Mood Disorders:  
A "Spectrum" Analysis
Learning Objectives

• Utilize evidence-based strategies to identify where patients lie on the mood disorder spectrum

• Optimize treatment strategies for patients based on where they lie along the mood disorder spectrum
PrePoll Question

How many patients do you see with symptoms of mixed depression each week?

1. 0
2. 1-5
3. 6-10
4. 11-15
5. 16-20
6. 21 or more
Sarah is a 20-year-old patient who presents with symptoms of depression (including sadness, feelings of worthlessness, and suicidal ideation) occurring every day for the past month. Which class of medication would be most suitable for this patient?

1. An antidepressant
2. A mood stabilizer
3. An antipsychotic
4. Either 1 or 2
5. There is not enough information about this patient's case to make an informed treatment decision
Clinical interview with Sarah reveals that she has a maternal aunt with bipolar disorder I. Further assessment reveals that Sarah feels distracted and as though her thoughts are racing. Upon speaking with her mother, it is discovered that Sarah has at times been more talkative than usual and irritable with her friends and family. Which class of medication would **NOT** be recommended as monotherapy for this patient?

1. An antidepressant
2. A mood stabilizer
3. An antipsychotic
4. There is not enough information about this patient's case to make an informed treatment decision
Stacey is a 25-year-old patient with bipolar depression who tends to endorse some manic symptoms during depressive episodes. Of the following symptoms, which is the most common subsyndromal mania symptom in patients with mixed depression?

1. Decreased need for sleep
2. Inflated self-esteem
3. Distractibility
4. Increased goal-directed activity
5. High-risk activity
A 33-year-old obese patient with treatment-resistant depression has agreed to a trial of an atypical antipsychotic. Considering this patient's current weight and the wish to avoid any treatment-induced weight gain, which of the following approved treatments would be the least optimal treatment for this patient?

1. Lurasidone
2. Olanzapine/fluoxetine combination
3. Quetiapine
The Mood Disorder Spectrum

<table>
<thead>
<tr>
<th>Depression</th>
<th>Depression with subsyndromal mania</th>
<th>Mixed states</th>
<th>Mania with subsyndromal depression</th>
<th>Mania</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Increasing #/severity of manic symptoms</td>
<td>Increasing #/severity of depressive symptoms</td>
<td></td>
</tr>
</tbody>
</table>

- Although categorical classifications may be useful for clinical practice, the overwhelming majority of the evidence points to a dimensional (spectrum) view of mood disorders
  - eg, treatment response (antidepressant vs. mood stabilizing agent) and links with family history of BP
- Individuals with unipolar depression and "a little bit of mania" are more likely to have an eventual diagnostic conversion to bipolar disorder

So You Think It's Unipolar Depression?

- Over one-third of unipolar patients are eventually re-diagnosed as bipolar
- As many as 60% of patients with BPII are initially diagnosed as unipolar
- Presence of even subthreshold (hypo)mania symptoms is strongly associated with conversion to bipolar disorder
  - Each (hypo)mania symptom increases risk by ~30%

Progression to Bipolar Disorder From MDD With Subthreshold Hypomania

19.6% of patients converted to bipolar disorder during follow-up

N=550 individuals followed for >1 year (mean follow-up: 17.5 years) after a diagnosis of major depression at intake.

Clues Across The Spectrum

<table>
<thead>
<tr>
<th>Clinical History</th>
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<tbody>
<tr>
<td>Unipolar</td>
</tr>
<tr>
<td>Family history of bipolar disorder</td>
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<tr>
<td>Early age at onset of first depressive episode (&lt;25 years)</td>
</tr>
<tr>
<td># of lifetime affective episodes</td>
</tr>
<tr>
<td>Postpartum depressive episodes</td>
</tr>
<tr>
<td># of hospitalizations</td>
</tr>
<tr>
<td>Rapid onset of depressive episodes</td>
</tr>
<tr>
<td>Greater severity of depressive episodes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment History</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unipolar</td>
</tr>
<tr>
<td>Worse response to antidepressants</td>
</tr>
<tr>
<td>Antidepressant-induced hypomania</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Symptoms</th>
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</thead>
<tbody>
<tr>
<td>Unipolar</td>
</tr>
<tr>
<td>Psychotic features</td>
</tr>
<tr>
<td>Atypical depressive symptoms</td>
</tr>
<tr>
<td>Subsyndromal hypomanic symptoms</td>
</tr>
<tr>
<td>Impulsivity</td>
</tr>
<tr>
<td>Aggression</td>
</tr>
<tr>
<td>Hostility</td>
</tr>
<tr>
<td>Comorbid SUD</td>
</tr>
</tbody>
</table>

<table>
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<tr>
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<tr>
<td>Worse response to antidepressants</td>
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<tr>
<td>Antidepressant-induced hypomania</td>
</tr>
</tbody>
</table>

Which Patients With Unipolar Depression Will Convert to Bipolar Disorder?

Which Patients With Unipolar Depression Will Convert to Bipolar Disorder?

Which Patients With Unipolar Depression Will Convert to Bipolar Disorder?

Which Patients With Unipolar Depression Will Convert to Bipolar Disorder?

% of Patients Resistant to Antidepressants

Non-Converters

Converters

Which Patients With Unipolar Depression Will Convert to Bipolar Disorder?

Which Patients With Unipolar Depression Will Convert to Bipolar Disorder?

Weeks Spent in a Psychiatric Hospital

- Non-Converters
- Converters

DIAGNOSIS ALONG THE SPECTRUM
A Rose By Any Other Name…

Depression | Depression with subsyndromal mania | Mixed states | Mania with subsyndromal depression | Mania

Increasing #/severity of manic symptoms | Increasing #/severity of depressive symptoms

"With mixed features" if subthreshold (hypo)manic symptoms co-occur with depressive episodes | "With mixed features" if subthreshold depressive symptoms co-occur with manic episodes

Major depressive disorder (unipolar depression) | Bipolar disorder II | Bipolar disorder I

DSM-5 DIAGNOSIS
Evolution of the DSM

• DSM-IV mixed episode
  – Diagnostic criteria for major depression and mania met at the same time

• DSM-5 mixed features specifier
  – Recognizes the presence of subthreshold (hypo)manic symptoms during a depressive episode
  – Specifier may be applied to major depressive disorder, bipolar II, or bipolar I
DSM-5 Mixed Features Specifier

- Full criteria for a MDE and ≥ 3 of these manic symptoms:
  - Elevated, expansive mood
  - Inflated self-esteem or grandiosity
  - More talkative than usual or pressure to keep talking
  - Flight of ideas or racing thoughts
  - Increase in energy or goal-directed activity (socially, at work or school, or sexually)
  - Increased or excessive involvement in activities that have a high potential for painful consequences (eg, engaging in unrestrained buying sprees, sexual indiscretions, foolish business investments)
  - Decreased need for sleep

- Diagnosis may be complicated by comorbid conditions, including untreated ADHD, personality disorders, and substance abuse

APA Diagnostic and Statistical Manual of Mental Disorders. 5th ed. 2013.
Mixed Features Commonly Encountered in Adults With Both Major Depressive Disorder and Bipolar Disorder: The International Mood Disorders Collaborative Project

% of Individuals Who Met Criteria For Mixed Features During an Index Major Depressive Episode

- MDD: 26.0% (n=149)
- BPII: 34.0% (n=65)
- BPI: 33.8% (n=49)
Depression With Mixed Features (DMX)

- Associated with:
  - Family history of BP
  - Suicidality
  - Antidepressant-induced mania
  - Young age of onset
  - Long duration of illness
  - Poor prognosis
  - Severe depression
  - Antidepressant resistance
  - Females
  - Comorbid anxiety
  - Comorbid SUD
  - Impulse control

The prognosis for depression with co-occurring (hypo)mania (DMX) is much worse than for pure unipolar depression or bipolar depression without mixed features.

Symptoms Most Commonly Seen in DMX

- Irritability
- Distractibility
- Psychomotor agitation
- Racing/crowded thoughts
- Increased talkativeness
- Emotional lability
- Rumination
- Initial or middle insomnia
- Dramatic expressions of suffering
- Impulsivity
- Risky behaviors

Symptoms Most Commonly Seen in DMX

- Psychomotor agitation: 60
- Racing thoughts/flight of ideas: 50
- Irritability: 30
- Distractibility: 20
- Talkativeness: 10
- Increased goal-directed activity: 5
- Risky behavior: 3
- Decreased need for sleep: 2
- Inflated self-esteem: 1
- Elevated mood: 0

DMX Diagnostic Criteria

- Although **irritability**, **distractibility**, and **psychomotor agitation** are among the most common symptoms of DMX, they are excluded from DSM-5 mixed features criteria due to the overlap of these symptoms with other disorders (eg, anxiety disorders) and between mania and depression.

- Some argue that these 3 particular symptoms are the defining features of DMX and that excluding them will lead to misdiagnosis and dangerous treatment strategies.
  - Imagine if we excluded psychosis as a diagnostic feature of schizophrenia?

Non-DSM Criteria for DMX

• Do not exclude agitation, irritability, or distractibility
  – Benazzi criteria
  – Koukopoulos criteria
  – Research-based diagnostic criteria
• Consider family history
• Consider age of onset of depression

Non-DSM Criteria for DMX

4X as many cases of DMX identified using research-based diagnostic criteria

Non-DSM Criteria for DMX

- All patients identified as DMX will indeed have DMX

**HOWEVER,**
- Only 5.1% of individuals who have DMX will be identified
- ~95% at risk of receiving inappropriate treatment

Which is potentially more detrimental?
- Misdiagnosing someone who is "pure unipolar" as DMX?
- Treating unidentified DMX with antidepressants?

Consequences of Misdiagnosis/Inappropriate Treatment

- Years (often a decade or more) of unnecessary suffering
- Treatment resistance?
- Reduced likelihood of responding to eventual appropriate mood stabilizer treatment
- Treatment-emergent activation syndrome (TEAS)
- Suicidality
Treatment Resistance

- Patients with DMX are less likely to respond to treatment-as-usual for major depressive disorder
- Diagnostic conversion from unipolar to bipolar is significantly related to treatment resistance
  - As many as two-thirds of patients whose diagnosis is converted from unipolar to bipolar disorder are treatment resistant
- Approximately half of patients with treatment-resistant "unipolar" depression may actually be bipolar
- Repeated exposure to antidepressants may lead to resistance to mood stabilizers and poorer outcomes in patients without "pure unipolar" depression
  - It may also be that patients with more antidepressant trials were always going to be resistant

Treatment-Emergent Activation Syndrome (TEAS)

- Over 20% of patients may experience TEAS related to antidepressants
- Most common with serotonin-norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs)
- Hypothetically related to high noradrenergic potency
- The presence of even minor, subthreshold (hypo)mania during a depressive episode increases the risk of TEAS

(Hypo)mania
Agitation
Anxiety
Panic attacks
Irritability
Hostility/aggression
Impulsivity
Insomnia
Suicidality

Higher Risk of TEAS

- Bipolar I > bipolar II
- History of antidepressant-induced mania
- Mixed depression
- Low TSH with TCA use
- Hyperthymic temperament
- TCA or SNRI use
- Absence of antimanic mood stabilizer
- Genetic factors
- Comorbid alcoholism
- Female gender + comorbid anxiety disorder

TSH: thyroid-stimulating hormone.

DMX and Suicidality

- Non-euphoric (hypo)manic symptoms (including psychomotor agitation, impulsivity, irritability, and racing/crowded thoughts) combined with depressive symptoms (ie, DMX) = recipe for suicidality
- Presence of mixed features increases risk of suicidality by 4X in both unipolar and bipolar depression
- DMX may underlie the connection between antidepressant use and suicidality
  - Most notably in the pediatric population, in which DMX is often the rule rather than the exception
  - Both young age of onset of depression and DMX symptoms indicate bipolarity

One of the Most Important Questions to Ask Any Patient With Depression

Any mania/hypomania symptoms and/or family history of bipolar disorder?

Every patient. Every time.
DMX and Family History

- Family history of BP
  - 4X higher in DMX than in "pure" unipolar depression
  - Highly associated with patients who have 2+ (hypo)manic symptoms during major depressive episodes (MDEs)
  - As common in DMX as in BP
  - Supports the idea of DMX as a "soft" bipolar disorder and a dimensional rather than a categorical view of mood disorders

Tools for Assessing DMX

See APPENDIX for more details on each assessment tool

- Bipolar Depression Rating Scale (BDRS)
  - Clinician-administered assessment of current symptoms
- Mini International Neuropsychiatric Interview (MINI)
  - Patient self-report assessing current (hypo)manic symptoms
- Clinically Useful Depression Outcome Scale with DSM-5 Mixed (CUDOS-M)
  - Patient self-report assessing current (hypo)manic symptoms
- Hypomania Checklist (HCL-32)
  - Patient self-report that screens for lifetime (hypo)manic symptoms
TREATMENT ALONG THE SPECTRUM
Major Depressive Episodes:
A Trace of Depression Means Treat With an Antidepressant

- Mania with subsyndromal depression
- Depression with subsyndromal mania
- Mixed States
Major Depressive Episodes: A Trace of Mania Means Treat With an Antipsychotic

- Mania
- Depression
- Mixed States
- Mania with subsyndromal depression
- Depression with subsyndromal mania

Antipsychotic
Issues With Existing Treatment Guidelines for DMX

• Any existing guidelines (and FDA approvals) for mixed bipolar disorder refer to DSM-IV criteria (co-occurring threshold-level MDE + threshold-level mania)
  – Recommendations are to treat as mania

• A diagnosis of MDD implies the use of unipolar depression treatment guidelines
  – Possibly ineffective and potentially harmful

• Treatment guidelines for bipolar depression are likely the most applicable to DMX
  – Many are not up to date with the latest clinical trial data (ie, atypical antipsychotics with mood-stabilizing properties)

• Very few studies have yet to focus specifically on DMX
Bipolar Spectrum-Based First-Line Monotherapy Treatment Recommendations

Depression

Depression with subsyndromal mania

Mixed states

Mania with subsyndromal depression

Mania

Increasing #/severity of manic symptoms

Increasing #/severity of depressive symptoms

Unipolar depression?
Bipolar disorder?
Does it matter in terms of choosing the best treatment?

Only those patients with essentially NO symptoms of (hypo)mania should be considered for antidepressant monotherapy

Antidepressant

Atypical Antipsychotic

Mood Stabilizer
Treatment Algorithm for Depression Without Mixed Features

Depression

- Any mania/hypomania symptoms and/or family history of BP?
  - Yes: See DMX treatment guidelines
  - No: Antidepressant monotherapy

  - Antidepressant monotherapy
    - Yes: Therapeutic response to antidepressant monotherapy?
      - Yes: Continue antidepressant monotherapy
      - No: Any mania/hypomania symptoms and/or family history of BP?
        - Yes: Resistant to 2 antidepressant monotherapy trials
        - No: Switch to alternate antidepressant monotherapy
    - No: Any mania/hypomania symptoms and/or family history of BP?
      - Yes: Resistant to 2 antidepressant monotherapy trials
      - No: Continue antidepressant monotherapy

Follow APA treatment guidelines but consider DMX treatment guidelines
Treatment Algorithm for Depression With Mixed Features (DMX)

- Discontinue/taper antidepressant
  - Yes
    - Patient on antidepressant monotherapy?
      - No
        - Discontinue/taper antidepressant
      - Yes
        - Initiate atypical antipsychotic
          - Therapeutic response?
            - No
              - Add or switch to mood stabilizer or switch to different atypical antipsychotic
                - No
                  - Add antidepressant
                - Yes
                  - Therapeutic response?
                    - No
                      - Consider ECT and novel/experimental options
                    - Yes
                      - Continue as maintenance therapy
  - No
    - Therapeutic response?
      - No
        - Add antidepressant
      - Yes
        - Continue as maintenance therapy
### Atypical Antipsychotics

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Evidence of Efficacy in DMX</th>
<th>FDA-Approved for BP Depression</th>
<th>FDA-Approved for BP Mania</th>
<th>FDA-Approved for BP Maintenance</th>
<th>FDA-Approved for MDD</th>
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</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓ (adjunct)</td>
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<tr>
<td>Asenapine</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<td>(with fluoxetine)</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Quetiapine</td>
<td>✓</td>
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<td>✓</td>
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</table>

Asenapine in DMX

Figure 1. Improvement in Depressive Symptoms as Assessed by Least Squares Mean Change From Baseline in MADRS Total Scores

- Error bars indicate standard error.
- *P < .05 vs placebo.
- †P < .05 vs olanzapine.
- Abbreviations: LOCF = last observation carried forward, LS = least squares, MADRS = Montgomery-Asberg Depression Rating Scale.

Asenapine in Mania With Depressive Symptoms (DSM-5 Specifier)

Cut-offs used to define depressive symptom severity in patients with ≥3 depressive features: mild (score ≥1 for MADRS items and ≥2 for PANSS items), moderate (score ≥2 MADRS, ≥3 PANSS), and severe (score ≥3 MADRS, ≥4 PANSS) symptoms; remission defined as MADRS ≤12; post hoc analysis.

Lurasidone in Bipolar Depression With Hypomanic Symptoms (DSM-5 Specifier)

MADRS responder rates (6-week LOCF-endpoint): groups with and without subsyndromal hypomania

**p < 0.01

<table>
<thead>
<tr>
<th>Group</th>
<th>Lurasidone (20–120 mg/day)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subsyndromal hypomania (baseline YMRS ≥4)</td>
<td>51.2</td>
<td>32.2</td>
</tr>
<tr>
<td>Subsyndromal hypomania (score of ≥2 for 2 or more YMRS items)</td>
<td>53.2</td>
<td>31.1</td>
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<tr>
<td>No subsyndromal hypomania</td>
<td>51.1</td>
<td>27.8</td>
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</table>

Change from baseline in YMRS score groups with and without subsyndromal hypomania

<table>
<thead>
<tr>
<th>Group</th>
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<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subsyndromal hypomania (baseline YMRS ≥4)</td>
<td>-2.4</td>
<td>-2.8</td>
</tr>
<tr>
<td>Subsyndromal hypomania (score of ≥2 for 2 or more YMRS items)</td>
<td>-2.3</td>
<td>-2.4</td>
</tr>
<tr>
<td>No subsyndromal hypomania</td>
<td>0.1</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Lurasidone Efficacy in DMX: Montgomery-Åsberg Depression Scale (MADRS)

Baseline Week 1 Week 2 Week 3 Week 4 Week 5 Week 6

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

Baseline Week 1 Week 2 Week 3 Week 4 Week 5 Week 6
0.0 -5.0 -10.0 -15.0 -20.0 -25.0

Effect size = 0.8

* p<0.05; ** p<0.01; *** p<0.001.

Mean daily dose of lurasidone was 36.2 mg/day.

Lurasidone Efficacy in DMX: Young Mania Rating Scale (YMRS)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=100)</th>
<th>Lurasidone (N=108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Change From Baseline</td>
<td>-4.9</td>
<td>-7.0**</td>
</tr>
<tr>
<td>BL mean</td>
<td>10.3</td>
<td>11.1</td>
</tr>
</tbody>
</table>

**p<0.01

Lurasidone Efficacy in DMX: Hamilton Anxiety Rating Scale (HAM-A)

Mean Change From Baseline

BL mean = 16.7 (Placebo, n=100)
BL mean = 17.0 (Lurasidone, n=108)

- BL mean = 16.7
- BL mean = 17.0

***p<0.001

Lurasidone Efficacy in DMX: Sheehan Disability Scale (SDS)

**Mean Change From Baseline**

- **Placebo (n=100)**: -6.4
- **Lurasidone (n=108)**: -11.2***

**BL mean = 20.5**

**BL mean = 19.9**

***p<0.001

Lurasidone Efficacy in DMX: Suicide and TEAS

Efficacy of Olanzapine Monotherapy in the Treatment of Bipolar Depression With Mixed Features

Quetiapine Efficacy in DMX:
Clinical Global Impression (CGI-BD)

Quetiapine Efficacy in DMX: MADRS


*\( p=0.0138 \)
Quetiapine Efficacy in DMX: YMRS

Not significant \((p=0.069)\)

Ziprasidone Monotherapy for DMX: Improvement in Depressive Symptoms

Ziprasidone Monotherapy for DMX: No Improvement in Manic Symptoms

Patients on atypical antipsychotics should be regularly monitored for side effects, including BMI.

<table>
<thead>
<tr>
<th>SEDATION</th>
<th>WEIGHT GAIN</th>
<th>EPS</th>
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<tbody>
<tr>
<td>Aripiprazole</td>
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<td>Clozapine</td>
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<td>Iloperidone</td>
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<td>Cariprazine</td>
<td>Cariprazine</td>
<td>Quetiapine</td>
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<td>Iloperidone</td>
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<tr>
<td>Clozapine</td>
<td>Paliperidone</td>
<td>Risperidone</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Olanzapine</td>
<td>Risperidone</td>
</tr>
</tbody>
</table>
No mood stabilizer is actually approved for use in depression of any kind (unipolar, mixed, bipolar)

There are some data for the efficacy of lamotrigine or valproate for bipolar depression

Lithium is well known for its anti-suicide effects; however, neither lithium nor carbamazepine monotherapy is recommended for the treatment of bipolar depression
Antidepressant Monotherapy for DMX?

• No
• Don't
• Seriously, just don't do it

Antidepressant monotherapy should probably **NOT** be used in patients with even the slightest **hint of (hypo)mania** (or a family history of bipolar disorder)

You will most likely not know if your depressed patient has ever had any (hypo)manic symptoms and/or family history of bipolarity unless you ask

  – Every patient. Every time.

Any patient on antidepressant monotherapy should be regularly monitored for response and emergence of hypomania
Combination Therapy

The treatment of DMX may require a combination of medications.

Common combinations for BP depression include:
- Atypical antipsychotic + mood stabilizer
- Atypical antipsychotic + antidepressant
  - Olanzapine-fluoxetine combination in particular
- Mood stabilizer + antidepressant

The combination of olanzapine or risperidone and carbamazepine is not recommended; always check the safety of any particular combination.

If an antidepressant is prescribed for DMX, it should be used in conjunction with a mood-stabilizing agent (atypical antipsychotic or mood stabilizer).

It is questionable whether adding an antidepressant to a mood stabilizer or an atypical antipsychotic has any therapeutic benefit.

Olanzapine-Fluoxetine Combination in the Treatment of Bipolar Depression With Mixed Features

No significant benefit from adding fluoxetine to olanzapine

Response defined as ≥ 50% reduction in the MADRS total score and < 2 concurrent manic/hypomanic symptoms (measured by the YMRS)

No Faster Recovery From Mixed Depression in Bipolar Disorder When Antidepressants Are Added to Mood Stabilizers (STEP-BD)

355 STEP-BD entrants with major depression + 1 or more manic symptoms

Kaplan-Meier Curve for Time to Recovering/Recovered by Antidepressant Use

Logrank Test
Chi-square = 0.205
DF = 1
P-value = 0.651

### Other Adjunctive Pharmacological Treatment Strategies

<table>
<thead>
<tr>
<th>Modafinil/armodafinil</th>
<th>Omega-3 fatty acids</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Stimulants may worsen symptoms (including irritability, agitation, and TEAS) in patients with DMX</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pramipexole</th>
<th>Ramelteon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folic acid</td>
<td>Celecoxib</td>
</tr>
<tr>
<td>Inositol</td>
<td>Topiramate for weight management</td>
</tr>
<tr>
<td>Ketamine</td>
<td>Benzodiazepines (short-term) for anxiety and agitation</td>
</tr>
<tr>
<td>N-acetyl cysteine</td>
<td></td>
</tr>
</tbody>
</table>

Nonpharmacological Interventions

- Electroconvulsive therapy (ECT)
- Transcranial magnetic stimulation (TMS)
- Sleep deprivation
- Individual or group psychoeducation
  - Focus on early warning signs of relapse
- Interpersonal and family therapy
- Cognitive behavioral therapy

Summary

• Not all patients with depression should be given an antidepressant

• The inappropriate overprescribing of antidepressants has contributed to drug-induced (hypo)manic episodes, treatment resistance, suicidality, and overall poor quality of life for many patients suffering from depression

• If there are any symptoms of (hypo)mania or a family history of bipolar disorder, an antipsychotic with mood-stabilizing properties may be the best option

• You will not know if a depressed patient has (hypo)manic symptoms or a positive family history of bipolar disorder unless you ask! Every patient. Every time.
How many patients do you see with symptoms of mixed depression each week?

1. 0
2. 1-5
3. 6-10
4. 11-15
5. 16-20
6. 21 or more
Posttest Question 1

Sarah is a 20-year-old patient who presents with symptoms of depression (including sadness, feelings of worthlessness, and suicidal ideation) occurring every day for the past month. Which class of medication would be most suitable for this patient?

1. An antidepressant
2. A mood stabilizer
3. An antipsychotic
4. Either 1 or 2
5. There is not enough information about this patient's case to make an informed treatment decision
Clinical interview with Sarah reveals that she has a maternal aunt with bipolar disorder I. Further assessment reveals that Sarah feels distracted and as though her thoughts are racing. Upon speaking with her mother, it is discovered that Sarah has at times been more talkative than usual and irritable with her friends and family. Which class of medication would NOT be recommended as monotherapy for this patient?

1. An antidepressant
2. A mood stabilizer
3. An antipsychotic
4. There is not enough information about this patient's case to make an informed treatment decision
Stacey is a 25-year-old patient with bipolar depression who tends to endorse some manic symptoms during depressive episodes. Of the following symptoms, which is the most common subsyndromal mania symptom in patients with mixed depression?

1. Decreased need for sleep
2. Inflated self-esteem
3. Distractibility
4. Increased goal-directed activity
5. High-risk activity
A 33-year-old obese patient with treatment-resistant depression has agreed to a trial of an atypical antipsychotic. Considering this patient's current weight and the wish to avoid any treatment-induced weight gain, which of the following approved treatments would be the least optimal treatment for this patient?

1. Lurasidone
2. Olanzapine/fluoxetine combination
3. Quetiapine
Bipolar Depression Rating Scale (BDRS)

• Clinician-administered assessment of **current** symptoms

<table>
<thead>
<tr>
<th>Severity of Disturbances to:</th>
<th>Mood</th>
<th>Motivation</th>
<th>Self-worth</th>
<th>Mood lability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep</td>
<td>Concentration/memory</td>
<td>Suicidality</td>
<td>Motor drive</td>
<td></td>
</tr>
<tr>
<td>Appetite</td>
<td>Anxiety</td>
<td>Guilt</td>
<td>Increased speech</td>
<td></td>
</tr>
<tr>
<td>Social engagement</td>
<td>Anhedonia</td>
<td>Psychosis</td>
<td>Agitation</td>
<td></td>
</tr>
<tr>
<td>Energy/activity</td>
<td>Affect</td>
<td>Irritability</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Mini International Neuropsychiatric Interview (MINI)

- Patient self-report assessing **current** (hypo)manic symptoms

---

**Since you have been experiencing your current manic episode, have you almost every day had times when:**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>You felt sad, empty, tearful, down, or depressed?</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>2a</td>
<td>You were less interested in most activities?</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>2b</td>
<td>You had less pleasure doing the activities you used to enjoy?</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>3</td>
<td>You were slowed down in your speech, thoughts, or movements?</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>4a</td>
<td>You had fatigue?</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>4b</td>
<td>You felt without energy?</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>5a</td>
<td>You had feelings of worthlessness?</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>5b</td>
<td>You felt excessively guilty?</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>6</td>
<td>You wished you were dead, considered hurting yourself, made plans to commit suicide or attempted suicide?</td>
<td>NO</td>
<td>YES</td>
</tr>
</tbody>
</table>

**Total =**

---

*If the total number of points is equal to or greater than 3, the patient presents a probable (hypomanic) manic episode with mixed features.*

Clinically Useful Depression Outcome Scale With DSM-5 Mixed Features (CUDOS-M)

- Patient self-report assessing current (hypo)manic symptoms

<table>
<thead>
<tr>
<th>Frequency of each symptom during the prior week</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all</td>
<td>Rarely</td>
<td>Sometimes</td>
<td>Often</td>
<td>Almost always</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptom</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>I felt so happy and cheerful, it was like a high</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I had many brilliant, creative ideas</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I felt extremely self-confident</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I slept only a few hours but woke full of energy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>My energy seemed endless</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I was much more talkative than usual</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I spoke faster than usual</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>My thoughts were racing through my mind</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I took on many new projects because I felt I could do everything</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I was much more social and outgoing than usual</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I did wild, impulsive things</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I spent money more freely than usual</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I had many more thoughts and fantasies about sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hypomania Checklist (HCL-32)

- Patient self-report that screens for **lifetime** (hypo)manic symptoms

<table>
<thead>
<tr>
<th>HCL-32</th>
<th>HCL-32 (continued)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I need less sleep</td>
<td>I am more flirtatious and/or am more sexually active</td>
</tr>
<tr>
<td>I feel more energetic and more active</td>
<td>I talk more</td>
</tr>
<tr>
<td>I am more self-confident</td>
<td>I think faster</td>
</tr>
<tr>
<td>I enjoy my work more</td>
<td>I make more jokes or puns when I am talking</td>
</tr>
<tr>
<td>I am more sociable (make more phone calls, go out more)</td>
<td>I am more easily distracted</td>
</tr>
<tr>
<td>I want to travel and/or do travel more</td>
<td>I engage in lots of new things</td>
</tr>
<tr>
<td>I tend to drive faster or take more risks when driving</td>
<td>My thoughts jump from topic to topic</td>
</tr>
<tr>
<td>I spend more money/too much money</td>
<td>I do things more quickly and/or more easily</td>
</tr>
<tr>
<td>I take more risks in my daily life (in my work and/or other activities)</td>
<td>I am more impatient and/or get irritable more easily</td>
</tr>
<tr>
<td>I am physically more active (sport etc.)</td>
<td>I can be exhausting or irritating for others</td>
</tr>
<tr>
<td>I plan more activities or projects</td>
<td>I get into more quarrels</td>
</tr>
<tr>
<td>I have more ideas, I am more creative</td>
<td>My mood is higher, more optimistic</td>
</tr>
<tr>
<td>I am less shy or inhibited</td>
<td>I drink more coffee</td>
</tr>
<tr>
<td>I wear more colorful and more extravagant clothes/make-up</td>
<td>I smoke more cigarettes</td>
</tr>
<tr>
<td>I want to meet or actually do meet more people</td>
<td>I drink more alcohol</td>
</tr>
<tr>
<td>I am more interested in sex, and/or have increased sexual desire</td>
<td>I take more drugs (sedatives, anti-anxiety pills, stimulants)</td>
</tr>
</tbody>
</table>