Solving Clinical Challenges in Bipolar Disorder

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Overview

Bipolar Disorder – Solving Clinical Challenges

1. Diagnostic Nosology
   - Challenges distinguishing bipolar from unipolar
2. Pharmacologic Treatment
   - Challenges with therapeutic vs side effects
3. Adverse Events
   - Challenges with weight gain/sedation and akathisia
4. Non-Pharmacologic Treatment
   - Challenges with access to evidence-based Rx

Diagnostic Boundaries of Bipolar Disorder

- Complex, variable phenomenology
  - Different subtypes, mood states, courses, age-dependent presentations
- Crucial differential diagnosis
  - MDD
- Confounding comorbidities
  - Substance abuse, anxiety disorders
  - Disruptive behavioral (ADHD, ODD, CD), cluster B disorders
- Measures to enhance diagnostic accuracy
  - Collateral information
  - DSM Screening
    - Mood Disorders Questionnaire
    - Beyond DSM
  - Onset age, atypical symptoms, course, treatment effects, family history

Diagnostic Challenges – Question 1

“Patients are famous for underestimating the number and intensity of past manic or hypomanic episodes, which can lead a clinician to inappropriately diagnosing these patients with a unipolar condition. Do you have any tips for how we can better “flush out” past manic type phenomena when we are first assessing a new patient?”
Diagnostic Challenges I

- Patients present with depression more than mood elevation
- Get collateral history from significant other (more sensitive rater of mood elevation)
- Look for mood elevation symptoms
  - Immediately before or after depressions
  - Triggered by pharmacotherapy
- In depressed patients, assess bipolar outcome risk factors
  - Depression onset prior to age 25; lifetime history of psychosis, 1° relative with mania
  - Presence of 1 risk factor doesn’t substantively increase bipolar outcome risk (which is approximately 25% overall)
  - In contrast, 2 or 3 risk factors substantively increase bipolar outcome risk (to approximately 50% and 67%, respectively)

Substance/Medication-Induced Bipolar and Related Disorder

- Prominent, persistent elevated/irritable/expansive and/or depressed mood/anhedonia
- During/soon after substance intoxication/withdrawal or medication exposure
- Substance/medication capable of producing above mood symptoms
- Not better explained by non-substance induced bipolar disorder
  - e.g., Symptoms persist < 1 month without substance/medication
- Not merely delirium
- Distress, social/occupational impact


Antidepressant Treatment-Emergent Evolution of Bipolar I Disorder from MDD

Antidepressant-Induced Mania More Common in Bipolar II Compared to Unipolar Depression

Meta-Analysis from Clinical Trials

Significance: TCA = SSRI > Placebo TCA > SSRI = Placebo

Switching to Mania (%)

Unipolar Depression

Bipolar II Depression

0.5% 0.7% 0.2%

11.2% 3.7% 4.2%

Meta-Analysis from Clinical Trials


Bipolar Mixed State Conceptualization in DSM-IV-TR vs DSM-5

Main Changes for Bipolar and Related Disorders in DSM-5 Compared to DSM-IV-TR

- “with mixed features” specifier added for Manic, Hypomanic, and Major Depressive Episodes
- Manic Episode with mixed features replaces Mixed Episode
- Antidepressant switching – full Manic/Hypomanic Episode emerging during antidepressant treatment and persisting beyond physiological treatment effect now sufficient for Manic/Hypomanic Episode

**DSM-5 Major Depressive Episode with mixed features (AKA Mixed Depression)**

- Predominant, full depressive episode and \( \geq 3 \) most days:
  - Elevated / expansive mood – Inflated self-esteem / grandiosity
  - Overtalkativeness – Racing thoughts
  - Increased goal-directed activity – Impulsivity
  - Decreased sleep need
- Mixed symptoms objectively evident, not usual behavior
- Mania trumps depression
- Not due to substance / medication

**"Overlapping" Symptoms Not Included in DSM-5 Mixed Specifier**

Symptoms characteristic of both poles:
- Psychomotor agitation (?)
- Distractibility
- Irritability
- Insomnia *per se*
- Indecisiveness

**History of Bipolar I Disorder in Outpatients with History of Major Depressive Episode**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Number of Patients with History of Mania (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression onset ( \leq 25 ) years</td>
<td>48.8% (84/172)</td>
</tr>
<tr>
<td>Family history of mania</td>
<td>66.7% (22/33)</td>
</tr>
</tbody>
</table>

Mean age = 37.5 years; \( P < .0001 \).


**Diagnostic Challenges II**

- Additional bipolar outcome risk factors
  - “Atypical” depressive symptoms
    - Hyperphagia, hypersomnia, anergia
    - Episode accumulation (\( \geq 5 \) lifetime depressions)
    - Postpartum mood elevation
    - Comorbid anxiety/substance use disorder
    - 3 consecutive generations with mood disorders
    - Hyperthymic/cyclothymic temperament

**Most Bipolar Disorder Patients Have at Least 1 Comorbid Axis I Disorder**

- \( 76.5\% \) of BD-I patients
- \( 83.0\% \) of BD-II patients

**Probabilistic Approach to Bipolar Depression**

<table>
<thead>
<tr>
<th>Bipolar I Depression if ( \geq 5 ):</th>
<th>Unipolar Depression if ( \geq 4 ):</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptomatology</strong></td>
<td><strong>Symptomatology</strong></td>
</tr>
<tr>
<td>Hypersomnia</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Hypophagia</td>
<td>Decreased appetite</td>
</tr>
<tr>
<td>Psychomotor retardation</td>
<td>Psychomotor agitation</td>
</tr>
<tr>
<td>Other &quot;atypical&quot; symptoms</td>
<td></td>
</tr>
<tr>
<td>Psychosis and/or pathological guilt</td>
<td>Somnolence</td>
</tr>
<tr>
<td>Mood lability or mania symptoms</td>
<td>Depression</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Onset and Course</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Earlier onset (&lt; 25 years)</td>
<td>Later onset (&gt; 25 years)</td>
</tr>
<tr>
<td>Multiple depressions (( \geq 5 ) episodes)</td>
<td>Long current depression (&gt; 6 months)</td>
</tr>
<tr>
<td>Family History</td>
<td></td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>No bipolar disorder</td>
</tr>
</tbody>
</table>

Confirmation of specific numbers requires further study.

Summary of Clinical Features of Risk of Bipolar Diathesis in Depression

- Onset: Early, postpartum
- Depressive episodes:
  - Hypersomnic-retarded, catatonic, psychotic
  - Acute, severe, psychotic
- Comorbidity: Substance abuse, minor antisocial acts
- Course:
  - Long, tempestuous course; brief well intervals
  - Educational, marital, occupational disruption
- Temperament:
  - Mood lability, energy-activity, daydreaming (BD-II)
- Family history:
  - Bipolar / 3 consecutive generation mood disorder
- Treatment response:
  - Pharmacologic hypomania (counts as BD-II in DSM-5)

Diagnostic Challenges – Question 2

“What are the strengths and limitations of DSM-5 when it comes to depressive episodes with mixed features?”

DSM-5 Bipolar Diagnostic Strengths and Limitations

- DSM-5 permits mixed depressions in both bipolar disorder and unipolar major depression
  - This could be good, allowing unipolar major depression subtyping and avoiding a bipolar disorder over-diagnosis
- DSM-5 doesn’t categorize concurrent threshold-level hypomania and MDD—permitting diagnosis of major depressive episode with mixed features or hypomanic episode with mixed features
  - This could be good, permitting predominant pole emphasis
- DSM-5 mixed depression requires 3 (rather than 2) “non-overlapping” opposite pole symptoms (ie, excludes psychomotor agitation, distractibility, and irritability)
  - This could be bad, making mixed depression too uncommon and not acknowledging importance of psychomotor agitation in depression

Diagnostic Challenges – Question 3

“What tools do you use in clinical arenas as standard measures of symptomology in bipolar disorder?”

Clinical Status Assessment

- Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) used the Clinical Monitoring Form (CMF) to establish Clinical Status at each visit
- STEP-BD CMF Clinical Statuses included
  - 4 DSM-IV syndromal episodes (Depressed, Hypomanic, Manic, Mixed)
  - 2 subsyndromal states (Continued Symptoms, Roughening)
  - 2 euthymic states (Recovered, Recovering)
- Clinical Statuses indicated if new mood interventions were
  - Practically mandated (for syndromal episodes)
  - Elective (for subsyndromal states)
  - Commonly avoided, unless side effects (for euthymic states)

Pharmacologic Challenges – Question 1

“How new 17-year-old female patient with first serious depression, with profound slowing and hypersomnia, but has anorexia instead of hyperphagia. Mother and maternal grandfather had bipolar I disorder. Would you commence an antidepressant in this young lady or would you treat her from the start with bipolar medications?”

Balancing Therapeutic and Adverse Effects

- Benefit (Efficacy) - NNT
  - Number of patients for 1 more good outcome
  - Lower is better – Preferably single-digit
- Risk (Tolerability) – NNH
  - Number of patients for 1 more poor outcome
  - Higher is better – Preferably at least double-digit
- Benefit:Risk Ratio (NNT vs NNH)
  - Want more benefit than risk
  - Strive for NNT lower than NNH
- Clinical urgency affects treatment selection
  - Urgent – prioritize efficacy
  - Non-urgent – prioritize tolerability

NNT = Number Needed to Treat; NNH = Number Needed to Harm.

Pharmacologic Challenges – Question 2

“How early in treatment should we be using lithium?”

Pharmacologic Challenges – Answer

“Use lithium early in treatment (generally before antipsychotics, but commonly after psychotherapy/antidepressants/lamotrigine) – especially for acute and preventive treatment of mood elevation.”

FDA-Approved Agents for Bipolar Disorder

<table>
<thead>
<tr>
<th>Year</th>
<th>Drug</th>
<th>Year</th>
<th>Drug</th>
<th>Year</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>1970</td>
<td>Lithium</td>
<td>2003</td>
<td>Olanzapine+fluoxetine combination</td>
<td>1974</td>
<td>Lithium</td>
</tr>
<tr>
<td>1994</td>
<td>Clozapine, ER (2005)</td>
<td>2008</td>
<td>Quetiapine, XR (adjunct)</td>
<td>2005</td>
<td>Aripiprazole*</td>
</tr>
<tr>
<td>2000</td>
<td>Olanzapine*</td>
<td>2013</td>
<td>Lurasidone*</td>
<td>2009</td>
<td>Olanzapine</td>
</tr>
<tr>
<td>2003</td>
<td>Risperidone*</td>
<td>2005</td>
<td>Aripiprazole*</td>
<td>2009</td>
<td>Quetiapine, XR (adjunct)</td>
</tr>
<tr>
<td>2004</td>
<td>Quetiapine, XR (2008)*</td>
<td>2008</td>
<td>Quetiapine, XR (adjunct)</td>
<td>2009</td>
<td>Quetiapine (adjunct)</td>
</tr>
<tr>
<td>2004</td>
<td>Ziprasidone</td>
<td>2009</td>
<td>Risperidone LAI*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>Aripiprazole*</td>
<td>2009</td>
<td>Ziprasidone (adjunct)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>Carbamazepine ERC</td>
<td>2009</td>
<td>Ziprasidone (adjunct)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>Aripiprazole*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>Cariprazine</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

*Adjunct and monotherapy. XR, ER, ERC = extended release oral; LAI = long-acting injectable.

Important unmet needs – well-tolerated treatments for acute depression and maintenance.
III. Side Effects
Management during Pharmacotherapy

Most Common/Problematic Side Effects

Ariov T (2016) – The Top 5 Side Effects of Psychotropics and How to Manage Them
1. Weight Gain
2. Anhedonia and Emotional Flattening
3. Sleep Disturbances
4. Sexual Dysfunction
5. Hyperprolactinemia

Ketter TA (2010)
1. Weight Gain (3 questions from 2017 Psych Congress attendees)
   - How to address weight gain in bipolar disorder?
   - Specific weight gain management tips (beyond usual diet and exercise)?
   - How to deal with weight gain and antimanic agents?
2. Akathisia (1 question from 2017 Psych Congress attendees)
   - How to address antipsychotic akathisia in bipolar depression?

Managing Medication Side Effects

- Carefully assess baseline (e.g., BMI, drowsiness, agitation/anxiety)
- Prior to intervention, warn of side/adverse effect risks
  - Especially weight gain/sedation and akathisia
- Assess specific adverse effects risks (e.g., weight/sedation/akathisia)
  - Age, gender, baseline weight/sedation/akathisia, medical disorders, medications
- Assess both potential benefits and harms of interventions
- Consider current mood state
  - Affects antidepressant/antipsychotic need/tolerability

Side Effect Challenges – Question 1

“How to address weight gain in bipolar disorder?”

Pharmacotherapy and Weight Gain in Bipolar Disorder

- Limited FDA-approved weight control treatments
  - Commonly not covered by insurance
- Antidepressants (before Mood Stabilizers)
  - Bupropion, non-paroxetine SSRIs, SNRIs
  - Before mirtazapine, paroxetine, MAOIs, TCAs
- Mood Stabilizers
  - Lamotrigine (before valproate)
  - Carbamazepine in reserve (less weight gain risk vs lithium, valproate)
- But more treatment complexity (drug interactions and side effects)
- Antipsychotics (only if absolutely necessary)
  - Cariprazine, lurasidone, aripiprazole
  - Quetiapine, risperidone
  - Ziprasidone (weight loss, but akathisia/unpredictable mood effects) in reserve
- Olanzapine
  - Very low dose olanzapine (1.25 mg/day) or clozapine (12.5 mg/day) may limit weight gain
  - Olanzapine-fluoxetine combination – minimal olanzapine, maximal fluoxetine
  - ≥ 7% gain – potentially significant, > 5 lb gain in 1st 3 weeks – ultimate catastrophic risk

Adjunctive Non-Stimulant Medications to Counter Weight Gain in Bipolar Disorder

- Topiramate 100–200 mg/day off-label, also
  - ≤ 92 mg/day + ≤ 15 mg/day phentermine in Qsymia™ on-label, independently off-label
- Zonisamide 300–400 mg/day off-label
- Metformin ≤ 2000 mg/day off-label
- Bupropion 300–450 mg/day off-label, also
  - ≤ 360 mg/day + ≤ 32 mg/day naltrexone in Contrave™ on-label, independently off-label
- Naltrexone ≤ 50 mg/day off-label, also
  - ≤ 32 mg/day + ≤ 360 mg/day bupropion in Contrave™ on-label, independently off-label
- Liraglutide (daily subcutaneous injections) on-label
  - From experienced medical provider
- Orlistat ≤ 360 mg/day on-label, but commonly yields diarrhea

Note that doses are listed for participant clarification purposes only. The clinical judgment of the treating provider should be utilized.
Adjunctive Stimulant/Stimulant-like Medications to Counter Weight Gain in Bipolar Disorder

- Some agents have abuse potential
- Long half-life agents for evening appetite attenuation, less abuse risk
- Can yield anxiety/agitation/restlessness
  - Lower doses, anxiolytics/dopamine blockers may address such problems
- Lisdexamfetamine ≤ 70 mg/day off-label
- Phentermine ≤ 37.5 mg/day on-label, also
  - ≤ 15 mg/day + topiramate ≤ 92 mg/day in Qsymia™ on-label, independently off-label
- Armodafinil ≤ 250 mg/day off-label
- Atomoxetine ≤ 120 mg/day off-label
- Lorcarserin (heart valve risk?) on-label

Side Effect Challenges – Question 2

“How to address antipsychotic akathisia in bipolar depression?”

Pharmacotherapy and Akathisia in Bipolar Disorder

- No FDA-approved anti-akathisia treatment
  - Reducing dose(s) of offending agents commonly most helpful
- Anxiolytics/calming agents (before Mood Stabilizers?)
  - Lorazepam – abuse potential; pramipexole/mirtazapine – mood destabilization potential
- Mood Stabilizers (before Antipsychotics)
  - Lithium, valproate, carbamazepine, lamotrigine unlikely to exacerbate akathisia
- Antipsychotics (before Activating Agents)
  - Quetiapine before risperidone before olanzapine before clozapine before
  - Ziprasidone before olanzapine (akathisia risks)
  - Olanzapine/clozapine (superior efficacy, low akathisia risk, but high weight gain risk) in reserve
  - Off-label brexpiprazole may have utility in some patients
- Activating Agents (only if absolutely necessary)
  - Activating (eg, levomilnacipran) only after calming (eg, paroxetine) antidepressants

IV. Treatment Challenges with Non-pharmacologic Treatments

Non-Pharmacologic Treatment Challenges – Question 1

“Which non-pharmacologic treatments for bipolar disorder do you offer and what are their success rates?”

Adjunctive Non-Pharmacologic Treatments for Bipolar Disorder

- **Adjunctive Evidence-Based Psychotherapies**
  - CBT, IPSRT, Family-Focused, Psychoeducation, Functional Remediation
  - Single-digit NNTs
- **Adjunctive Neuromodulation**
  - TMS, ECT, ± DBS
  - Some have single-digit NNTs
- Success rates comparable to approved pharmacotherapies
  - Single-digit NNTs

CBT = cognitive-behavioral therapy; DBS = deep brain stimulation; ECT = electroconvulsive therapy; IPSRT = interpersonal and social rhythm therapy; TMS = transcranial magnetic stimulation.
Non-Pharmacologic Treatment Challenges – Questions 2 and 3

“What non-pharmacologic treatments do you recommend to a busy community-based psychiatrist?”

“Which forms of psychotherapy have the strongest supportive evidence in treatment of bipolar disorder?”

Symptomatic Much More Than Functional Recovery in Bipolar Disorder

6 Months after Hospitalization

- 78% (33/42) mild or no affective symptoms
- 21% (9/42) employed full time at expected level

Conclusions

Bipolar Disorder – Solving Clinical Challenges

1. Diagnostic Nosology
   - Challenges distinguishing bipolar from unipolar

2. Pharmacologic Treatment
   - Challenges with therapeutic vs side effects

3. Adverse Events
   - Challenges with weight gain/sedation and akathisia

4. Non-Pharmacologic Treatment
   - Challenges with access to evidence-based Rx

Practical Take-Aways

Bipolar Disorder – Solving Clinical Challenges

- Diagnosis
  - Collateral significant other history crucial
- Pharmacologic Treatment
  - Prioritize FDA-approved interventions
- Adverse Effects
  - Balance therapeutic AND adverse effects, integrating urgency
  - Antidepressants before mood stabilizers before antipsychotics
- Non-Pharmacologic Treatment
  - Psychoeducation, Family-Focused, IPSRT, CBT
  - Functional Remediation

Psychotherapies had single-digit NNTs, comparable to approved pharmacotherapies.