Antidepressant Utilization in Bipolar Disorder: What Is the Evidence?
Today’s Speakers

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New York, NY
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Key Objectives

Overview of antidepressant utilization in bipolar disorder (BD)

Case Study: Ms. A*
Assess patient for BD and discuss treatment options

Case Study: Ms. A*
Discuss alternative scenarios that may influence treatment decisions

Summary of clinical evidence and remaining uncertainties about the role of antidepressants in BD

*Case study was developed based on the combined experience of clinicians and does not reflect an actual patient.
Antidepressant Utilization in Bipolar Disorder
Audience Polling Question

How often do you prescribe antidepressants for patients diagnosed with bipolar disorder?

A. Never
B. Rarely
C. Sometimes
D. Often
Antidepressants Are Commonly Used in Treatment Regimens for BD

Use of Antidepressants in BD in Real-World Settings

Approximately 30% to 50% of patients with BD receive antidepressants, according to real-world studies\textsuperscript{1-3}

- Modern antidepressants (eg, SSRIs/SNRIs) are used far more frequently than older antidepressants (eg, TCAs)\textsuperscript{2}
- Antidepressants are most often prescribed in combination with mood stabilizers and atypical antipsychotics\textsuperscript{3}
- Less than 5% of patients receive antidepressants as monotherapy\textsuperscript{3}

BD, bipolar disorder; SNRI, selective norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Antidepressant Use in BD

- In randomized trials, antidepressant use in BD has yielded mixed results

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Response rates, %</th>
<th>Switch risk, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDRI</td>
<td>33–55</td>
<td>11–20</td>
</tr>
<tr>
<td>MAOI</td>
<td>46–81</td>
<td>4–21</td>
</tr>
<tr>
<td>SSRI</td>
<td>36–86</td>
<td>0–12</td>
</tr>
<tr>
<td>SNRI</td>
<td>36–48</td>
<td>6–13</td>
</tr>
<tr>
<td>TCA</td>
<td>41–57</td>
<td>8–50</td>
</tr>
</tbody>
</table>

Response and Switch Rates From Randomized Trials

International Society for Bipolar Disorders Task Force Consensus

- Current evidence for antidepressant use in BD is limited; much evidence is methodically weak
- Insufficient evidence to endorse the use of antidepressants in BD, although individual patients may see benefits

BP, bipolar disorder; MAOI, monoamine oxidase inhibitor; NDRI, norepinephrine-dopamine reuptake inhibitor; SNRI, selective norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.


The information provided by PsychU is intended for your educational benefit only. It is not intended as, nor is it a substitute for, medical care, advice, or professional diagnosis. Users seeking medical advice should consult with their physician or other healthcare professional.
# Factors That May Influence Treatment Decisions

<table>
<thead>
<tr>
<th>Course(^1)</th>
<th>Episode characteristics(^1)</th>
<th>Residual symptoms(^2)</th>
<th>Patient sex(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comorbid psychiatric illness(^1)</td>
<td>Biomarkers(^4)</td>
<td>Prior personal treatment response(^1)</td>
<td>Tolerance of adverse effects(^1)</td>
</tr>
</tbody>
</table>

**Factors That May Influence Treatment Decisions:**

- General medical condition and risk factors\(^5\)
- Therapeutic priority\(^1\)
- Patient’s view of treatment\(^1\)

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Example of a Simple Schema for Practice of Personalized Medicine

Iterative Process of Clinical Activity

- Accurate diagnosis
- Assess outcome
- Systematically measure outcome

Decision to intervene

Weigh evidence and individual factors

Menu of reasonable choices

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<td>++</td>
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<tr>
<td>C</td>
<td>+++</td>
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</table>

Review treatment options

Implements intervention

Negotiate a plan

Educate the patient

Case Study: Ms. A*

*Case study was developed based on the combined experience of clinicians and does not reflect an actual patient.
Case Study: Introduction to Ms. A*

- **Patient**: Ms. A, a 42-year-old media specialist
- **Chief complaint**: Depression, rule out bipolar disorder
- **Goal**: Assess patient for bipolar disorder and determine treatment options

*Case study was developed based on the combined experience of clinicians and does not reflect an actual patient.*
**Case Study: Ms. A’s Past Psychiatric History***

<table>
<thead>
<tr>
<th>Year Range</th>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990–1994</td>
<td>During high school, briefly hospitalized and diagnosed with acute mania (confounded by heavy marijuana use)</td>
</tr>
<tr>
<td>1994–2000</td>
<td>Maintained on mood stabilizer (middle of the therapeutic range) under care of Dr. Y; graduated with high honors from a prestigious university and completed law school; took a job with a family-owned media company in Manhattan</td>
</tr>
<tr>
<td>2001–2004</td>
<td>After 3 years in stable remission, transitioned medication management to PCP; continued mood stabilizer without change for next 3 years; married and moved to Boston</td>
</tr>
<tr>
<td>2005–2009</td>
<td>Gradually felt depressed, with increasing difficulty getting out of bed; 3-month leave of absence; improved within 2 weeks with CBT; returned to work and remained well for the next 4 years</td>
</tr>
<tr>
<td>2010–2012</td>
<td>Treated for infertility for 2 years without success; stopped medications while trying to conceive</td>
</tr>
<tr>
<td>2013–2015</td>
<td>“My mood was up and down for a couple years after leaving the IVF clinic.” During this time she had 2 brief affairs.</td>
</tr>
<tr>
<td>2016–Nov 2017</td>
<td>Euthymic and functioning well</td>
</tr>
</tbody>
</table>

CBT, cognitive-behavioral therapy; IVF, in vitro fertilization; PCP, primary care physician.

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Case Study: Ms. A’s Current Episode*

November 2017 to present

Ms. A reports feeling trapped in her job and marriage and cannot see any clear solutions. She wonders whether she can continue on at work and reports that she “cannot sleep… it can take me 3 hours to decide which shoes to wear… feel tired all the time…life is pointless”

Medical history

• Unremarkable except for premenstrual migraine headaches during college, infertility, and mild hypothyroidism (corrected with treatment) while on current medication
• Does not smoke, rarely drinks, and denies recreational drug use

Current medication

Thyroid replacement; Omega 3, 2000 mg; Vitamin D 1000 U

*Case study was developed based on the combined experience of clinicians and does not reflect an actual patient.
Case Study: Ms. A’s Current Scores for DSM Major Depression Criteria¹,*

Ms. A’s MADRS-CSR² total score was 35

- Depressed mood
- Sleep
- Decreased interest
- Guilt/Low esteem
- Decreased energy
- Decreased concentration
- Appetite
- Psychomotor
- Suicidal ideation/Morbid thought

MADRS-CSR: Montgomery-Asberg Depression Rating Scale Computer-simulated Rater

DSM: Diagnostic and Statistical Manual of Mental Disorders; MADRS-CSR: Montgomery-Asberg Depression Rating Scale Computer-simulated Rater; WNL: within normal limits.

*Case study was developed based on the combined experience of clinicians and does not reflect an actual patient.

1. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. 2013.
Case Study: Ms. A’s Current Scores for DSM Hypomania/Mania Criteria¹*

Ms. A’s YMRS-CSR² total score was 9

- Elevated mood
- Irritability
- Increased self-esteem
- Decreased sleep
- Talking
- Flight of ideas
- Distractible
- Increased goal activity
- Psychomotor agitating
- Risk taking

YMRS-CSR: Young Mania Rating Scale Computer-simulated Rater

DSM, Diagnostic and Statistical Manual of Mental Disorders; WNL, within normal limits; YMRS-CSR, Young Mania Rating Scale Computer-simulated Rater.

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# Case Study: Ms. A’s Lifetime Illness Characteristics Summary*

<table>
<thead>
<tr>
<th>Bipolarity index</th>
<th>Highest high episode</th>
<th>Age of onset</th>
<th>Course of illness</th>
<th>Response to treatment</th>
<th>Family history</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>Most convincing characteristic</td>
<td>16</td>
<td></td>
<td>Excellent response to initial mood stabilizer; sustained recovery after first month</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Other convincing characteristics</td>
<td></td>
<td></td>
<td>Single manic/euphoric episode, initially confounded by marijuana use</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Known associated feature suggestive of the disorder</td>
<td></td>
<td>Multiple brief depressive episodes with full interepisode recovery</td>
<td>Grandfather’s sister hospitalized for manic depression</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Nonspecific feature suggestive of the disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>No evidence of the disorder</td>
<td></td>
<td></td>
<td></td>
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Based on the evidence described for Ms. A, which do you believe to be the most likely diagnosis?*

A. Bipolar I disorder

B. Bipolar II disorder

C. Bipolar disorder, unspecified

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Potential Strategies for Management of BD Based on Clinical Experience*

• Construct your initial “menu” of reasonable choices
  — Consider evidence-based treatments and guideline recommendations

• Revise menu based on measured results
  — Aim for definitive outcome
  — Stop ineffective/intolerable treatments
  — Continue what works

BD, bipolar disorder.
*Based on the combined clinical experience of clinicians.
Case Study: Consideration of Factors for Antidepressant Treatment*

Dr. G
Factors that suggest standard antidepressants are appropriate for patients like Ms. A

Dr. S
Factors that suggest standard antidepressants are inappropriate for patients like Ms. A

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**Case Study: Ms. A***

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Case Study: Ms. A*
Alternative Scenario 1

What is the effect on your clinical decision if the patient had a previous known positive response during treatment with an SSRI?

SSRI, selective serotonin reuptake inhibitor.

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Case Study: Ms. A*
Alternative Scenario 2

What is the effect on your clinical decision if the diagnosis was “bipolar disorder, unspecified” (formerly bipolar disorder NOS)?

NOS, not otherwise specified.
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Case Study: Ms. A*
Alternative Scenario 3

What is the effect on your clinical decision if the patient has a comorbid generalized anxiety disorder and panic disorder?

Would that affect the inclination to use an SSRI for a current MDE?

MDE, major depressive episode; SSRI, selective serotonin reuptake inhibitor.
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Case Study: Ms. A*
Alternative Scenario 4

What is the effect on your clinical decision if the patient’s self report is discordant with findings on the YMRS-CSR?

Original scenario:
YMRS-CSR total, 9

Alternative scenario:
YMRS-CSR total, 35

Constant and severe

DSM threshold

Subthreshold

Questionable/ Rare

WNL

Elevated mood
Irritability
Increased self-esteem
Decreased sleep
Talking
Flight of ideas
Distractable
Increased goal activity
Psychomotor agitation
Risk taking

YMRS-CSR
Self report

DSM, Diagnostic and Statistical Manual of Mental Disorders; WNL, within normal limits; YMRS-CSR, Young Mania Rating Scale computer-simulated rater.

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Summary & Conclusions
Example of a Simple Schema for Practice of Personalized Medicine

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Decision to intervene

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Educate the patient

Systematically measure outcome

Implement intervention

Negotiate a plan

Assess outcome

Antidepressant Use in Patients With BD: Summary of Evidence*

• No standard antidepressant therapy has proven effective in patients with BD I\(^1\)
• Antidepressants are not appropriate as monotherapy or adjunctive therapy for patients with depression who meet mania/hypomania criteria\(^2\)
• The absolute risk of treatment-emergent hypomania/mania may not be high for most patients (10% to 25%)\(^3\)
  – Only agents proven to increase rate of treatment-emergent mania/hypomania are TCAs and an SNRI\(^2,3\)
  – Higher relative risk for patients with a history of treatment-emergent mania, BD I subtype, and mixed episodes\(^3\)
• Effective management of antidepressant treatment may reduce the risk of treatment-emergent mania/hypomania*
  – Discontinue treatment when ineffective at adequate dose after 2 to 6 weeks*
  – Provide concomitant treatment with antimanic/mood stabilizer\(^2\)

BD, bipolar disorder; BD I, bipolar I disorder; SNRI, selective norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant.

*The information on this slide is based on the combined clinical experience of clinicians.

Antidepressant Use in Patients With BD: Remaining Uncertainties*

- What is the relative risk associated with rechallenging patients with prior history of treatment-emergent mania/hypomania with
  - An antidepressant of a different class?
  - The same antidepressant coadministered with an antimanic agent (mood stabilizer)?
- Is there a dose relationship with the risk of treatment-emergent mania/hypomania?
- Do all features of mania carry the same risk during a mixed episode?
- Does the timing of past rapid cycling influence the risk of treatment-emergent mania/hypomania?
- Does a patient with a recent history of rapid cycling carry the same risk as a patient with a distant history of rapid cycling?
- To what degree should clinicians honor a patient’s willingness to accept the risk of treatment-emergent mania/hypomania?

BD, bipolar disorder.
*The information on this slide is based on the combined clinical experience of clinicians.
Conclusions

There are known risk factors for mood destabilization with standard antidepressant therapy for patients with BD.

Significant uncertainties surrounding the role of standard antidepressant therapy for patients with BD still remain.

The appropriateness of antidepressant therapy for individual patients must be determined on a case-by-case basis.

BD, bipolar disorder.
QUESTIONS
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