

How do you use this pragmatically with your patients?
Mid-Day Bright Light Therapy for Bipolar Depression

6-week RCT of 7000-lux bright white light (n=23) vs 50-lux dim red light (n=23)

15-minute exposure between noon and 2:30 PM titrated by 15 minutes to target dose of 60 minutes/day by Week 4

All took a mood stabilizer alone (22%) or with an antidepressant (78%)

Remission at Weeks 4–6

Adjusted OR=12.64, $P=0.004$

---

Question

What is your favorite nonpharmacologic treatment in bipolar I disorder?

Depends on the patient!
<table>
<thead>
<tr>
<th>Features</th>
<th>Modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic understanding of BD</td>
<td>Psychoeducation</td>
</tr>
<tr>
<td>Distorted attitudes and beliefs</td>
<td>Cognitive-behavioral therapy (CBT)</td>
</tr>
<tr>
<td>Apathy/anergia</td>
<td>Behavioral activation</td>
</tr>
<tr>
<td>Poor impulse control/mood reactivity</td>
<td>Dialectical behavior therapy (DBT)/MBSR</td>
</tr>
<tr>
<td>Coping with chronic illness</td>
<td>Acceptance and commitment therapy (ACT)</td>
</tr>
<tr>
<td>Self-sabotage/relationship dissatisfaction</td>
<td>Psychodynamic</td>
</tr>
<tr>
<td>Circadian dysrhythmias/managing social rhythm disruptions</td>
<td>Interpersonal and social rhythm therapy (IPSRT)</td>
</tr>
<tr>
<td>High family expressed emotion</td>
<td>Family-focused therapy (FFT)</td>
</tr>
</tbody>
</table>
# Daily Mood Chart

## How to use the Mood Chart
- At the end of each day rate your mood – the “Highest” or “Lowest” that you felt that day
- Place a dot in the box that best describes your mood
- If you have had High and Low moods on the same day place two dots
- List the number of hours you slept each day
- Weigh yourself on the 14th & 28th day of each month and record

### Mood Rating Scale

<table>
<thead>
<tr>
<th>HIGH MOOD</th>
<th>+3</th>
<th>+2</th>
<th>+1</th>
</tr>
</thead>
<tbody>
<tr>
<td>NORMAL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOW MOOD</td>
<td>-1</td>
<td>-2</td>
<td>-3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DAY</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
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<th>26</th>
<th>27</th>
<th>28</th>
<th>29</th>
<th>30</th>
<th>31</th>
</tr>
</thead>
</table>

| HOURS SLEPT |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |

| WEIGHT ON DAY 14 & 28 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |

## Anxiety

### Medication

<table>
<thead>
<tr>
<th>MEDICATION (name/mg)</th>
<th>Place a checkmark if medication was taken each day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Irritability

## Alcohol/Drugs

- Rate any anxiety or irritability that you may have on a scale from 0-3 (3=high) and record daily
- List your medications and place a check mark daily if you took your medicine
- Place an “A” if you drank Alcohol or a “D” if you used any drug that was not prescribed by a doctor.
Practical Take-Aways

- Diagnostic accuracy hinges on a careful clinical interview, longitudinal history, use of collateral historians
- Recognize comorbidities vs differential diagnoses
- Treat complex pharmacotherapy regimens like personnel rosters with definable roles for each component
- Deprescribe unnecessary, redundant, inappropriate, or ineffective medications
- Use mood charting or similar measurement-based tracking tools for gauging symptom change over time