Bipolar Disorder: Importance of Residual Symptoms and Impact on Outcomes
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Dr. Tohen and Dr. Goldberg are compensated contractors of OPDC
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Overview

Prevalence and impact of bipolar disorder
Multifaceted nature of bipolar disorder
Impact of residual symptoms on outcomes
Bipolar disorder treatment guidelines
Audience Polling Question

Of the patients you see, approximately what percentage have a diagnosis of bipolar disorder?

A. 0%–25%
B. 26%–50%
C. 51%–75%
D. 76%–100%
PREVALENCE AND IMPACT OF BIPOLAR DISORDER
Bipolar Disorder: Course of Illness

### Lifetime Prevalence of Bipolar Disorder

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bipolar I</td>
<td>0.6%</td>
</tr>
<tr>
<td>Bipolar II</td>
<td>0.4%</td>
</tr>
<tr>
<td>Subthreshold bipolar</td>
<td>1.4%</td>
</tr>
<tr>
<td>Bipolar spectrum</td>
<td>2.4%</td>
</tr>
</tbody>
</table>

- Bipolar disorder is a chronic illness characterized by frequent recurrent affective episodes
- Approximately 70% of patients relapse within 4 years

2. Judd et al. *Arch Gen Psychiatry.* 2008;65:386-394.
# Bipolar Disorder and Comorbidities

## Lifetime Comorbid Axis I Disorders Among Patients with Bipolar Diagnosis (N=288)

<table>
<thead>
<tr>
<th>Substance use disorders</th>
<th>Anxiety disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substance use disorders (overall)</td>
<td>42</td>
</tr>
<tr>
<td>Alcohol</td>
<td>33</td>
</tr>
<tr>
<td>Marijuana</td>
<td>16</td>
</tr>
<tr>
<td>Stimulant</td>
<td>9</td>
</tr>
<tr>
<td>Anxiety disorders (overall)</td>
<td>42</td>
</tr>
<tr>
<td>Panic disorder/ agoraphobia</td>
<td>20</td>
</tr>
<tr>
<td>Social phobia</td>
<td>16</td>
</tr>
</tbody>
</table>

Bipolar Disorder: Morbidity and Mortality

- One of the leading causes of chronic disability worldwide\(^1\)
- Reduces life expectancy by an average of 8 to 9 years\(^1\)
- Increased mortality from cardiovascular disease, diabetes, COPD, influenza or pneumonia, and unintentional injuries\(^1\)
- Increased risk of suicide compared to general population\(^2\)
- Deterioration across multiple functional domains\(^3\)

COPD, chronic obstructive pulmonary disease.

Bipolar Disorder: Economic Burden

Estimated Costs\(^a\) of Bipolar I and Bipolar II in the United States (2009 USD)

- **Direct costs** $30.7 billion
- **Indirect costs** $120.3 billion

**Total costs** $151 billion

Since estimated costs are based on assumptions of bipolar prevalence in the United States and do not account for cases of subthreshold bipolar disorder, this estimated total cost is likely a significant underestimate of the actual total cost.

Dilsaver SC. *Journal of Affective Disorders*. 2011;79-93.
MULTIFACETED NATURE OF BIPOLAR DISORDER
Bipolar Disorder Is Multidimensional

Increased mood

Mania

Hypomania

Increased mood

Mixed

Decreased mood

Subsyndromal depression (hypomania or hyperthymia)

Depression

Subsyndromal mania

Defining Relapse (Manic Episode)

Defining Relapse (Depressive Episode)

## Defining Response

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Syndromal response</th>
<th>Symptomatic response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bipolar depression</strong></td>
<td>≥50% improvement on each of the core symptoms of depression*</td>
<td>Percentage improvement from baseline in severity of depression symptoms using HAM-D, MADRS, IDS, or BDRS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exclude social and occupational functioning</td>
</tr>
<tr>
<td><strong>Bipolar mania</strong></td>
<td>≥50% improvement on each of the core symptoms of mania*</td>
<td>Percentage improvement from baseline in severity of mania symptoms using YMRS or MRS</td>
</tr>
</tbody>
</table>

BDRS, Bipolar Depression Rating Scale; CGIS, Clinical Global Impression Scale; DSM, Diagnostic and Statistical Manual of Mental Disorders; HAM-D, Hamilton rating scale for depression; IDS, Inventory for Depression Symptomatology; MADRS, Montgomery-Asberg Depression Scale; MRS, Mania Rating Scale; YMRS, Young Mania Rating Scale. *Defined in the DSM criteria; assessing only those with scores of >4 as measured on a scale of 1 to 7.

## Defining Remission

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Syndromal remission</th>
<th>Symptomatic remission</th>
</tr>
</thead>
</table>
| **Bipolar depression** | • Sad mood and/or loss of interest/pleasure may not be present and ≤3 of remaining core criteria meaningfully present*  
  • CGI ≤2 | • HAM-D-17 ≤5 or ≤7  
  • MADRS score ≤5 or ≤7 or BDRS score ≤8  
  • Exclude daily functioning |
| **Bipolar mania** | • DSM-IV criterion†  
  – A ≤2  
  – No B criterion rated >3  
  – ≤2 B criteria =3  
  • Initial mixed episodes fulfill recovery criteria; no depression criterion >3; ≤3 criteria =3  
  • CGI-BP ≤2  
  • YMRS <8 or <5 | • YMRS <8 or <5 |

BDRS, Bipolar Depression Rating Scale; CGI-BP, Clinical Global Impression for Bipolar Illness; DSM, Diagnostic and Statistical Manual of Mental Disorders; HAM-D, Hamilton rating scale for depression; MADRS, Montgomery-Asberg Depression Scale; YMRS, Young Mania Rating Scale. *Score >3 within a range of 1 to 7. †Focused on core affective symptoms and the 7 criterion symptom domains identified in DSM to diagnose a manic episode.

DISCUSSION
Defining Recovery

ISBD Task Force definition

≥8 consecutive weeks of virtual absence of depressive and manic or hypomanic symptoms\(^1\)

SAMHSA definition

"Process of change through which individuals improve their health and wellness, live a self-directed life, and strive to reach their full potential"\(^2\)

Four Major Dimensions Support a Life in Recovery

- Health
- Home
- Purpose
- Community

ISBD, International Society for Bipolar Disorders; SAMHSA, Substance Abuse and Mental Health Services Administration.
Functional Recovery

2-Year Recovery After Index Manic or Mixed Episode in Patients With Bipolar Disorder (N=166) After First Hospitalization for Manic or Mixed Episode

- Syndromal recovery: 97.6%
- Symptomatic recovery: 71.7%
- Functional recovery: 43.1%

New Illness Despite Syndromal Recovery

- Within 2 years of first hospitalization, 40% of patients experienced new episodes of mania or depression
- Majority of patients who experienced new illness switched into an episode of depression

Onset of New Illness Without Recovery From Index Manic or Mixed Episode

- Total, 19.3%
  - Switch to psychosis (without mania): 13.3%
  - Switch to mixed: 4.2%
  - Switch to depression: 1.8%


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Time to Onset of New Episode of Mania or Depression

Time to a New Episode of Mania Is Shorter Following Index Manic vs Index Mixed Episodes

Time to a New Episode of Depression Is Much Shorter Following Index Mixed vs Index Manic Episodes

## Risk Factors Influencing Recurrence And Other Disease Parameters

<table>
<thead>
<tr>
<th>Outcome of interest</th>
<th>Identified predictors</th>
</tr>
</thead>
</table>
| **Psychosocial outcomes**¹,* | • Occupational status  
• History of ≥1 previous episodes  
• Residential status  
• History of alcoholism  
• Psychotic features during index episode  
• Male sex |
| **Syndromal recovery**²      | • Shorter hospitalization for index episode  
• Female sex  
• Age  
• Lower baseline depression ratings  
• Marital status |
| **Functional recovery**²     | • Increasing age  
• Race  
• Shorter hospitalization for index episode  
• Marital status |
| **Time to relapse**¹         | • History of alcoholism  
• Psychotic features during index episode  
• Occupational status  
• Depressive symptoms during index episode |
| **Mania recurrence**²        | • Initial mood-congruent psychosis  
• Lower premorbid occupational status  
• Initial manic presentation |
| **Depression onset**²        | • Occupational status  
• Initial mixed presentation  
• Comorbidities |

*Psychosocial outcomes include occupational and residential status.

## Audience Polling Question

**What percentage of your patients with bipolar disorder experience residual symptoms?**

<table>
<thead>
<tr>
<th>Option</th>
<th>Percentage Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0%–25%</td>
</tr>
<tr>
<td>B</td>
<td>26%–50%</td>
</tr>
<tr>
<td>C</td>
<td>51%–75%</td>
</tr>
<tr>
<td>D</td>
<td>76%–100%</td>
</tr>
</tbody>
</table>
IMPACT OF RESIDUAL SYMPTOMS ON OUTCOMES
Subsyndromal Symptoms
Highly Prevalent

<table>
<thead>
<tr>
<th>State</th>
<th>Upper boundary</th>
<th>Lower boundary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subsyndromal depression</td>
<td>Score of 14 on HAM-D or MADRS and score of 16 on BDRS</td>
<td>Total score of 8 on HAM-D or MADRS and score of 9 on BDRS</td>
</tr>
<tr>
<td>Subsyndromal mania</td>
<td>Score of 14 on MRS or YMRS</td>
<td>Total score of 8 on MRS or YMRS</td>
</tr>
</tbody>
</table>

- Estimated lifetime prevalence of subsyndromal manic/hypomanic symptoms is approximately 5%\(^2\)
  - Lifetime subsyndromal manic symptoms may be 3 times more common than full manic or hypomanic symptoms
- Subthreshold bipolar disorder may be \(\geq 5\) times more prevalent than DSM-based syndromal bipolar disorder\(^2\)

BDRS, Bipolar Depression Rating Scale; HAM-D, Hamilton rating scale for depression; MADRS, Montgomery-Asberg Depression Scale; MRS, Mania Rating Scale; YMRS, Young Mania Rating Scale.

Residual Symptoms and Prediction of Recurrence

Objective
Determine features associated with risk of manic or depressive recurrence in bipolar disorder in a multicenter, prospective, naturalistic study (STEP-BD)

Patients with BPD (N=858) who achieved recovery during follow-up
Mean age, 39.9 ± 12.7 years
Median follow-up, 56.2 weeks after recovery

Participants seen in follow-up as often as clinically indicated
Clinical state assessed at each visit with a clinical monitoring form that collects DSM-IV criteria for depressive, manic, hypomanic, or mixed states

BPD, bipolar disorder; DSM, Diagnostic and Statistical Manual of Mental Disorders; STEP-BD, Systematic Treatment Enhancement Program for Bipolar Disorder.
STEP-BD: Residual Symptoms Predict Manic or Depressive Recurrence

Residual Manic Symptoms and Time to Recurrence in Subjects with BPD Over 2 Years

Residual Symptoms and Impact on Time to Recurrence

**Objective**
Determine if continued presence of subsyndromal residual symptoms during recovery associated with significantly faster episode recurrence than asymptomatic recovery in a multicenter, prospective, naturalistic NIMH Collaborative Depression Study (CDS).

Patients with bipolar disorder I (N=136) and bipolar disorder II (N=87) who entered the CDS during an episode of major depression and/or mania

Mean age, 37.4 ± 13
Median follow-up, 17 years

Patients interviewed every 6 months for first 5 years, then yearly

Patients were assessed using variations of the Longitudinal Interval Follow-up Evaluation

CDS, Collaborative Depression Study; NIMH, National Institute of Mental Health.

Judd et al. *Arch Gen Psychiatry*. 2008;65:386-394.
Residual Symptoms Shorten Time to Recurrence: NIMH Collaborative Depression Study

- Risk of recurrence
  - 3.4 times higher if residual symptoms were present vs absent ($P<0.001$)
- Time to recurrence
  - 5 times faster if residual symptoms were present vs absent (24 weeks vs 123 weeks)
- History of $\geq$4 affective episodes correlated with time to next major affective episode ($P=0.007$)
  - Not significant after Bonferroni correction

Residual Symptoms and Functional Outcome

Objective
Assess the impact of residual symptoms on overall functioning and specific functional impairment in euthymic outpatients with bipolar disorder in a multicenter, noninterventional study

Euthymic outpatients with bipolar disorder (N=468)
Mean age, 47.7 ± 12.5 years

Assessment of residual symptoms and functioning
Residual symptoms were measured using the BDRS and YMRS; disability was assessed using the FAST

BDRS, Bipolar Depression Rating Scale; FAST, Functioning Assessment Short Test; YMRS, Young Mania Rating Scale
Residual Symptoms Impact Overall and Domain-Specific Functioning

Residual Depressive Symptoms Impact Overall Functioning in Nearly All Domains

<table>
<thead>
<tr>
<th>Domain</th>
<th>Impact Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autonomy</td>
<td>Residual depressive symptoms, Residual manic symptoms, Occupational stigma</td>
</tr>
<tr>
<td>Occupational functioning</td>
<td>Residual depressive symptoms, Emotional inhibition</td>
</tr>
<tr>
<td>Cognitive functioning</td>
<td>Residual depressive symptoms, Perceived concentration impairment</td>
</tr>
<tr>
<td>Financial issues</td>
<td>Residual manic symptoms</td>
</tr>
<tr>
<td>Interpersonal relationships</td>
<td>Residual depressive symptoms, Family stigma</td>
</tr>
<tr>
<td>Leisure time</td>
<td>Residual depressive symptoms, Sexual dysfunction, Occupational stigma</td>
</tr>
</tbody>
</table>

DISCUSSION
Cognitive Deficits in Bipolar Disorder

• May be present during early stages of bipolar disorder\(^1,2\)
• Are apparent during acute illness and during remission\(^3\)
• Deficits in executive function, attention, and verbal memory are common\(^2\)
• May help explain impairment in daily function\(^3\)
• Related to poor functional outcomes\(^3\)

Impact of Subsyndromal Depression and Cognitive Deficits on Functional Outcomes

Patients with bipolar disorder perform poorer than healthy controls in measures of executive function, attention, and verbal memory

- Impairments in verbal memory, attention, and subsyndromal depression predict score on the General Assessment of Functioning (GAF)

- Impairments in attention and executive function predicted scores on the Functioning Assessment Short Test (FAST)

# Subsyndromal Symptoms and Work Disability

Mean Percentage of Days With Subsyndromal Symptoms by Employment Status

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Disabled (n=75)</th>
<th>Full-time (n=135)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subsyndromal depression</td>
<td>29%</td>
<td>15%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Subsyndromal mania</td>
<td>9%</td>
<td>7%</td>
<td>NS</td>
</tr>
<tr>
<td>Severe subsyndromal depression</td>
<td>8%</td>
<td>4%</td>
<td>NS</td>
</tr>
<tr>
<td>Severe subsyndromal mania</td>
<td>1%</td>
<td>1%</td>
<td>NS</td>
</tr>
</tbody>
</table>

BIPOLAR TREATMENT GUIDELINES
Bipolar Treatment Guidelines

- Numerous practice guidelines and treatment algorithms have been developed\(^1\)
  - Many have not received an update in recent years
- Adherence to guidelines has been associated with improved outcomes\(^2\)

# Pharmacologic and Psychosocial Treatments

## Acute Mania
Oral antipsychotic medications and mood stabilizers (MS) or combination of antipsychotic plus MS

## Maintenance
Continuation of acute antipsychotic medication, mood stabilizers, or combination treatment

## Intramuscular injections
Used when oral medications are refused or cannot be administered reliably

## Electroconvulsive therapy (ECT)
Used in acute and maintenance phases

## Psychoeducation

## Cognitive behavioral therapy (CBT)

## Interpersonal and social rhythm therapy (IPSRT)

## Family-focused treatments

## Internet-based strategies

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Elements of Care: Meeting Patient Needs

- Utilize evidence-based care
- Assess for adherence
- Monitor for efficacy and safety
- Utilize measurement-based care
Summary and Key Points

Although bipolar disorder is a chronic disorder with lifelong episodes, recovery is possible for some individuals.

Predictors of relapse are important for clinicians to recognize for appropriate treatment.

Residual symptoms are associated with recurrence and poor functional outcomes.

Increased clinician use of treatment guidelines, measurement-based care, and understanding of adherence issues may be beneficial for patient outcomes.