Screening, Diagnosis, and Treatment of Patients with Both Bipolar Disorder and Borderline Personality Disorder

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Brown Medical School
Providence, Rhode Island

3 Ds of Treatment

- Diagnosis
- Discuss
- Decide

Step 1

- Diagnosis
  - Good treatment begins with a good diagnostic evaluation

Frequency of Co-occurrence

- Frequency of BD in patients with BPD
  - BD-I (9 studies, 634 patients) – 9.3%
  - BD-II (8 studies, 949 patients) – 10.9%

- Frequency of BPD in patients with BD-I (12 studies, 598 patients) – 10.7%
- Frequency of BPD in patients with BD-II (7 studies, 261 patients) – 22.9%

Underrecognition of Bipolar Disorder

- Surveys of members of the National Depressive and Manic-Depressive Association
  - 1994 Survey Results
    - 73% reported at least 1 incorrect diagnosis
  - 2000 Survey Results
    - 69% reported at least 1 incorrect diagnosis
    - 4 physicians and 8 to 10 years until correct diagnosis

BPD = borderline personality disorder; BD = bipolar disorder; BD-I = bipolar I disorder; BD-II = bipolar II disorder.

Is Bipolar Disorder Underrecognized?

Proving a Disorder is Underdiagnosed

Nonbipolar

Re-evaluate

Nonbipolar

Bipolar

Studies of Underdiagnosis of Bipolar Disorder

- Angst et al. (2010)
- Angst et al. (2011)
- Benazzi (1997)
- Ghaemi et al. (2000)
- Ghaemi et al. (1999)
- Hantouche et al. (1998)
- Manning et al. (1997)
- Mantere et al. (2008)
- McCombs et al. (2007)

Why is Bipolar Disorder Underrecognized?

- First episode is often depression
- Failure to inquire
- Average duration of depressive episodes is longer than manic/hypomanic episodes
- When symptomatic, the majority of the time is in depressive phase
  - 67% depressed
  - 13% mixed
  - 20% manic/hypomanic
- Many individuals do not come for treatment of hypomanic episodes
- State dependent recall
- Method of inquiry

Clinical Implications of Underrecognizing Bipolar Disorder

- Undertreatment with mood stabilizer agents
- Possible overtreatment with antidepressant medications
- Poorer outcome
- Increased costs of care

Efforts to Improve the Recognition of Bipolar Disorder

- Physician education
- Direct to consumer advertising
- Development of screening scales

Is Bipolar Disorder Overdiagnosed?
Bipolar Disorder Overdiagnosis in Patients with Substance Abuse

- Participants
  - 21 patients participating in substance treatment program
  - All had been previously diagnosed with bipolar disorder
- Method
  - Interviewed with the SCID
  - Prior hospital records reviewed when possible (though this did not alter SCID diagnosis)
- Results
  - Only 9 of 21 (42.9%) patients met diagnostic criteria for bipolar disorder

SCID = Structured Clinical Interview for DSM-IV.

Bipolar Disorder Overdiagnosis in Patients with Substance Abuse – Second Study

- Participants
  - 85 patients admitted to dual diagnosis unit
  - All carried a diagnosis of bipolar disorder from their outpatient psychiatrist
- Method
  - Interviewed with the SCID by senior author
  - Information obtained from outpatient psychiatrist and family meetings
- Results
  - Only 28 of 85 (33%) patients met diagnostic criteria for bipolar disorder


Reasons for Bipolar Disorder Overdiagnosis in Patients with Substance Abuse

Reasons for not meeting bipolar disorder criteria
1. Insufficient number of symptoms—55%
2. Insufficient duration—12%
3. Unable to identify abstinent periods—36%
4. Mood episodes only occur within 1 month of significant substance misuse (ie, intoxication, withdrawal)—63%


Proving a Disorder is Overdiagnosed

Nonbipolar → Bipolar
Re-evaluate

Nonbipolar → Nonbipolar → Nonbipolar → Bipolar

The Rhode Island MIDAS Project

- MIDAS = Methods to Improve Diagnostic Assessment and Services
- www.rhodeislandhospital.org/services/mental-health/midas-.html

Underrecognition of Psychiatric Diagnostic Comorbidity

Broad-based SCID studies
Shear et al (2000)
Miller et al (2001)

Single-disorder studies
Davidson et al (1990)—PTSD
Markowitz et al (1989)—dysthymic disorder

PTSD = posttraumatic stress disorder.
Methods

- Participants
  - 700 psychiatric outpatients
  - 58.3% female
  - Mean age 39.9 years
- Measures
  - Self-report of prior diagnosis of bipolar disorder
  - SCID
  - FH-RDC

Diagnosis of Bipolar Disorder

- Self-report of prior bipolar diagnosis 20.7%
- SCID diagnosis of bipolar disorder 12.9%
- SCID confirmation of prior diagnosis 43.4%

Agreement between SCID and Self-Report of Prior Bipolar Diagnosis

<table>
<thead>
<tr>
<th>SCID Bipolar Diagnosis (&quot;Gold Standard&quot;)</th>
<th>Present</th>
<th>Absent</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-reported Prior Dx of Bipolar D/O</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>63</td>
<td>82</td>
<td>145</td>
</tr>
<tr>
<td>No</td>
<td>27</td>
<td>528</td>
<td>555</td>
</tr>
<tr>
<td>Total</td>
<td>90</td>
<td>610</td>
<td>700</td>
</tr>
</tbody>
</table>

But What about Validity?

Proving a Disorder is Overdiagnosed

<table>
<thead>
<tr>
<th>Bipolar</th>
<th>Nonbipolar</th>
<th>Re-evaluate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bipolar</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonbipolar</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Family History of Bipolar Disorder in First-Degree Relatives

<table>
<thead>
<tr>
<th>SCID Bipolar</th>
<th>Previous Bipolar-Not Confirmed</th>
<th>Not Bipolar</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>Relatives at Risk</td>
<td>Morbid Risk</td>
<td>Relatives at Risk</td>
</tr>
<tr>
<td>Bipolar Disorder</td>
<td>326</td>
<td>345</td>
</tr>
<tr>
<td>Nonbipolar</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3-group $X^2 = 27.1$, $P < .001$
A > C $X^2 = 27.3$, $P < .001$
A > B $X^2 = 6.34$, $P < .02$
B = C $X^2 = 1.21$, ns
Why is Bipolar Disorder Overdiagnosed?

- Missed diagnoses on the SCID
- Antidepressant induced mania/hypomania
- Direct to consumer advertising
- Inappropriate use of screening questionnaires
- Diagnose what you can treat
- "Campaign" to improve diagnostic recognition

Clinical Implications of Overdiagnosing Bipolar Disorder

- Overtreatment with mood stabilizer agents
- Overprescription of medications generally
- Overexposure to medication side effects
- Never-ending search for the “magic pill”
- Undertreatment with psychotherapy

Is There a Risk of Overdiagnosing BPD in Patients with Bipolar Disorder?

Yes
Of course

Is There a Risk of Overdiagnosing Bipolar Disorder in Patients with BPD

Yes
And we have data

BPD = borderline personality disorder.

Agreement between SCID and Self-Report of Prior Bipolar Diagnosis

<table>
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<td>Total</td>
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<td>610</td>
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</tbody>
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What Diagnoses are Associated with the Overdiagnosis of Bipolar Disorder?

- Comparison groups
  - 82 patients overdiagnosed with bipolar disorder
  - 528 never diagnosed with bipolar disorder

What Diagnoses are Associated with the Overdiagnosis of Bipolar Disorder? Results of Univariate Analyses

<table>
<thead>
<tr>
<th>DSM-IV Disorder</th>
<th>Bipolar Disorder Overdiagnosed (n = 82)</th>
<th>Never Bipolar (n = 528)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current PTSD</td>
<td>25.6%</td>
<td>11.4%</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Lifetime MDD</td>
<td>82.9%</td>
<td>67.6%</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>Lifetime eating disorder</td>
<td>19.4%</td>
<td>11.4%</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Lifetime ICD</td>
<td>18.3%</td>
<td>9.7%</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Antisocial personality disorder</td>
<td>7.3%</td>
<td>2.1%</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>BPD</td>
<td>24.4%</td>
<td>6.1%</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

MDD = major depressive disorder; ICD = impulse control disorder.

What Diagnoses are Associated with the Overdiagnosis of Bipolar Disorder? Logistic Regression Analysis

<table>
<thead>
<tr>
<th>DSM-IV Disorder</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current PTSD</td>
<td>1.9</td>
<td>1.0-3.5</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Lifetime MDD</td>
<td>1.7</td>
<td>0.9-3.2</td>
<td>ns</td>
</tr>
<tr>
<td>Lifetime eating disorder</td>
<td>1.4</td>
<td>0.7-2.7</td>
<td>ns</td>
</tr>
<tr>
<td>Lifetime ICD</td>
<td>2.0</td>
<td>1.0-3.9</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Antisocial personality disorder</td>
<td>2.2</td>
<td>0.7-6.6</td>
<td>ns</td>
</tr>
<tr>
<td>BPD</td>
<td>3.7</td>
<td>1.9-7.2</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>


Screening

• Part 1 of a 2-stage diagnostic process
• Goal of screening
  – Improve diagnostic detection
• Characteristics of a good screening test
  – High sensitivity
  – High negative predictive value

Mood Disorders Questionnaire (MDQ)

• 3 parts
  – 13 yes/no symptom questions
  – 1 yes/no co-occurrence question
  – 1 4-point rating of impairment
• Cutoff
  – > 7 symptom items
  – Co-occur
  – Moderate or serious impairment


20 Studies of the MDQ

• 5479 participants
• Sensitivity—61.3%
• Specificity—87.5%
• Positive Predictive Value—58.0%
• Negative Predictive Value—88.9%

Performance of the MDQ in Different Settings

<table>
<thead>
<tr>
<th>Sample</th>
<th>N</th>
<th>BD Prevalence</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gen Pop</td>
<td>1875</td>
<td>5.8%</td>
<td>25.9%</td>
<td>97.9%</td>
<td>43.1%</td>
<td>95.6%</td>
</tr>
<tr>
<td>Psych Outpts</td>
<td>943</td>
<td>14.7%</td>
<td>64.7%</td>
<td>82.3%</td>
<td>38.8%</td>
<td>93.1%</td>
</tr>
<tr>
<td>Mood Disorder</td>
<td>2052</td>
<td>39.1%</td>
<td>64.7%</td>
<td>81.1%</td>
<td>68.7%</td>
<td>78.2%</td>
</tr>
</tbody>
</table>

PPV = positive predictive value; NPV = negative predictive value.

Sensitivity of the MDQ for Bipolar I and Bipolar II Disorders

- 12 studies
- 12/12 studies found higher sensitivity for BD-I
- Summing across studies
  - BD-I—66.3%
  - BD-II—36.6%

Problems with the MDQ as a Screening Scale

- Inadequate sensitivity
  - 1st stage of 2-stage evaluation process
  - Sensitivity in psychiatric patients and mood disorder patients—64.7%
- Establishment of cut-off
  - Maximize agreement with gold standard
  - Maximize sensitivity

Misuse of the MDQ as a Case-Finding Measure

Impact of Bipolar Disorder on a US Community Sample

- Compared MDQ+ and MDQ- participants on indices of psychosocial impairment
- Reason for study:
  - because “it is essential that health care providers fully understand the nature and intensity of the psychosocial impact of bipolar disorder in the United States, so that appropriate diagnostic procedures and treatments are offered earlier in the course of the disease to prevent human suffering and reduce the burden of illness.”
- No mention of modest PPV of MDQ in general population

Use of Health Care Services among Persons Who Screen Positive for Bipolar Disorder

- More than half of MDQ positives were not diagnosed with bipolar disorder by treating clinicians
- Authors indicated that these clinicians “failed to detect” or “misdiagnosed” bipolar disorder
- Authors noted a low percentage of these individuals were prescribed mood stabilizers and a high percentage were prescribed antidepressants
  - Indicated these patients were “inappropriately treated”
- Conclusion: The results of this US-population-based study indicate that bipolar disorder is an underdiagnosed and often inappropriately treated illness. Underdiagnosis and inappropriate treatment of bipolar disorder were particularly common in the primary care setting but were also alarmingly high among psychiatrists, who did not detect bipolar disorder among approximately half of respondents who screened positive for the disorder on the MDQ.
Bipolar I and II Disorders in a Random and Representative Australian Population

- "2.5% lifetime prevalence for bipolar I and II disorders represents a credible assessment in this Australian population\)


Titles of Other Papers

- Bipolar Disorders in Australia: A Population-based Study of Excess Costs
- Bipolar Depression in a Low-income Primary Care Clinic
- Fibromyalgia and Bipolar Disorder: A Potential Problem?
- Risk Factors of Treatment Resistance in Major Depression: Association with Bipolarity


Problems with the MDQ as a Case-Finding Measure

- Low Positive Predictive Value
  - Positive predictive value is influenced by disorder prevalence
  - The majority of individuals who are MDQ positive, do not have bipolar disorder

Screening for Bipolar Disorder and Finding BPD

- 480 psychiatric outpatients interviewed with SCID
  - 52 diagnosed with bipolar disorder
  - 44 diagnosed with BPD
    - 12 diagnosed with both
- Patients completed the MDQ
  - 98 screened positive on the MDQ
    - 23 diagnosed with bipolar disorder
    - 27 diagnosed with BPD


A Critique of the Concept of Using a Questionnaire to Screen for Bipolar Disorder

Why is bipolar disorder underdiagnosed?
- Are clinicians failing to inquire about a history of mania or hypomania?
- Are they failing to inquire properly?
- Are they asking questions that are insufficiently sensitive for detecting bipolar disorder?
- Are they failing to correctly interpret patients' responses to appropriate inquiry?

Problems with Using the MDQ in a Mental Health Setting
- Inadequate sensitivity
- Modest positive predictive value
  - Still need a competent psychiatric evaluation
  - Risk of overdiagnosis

Underdiagnosis of BPD

- 500 patients evaluated by psychiatrists with unstructured interview
- Separate sample of 409 administered SIDP-IV

Results
- More BPD diagnoses made on SIDP-IV 14.4% vs 0.4%
- When SIDP-IV information presented to clinicians more BPD diagnoses were made (9.2% vs 0.4%)

Other Studies Comparing Prevalence of BPD Based on Clinical and Structured Interviews

- Comtois et al (2014)
  - 159 community mental health center patients
  - Structured interview—15.1%
  - Clinical interview—6.9%

  - College mental health clinic
  - Structured interview—20%
  - Clinical interview—1.6%/4.2%


Screening

- Screening for BPD
  - Screening scales not used
  - Psychiatric review of systems
  - Polythetically defined criteria
- Can a “gate criterion” be identified to screen for BPD
  - High sensitivity
  - High negative predictive value

Audience Question

1. Avoid abandonment
2. Unstable relationships
3. Identity disturbance
4. Impulsivity
5. Suicidality/self-injury
6. Affective instability
7. Emptiness
8. Anger
9. Stress-induced paranoia/dissociation

Analysis of the MIDAS Project Data

- 3674 psychiatric outpatients
  - 60.2% female
  - 87.1% white
  - 38.8 years
- Semi-structured interview
  - BPD section of the SIDP-IV


Results

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odd-even split</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odd ID numbers</td>
<td>94.3%</td>
<td>81.6%</td>
<td>37.5%</td>
<td>99.2%</td>
</tr>
<tr>
<td>Even ID numbers</td>
<td>91.4%</td>
<td>82.3%</td>
<td>38.2%</td>
<td>98.8%</td>
</tr>
<tr>
<td>Temporal split</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First third (n = 1225)</td>
<td>92.5%</td>
<td>76.9%</td>
<td>32.8%</td>
<td>98.8%</td>
</tr>
<tr>
<td>Second third (n = 1225)</td>
<td>91.5%</td>
<td>83.7%</td>
<td>39.7%</td>
<td>98.8%</td>
</tr>
<tr>
<td>Last third (n = 1234)</td>
<td>94.5%</td>
<td>85.1%</td>
<td>42.6%</td>
<td>99.3%</td>
</tr>
<tr>
<td>Total sample (N = 3674)</td>
<td>92.8%</td>
<td>81.9%</td>
<td>37.9%</td>
<td>99.0%</td>
</tr>
</tbody>
</table>


Audience Question

1. Avoid abandonment
2. Unstable relationships
3. Identity disturbance
4. Impulsivity
5. Suicidality/self-injury
6. Affective instability
7. Emptiness
8. Anger
9. Stress-induced paranoia/dissociation
Other Studies of Sensitivity of BPD Criteria

<table>
<thead>
<tr>
<th>Author</th>
<th>Sample</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farmer et al (2002)</td>
<td>149 “symptomatic volunteers”</td>
<td>92%</td>
</tr>
<tr>
<td>Grilo et al (2004)</td>
<td>130 Hispanic substance abusers</td>
<td>97%</td>
</tr>
<tr>
<td>Grilo et al (2001)</td>
<td>668 patients</td>
<td>94%</td>
</tr>
<tr>
<td>Korfine et al (2009)</td>
<td>45 hospitalized and community BPD</td>
<td>91%</td>
</tr>
<tr>
<td>Leppanen et al (2013)</td>
<td>71 BPD patients in psychotherapy trial</td>
<td>89%</td>
</tr>
<tr>
<td>Nurnberg et al (1991)</td>
<td>100 psychiatric outpatients</td>
<td>100%</td>
</tr>
<tr>
<td>Pfohl et al (1986)</td>
<td>131 psychiatric patients</td>
<td>93%</td>
</tr>
<tr>
<td>Reich et al (1990)</td>
<td>159 psychiatric outpatients</td>
<td>97%</td>
</tr>
</tbody>
</table>

Step 2

- Explain diagnosis
- Provide educational information

Step 3

- Discuss treatment options

Problems with the Treatment Literature

- Lack of generalizability

Generalizability of Treatment Studies of BPD

- Examined exclusion criteria that occurred in > 10% of 32 medication studies of bipolar depression in a review by Frye (2011)
  - Impact of each criterion
  - Impact of meeting any criterion
- Applied criteria to
  - 785 individuals diagnosed with bipolar depression in NESARC study
  - Subset of 276 individuals who received treatment in past year

Generalizability of Medication Treatment Studies of BPD

<table>
<thead>
<tr>
<th>Exclusion Criterion</th>
<th>% Excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychosis</td>
<td>5.2</td>
</tr>
<tr>
<td>Current substance use disorder</td>
<td>29.9</td>
</tr>
<tr>
<td>Lifetime bipolar disorder</td>
<td>29.7</td>
</tr>
<tr>
<td>Current major depressive disorder</td>
<td>16.2</td>
</tr>
<tr>
<td>Significant suicidal risk</td>
<td>2.2</td>
</tr>
<tr>
<td>Significant medical condition</td>
<td>32.5</td>
</tr>
<tr>
<td>Pregnancy/breastfeeding</td>
<td>1.2</td>
</tr>
<tr>
<td>Current psychotropic medication</td>
<td>NA</td>
</tr>
<tr>
<td>Any criterion</td>
<td>75.9%</td>
</tr>
</tbody>
</table>

NESARC = National Epidemiological Survey on Alcohol and Related Conditions.
Generalizability of Psychotherapy Treatment Studies of BPD

8 criteria used in > 10% psychotherapy trials

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<td>5.2</td>
</tr>
<tr>
<td>Current substance use disorder</td>
<td>29.9</td>
</tr>
<tr>
<td>Lifetime bipolar disorder</td>
<td>29.7</td>
</tr>
<tr>
<td>Currently in therapy</td>
<td>NA</td>
</tr>
<tr>
<td>Intellectual disability</td>
<td>NA</td>
</tr>
<tr>
<td>Any criterion</td>
<td>51.3%</td>
</tr>
</tbody>
</table>


Generalizability of Medication Treatment Studies of Bipolar Depression

7 criteria used in > 10% medication trials

<table>
<thead>
<tr>
<th>Exclusion Criterion</th>
<th>% Excluded All Participants (n = 785)</th>
<th>% Excluded Tx Seeking (n = 276)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current drug use disorder</td>
<td>12.4</td>
<td>13.7</td>
</tr>
<tr>
<td>Current alcohol use disorder</td>
<td>23.3</td>
<td>19.4</td>
</tr>
<tr>
<td>Significant medical condition</td>
<td>19.5</td>
<td>26.3</td>
</tr>
<tr>
<td>Psychosis</td>
<td>5.7</td>
<td>11.9</td>
</tr>
<tr>
<td>Significant suicidal risk</td>
<td>24.1</td>
<td>32.0</td>
</tr>
<tr>
<td>Pregnancy/breastfeeding</td>
<td>6.6</td>
<td>7.9</td>
</tr>
<tr>
<td>Current psychotropic medication</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Any criterion</td>
<td>58.7%</td>
<td>63.9%</td>
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Real-World Pharmacologic Treatment of BPD: European Drug Safety Project

Patients
- 2195 inpatients
- 58 hospitals in Germany, Switzerland, Austria
- Principal diagnosis of BPD (2.5%) of all patients in the study
- Comorbid diagnoses not recorded
- Cross-sectional analysis

European Drug Safety Project Results

Rates of Polypharmacy
- Mean number of medications = 2.8
- 54% on 3+ psychoactive medications

Medications used
- Antidepressants 70.0%
- Antipsychotics 69.1%
- Anticonvulsants 32.5%
- Benzodiazepines 29.6%


European Drug Safety Project Results: Changes over Time

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Quetiapine</td>
<td>7.5%</td>
<td>32.9%</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>5.8%</td>
<td>7.2%</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>13.3%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Risperidone</td>
<td>5.4%</td>
<td>5.4%</td>
</tr>
<tr>
<td>SSRIs</td>
<td>39.2%</td>
<td>39.2%</td>
</tr>
<tr>
<td>SNRIs</td>
<td>6.6%</td>
<td>18.2%</td>
</tr>
</tbody>
</table>

SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor.

Cochrane Review of Pharmacotherapy of BPD

- Search up to June 2008
- 27 randomized controlled trials
- Total of 1714 participants (2 studies > 300 patients, most of small N)
- Most common exclusion criteria
  - Bipolar disorder, psychosis, current MDD, substance use disorder, suicidal ideation

Cochrane Review—Medications Studied in Placebo Controlled Trials

<table>
<thead>
<tr>
<th>Medication</th>
<th># Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine</td>
<td>6</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>1</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>1</td>
</tr>
<tr>
<td>First-generation</td>
<td>5</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>2</td>
</tr>
<tr>
<td>Topiramate</td>
<td>3</td>
</tr>
<tr>
<td>Valproate</td>
<td>2</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>1</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>2</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>1</td>
</tr>
<tr>
<td>Mianserin</td>
<td>1</td>
</tr>
<tr>
<td>Omega-3 Fatty Acids</td>
<td>2</td>
</tr>
<tr>
<td>Phenerazine</td>
<td>1</td>
</tr>
</tbody>
</table>


Cochrane Review of Pharmacotherapy of BPD—Results of Meta-Analysis

- First-generation antipsychotics
  - Haloperidol: anger
- Second-generation antipsychotics
  - Aripiprazole: anger, impulsivity, interpersonal relationships, depression, anxiety
  - Olanzapine: anger, affective instability
  - Ziprasidone: no benefit


Cochrane Review of Pharmacotherapy of BPD—Results of Meta-Analysis

- Antidepressants
  - No benefit
- Mood Stabilizers
  - Valproate: anger, interpersonal relationships
  - Lamotrigine: anger, impulsivity
  - Topiramate: anger, interpersonal problems, impulsivity
- Omega-3 Fatty Acids
  - Suicidality, depression


Cochrane Review of Pharmacotherapy of BPD—Conclusions

1) No evidence of efficacy for symptoms of: abandonment, emptiness, identity disturbance, dissociation
2) Robustness of findings is low
   - Few studies
   - Small sample sizes for most studies
   - Varied measures
   - Exclusion criteria reduce generalizability
3) No evidence of efficacy of polypharmacy, and therefore this should be avoided when possible


Cochrane Review of Pharmacotherapy of BPD—Conclusions

4) Mood stabilizers first-line treatment for affective dysregulation. Second-generation antipsychotics also effective
5) Mood stabilizers preferred for impulsivity
6) Little evidence for efficacy of SSRIs. No studies of SSRIs in patients with MDD and BPD


Review—Medications for Bipolar Depression

<table>
<thead>
<tr>
<th>Medication</th>
<th># Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine</td>
<td>1</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>2</td>
</tr>
<tr>
<td>Olanzapine-fluoxetine</td>
<td>2</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>5</td>
</tr>
<tr>
<td>Lithium</td>
<td>2</td>
</tr>
<tr>
<td>Valproate</td>
<td>1</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>7</td>
</tr>
<tr>
<td>Antidepressant alone</td>
<td>5</td>
</tr>
<tr>
<td>Antidepressant + mood stabilizer</td>
<td>7</td>
</tr>
</tbody>
</table>

Review—Medications for Bipolar Depression

<table>
<thead>
<tr>
<th>Medication</th>
<th>Δ HAMD</th>
<th>Δ MADRS</th>
<th>Remission</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>--</td>
<td>ND</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>--</td>
<td>--</td>
<td>ND</td>
<td>+</td>
</tr>
<tr>
<td>Valproate</td>
<td>ND</td>
<td>ND</td>
<td>--</td>
<td>+</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>--</td>
<td>ND</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>ND</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Olan-Flu combo</td>
<td>ND</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>


Review—World Psychiatric Association Report on Treatment for Bipolar Depression

- Strongest empirical support for quetiapine and olanzapine-fluoxetine combination
- Treatment of comorbid conditions:
  - No mention of BPD


Treatment Studies of Patients with BPD and Bipolar Disorder

- Very little data
- Post hoc analyses in 2 controlled studies comparing outcome in BD-I patients with and without BPD
  - Swartz et al (2005) treatment study of pharmacology algorithm + Interpersonal and Social Rhythm Therapy


Placebo-Controlled Studies of BPD and Bipolar Disorder

Patients: 30 with BPD and history of BD-II
Exclusion: current MDD, hypomania, BD-I
Medication: Divalproex sodium (mean dose 850 mg)
Duration: 24 weeks
Measures: SCL-90, modified Overt Aggression Scale

Results: Divalproex sodium significantly more effective on
SCL-90 interpersonal sensitivity
SCL-90 anger/hostility
modified Overt Aggression Scale

SCL = Symptom Checklist.

Official Treatment Guidelines for BPD

APA
1. Psychotherapy is first-line treatment
2. Recommend symptom-specific medication treatment
   • SSRIs for affective dysregulation or impulsivity
   • Mood stabilizers for impulsivity
   • Antipsychotics for cognitive-perceptual Sx

NICE (National Institute of Clinical Excellence)
1. Psychotherapy is first-line treatment
2. Do not recommend medication for BPD symptoms
3. Recommend medication for comorbid conditions


### Empirical Data on the Treatment of Patients with Bipolar Disorder and BPD

Practically none

### In the Absence of Data

**What Do You Do?**

#### A. General Principles of "Medication Management"

- Humility
- Do not let patients define themselves by their disorder
- Collaborative
- Do not be rigid
- Set limits
- Be willing to be wrong
- Think long-term

#### In the Absence of Much Data

**What Do You Do?**

8. Set expectations regarding medication
   - Prevent mania/hypomania recurrence
   - Do not let patients “bipolarize” affective instability
   - Emotional control vs demoralization/symptom relief
9. Remember that improvement may be the placebo effect
10. Keep medications to lowest number
11. Try to avoid medicating transient low distress tolerance
12. Adequate duration and dosage
13. Switching preferred to augmenting
14. Measure outcome at every visit (www.outcometracker.org)
15. Involve the family
16. Focus on functioning and symptom management rather than symptom elimination
17. Acceptance
18. Promote healthy lifestyle

#### B. Other medication/treatment issues

- Addiction issues (benzodiazepines, stimulants)
- Ongoing psychotherapy
  » Sometimes require it, sometimes wait

#### C. Selecting medication(s)

- Dialogue regarding mood stabilizer
- If partial response what should be added?
- Should antidepressants be used?

### Data We Need

1. Placebo-controlled studies of MDD and BPD
2. Placebo-controlled studies of bipolar disorder and BPD
3. Controlled open-label studies of polypharmacy in patients with bipolar disorder and BPD
4. Increased external validity of placebo-controlled studies —role of the FDA
Practical Take-Aways

- 20% of patients with bipolar disorder have borderline personality disorder
- Assessment of the affective instability criterion of borderline personality disorder can be used to screen for the disorder
- Do not let patients with bipolar disorder define themselves by their disorder
- There are no placebo-controlled studies of patients with borderline personality disorder and bipolar depression