Management of Bipolar Disorder
When First-Line Interventions Fail – Practical Tips
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Overview
Treatment-Resistant Bipolar Disorder

- Candidates for beyond first-line interventions
  - Inadequate efficacy, safety/tolerability, feasibility
  - Urgent efficacy need
- Clinical circumstances important
  - Accurate diagnoses (primary vs secondary)
  - Illness phase (acute mania/depression, maintenance)
  - Illness characteristics (rapid cycling, comorbidities, med Hx)
  - Efficacy need (urgent vs non-urgent care)
- Primary priority (efficacy vs tolerability)
- Beyond first-line intervention options include
  - Switching (no efficacy and/or inadequate tolerability)
  - Augmenting (partial efficacy and adequate tolerability)
  - Adjunctive psychosocial treatments

Established Clinical Correlates of Treatment-Resistant Bipolar Disorder

- Bipolar Depression
  - Commonly antidepressant-resistant/exacerbated
  - Antidepressant-resistance commonly already demonstrated
- Mixed Episodes (DSM-IV-TR)
  - Commonly lithium-resistant
  - Commonly antidepressant-resistant/exacerbated
- Rapid Cycling
  - Commonly mood stabilizer-resistant
  - Commonly antidepressant-resistant/exacerbated
- Comorbid Disorders
  - Alcohol/substance use and anxiety disorders most common
- “Not otherwise specified” Subtype
  - Meddiagnosis (eg, personality disorder, BD-I, BD-II)
  - Missed diagnosis (eg, personality disorder, BD-I, BD-II)
  - Adjuvice psychotherapy – commonly underutilized, can be crucial

Unfavorable Illness Correlates of Early-Onset Bipolar Disorder

- Early (Childhood > Adolescent) Onset
  - Confounded/confounded by multiple unfavorable illness characteristics
- Episode Accumulation (eg, ≥ 10 episodes)
  - “Kindling” Hypothesis (episodes beget illness/episode-related worsening)
  - Spontaneous/frequent/severe, Rx responsive
- Additional Comorbid Disorders
  - Personality and eating disorders
  - Less common than alcohol/substance use and anxiety disorders
- Major Depressive Episode with mixed features (DSM-5)
  - AKA “Mixed Depression”
  - Limited data suggest antidepressants problematic
- Long Illness Duration (eg, ≥ 15 years)
  - Confounded by early onset, episode accumulation, and aging
- “Unfavorable” Bipolar II Subtype
  - Chronic, treatment-resistant, depressive illness (ie, BD clinic selection bias)
  - Rather than episodic, treatment-responsive, psychotic illness (ie, not BD-I)

Unfavorable Illness Characteristic Prevalence:
Childhood- > Adolescent- > Adult-Onset Bipolar Disorder

- “Unfavorable” Illness Correlates of Early-Onset Bipolar Disorder
  - Bipolar Disorder Onset Age
    - Childhood-age 15 years
    - Adolescent-age 15-20 years
    - Adult-age 21 years

- Unfavorable Illness Characteristic Prevalence:
  - Bipolar Disorder vs adult-onset
First-Line Treatments

- **Common usage definitions**
  - Preferred, standard, or first choice (Merriam-Webster Dictionary)
  - First chosen for particular illness (Cambridge Dictionary)
  - First given for disease (National Cancer Institute Dictionary of Cancer Terms)
  - Top priority for most patients in such clinical circumstances

- **Operational definition**
  - Optimal efficacy/tolerability feasibility for patients in such clinical circumstances

- **Feasibility factors**
  - Accessibility (including cost)
  - Acceptability (including adherence)
  - Ease of use (including drug interactions and dietary restrictions)

- **Efficacy/tolerability evidence levels for individuals**
  - Observational (historical - patient or first-degree relative(s))
  - In that particular patient in similar clinical circumstances
  - In that patient’s first-degree relative(s) in similar clinical circumstances
  - Evidence-based (RCTs)
  - In similar patient population in similar clinical circumstances

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NOT First-Line Bipolar Treatments

- **Acute hypo/mania**
  - Efficacy = tolerability (ie, “balanced”) priority (non-urgent care, outpatient)
  - Carbamazepine monotherapy (selected second-line)
  - Olanzapine, risperidone, quetiapine monotherapy (third-line)
  - Lithium/divalproex + SGA combinations (third-line)
  - Efficacy > tolerability priority (urgent care, inpatient)
  - Clozapine (fourth-line)

- **Acute bipolar depression**
  - Efficacy = tolerability (ie, “balanced”) priority (non-urgent care, outpatient)
  - Nutriceuticals (fourth-line; limited efficacy data)
  - Efficacy > tolerability priority (urgent care, inpatient)
  - Olanzapine + fluoxetine combination (third-line)

- **Bipolar maintenance**
  - Efficacy = tolerability (ie, “balanced”) priority (non-urgent care, outpatient)
  - SGAs (second- and third-line)

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First-Line Bipolar Treatments

- **Acute hypo/mania**
  - Efficacy = tolerability (ie, “balanced”) priority (non-urgent care, outpatient)
  - Lithium/divalproex monotherapy
  - Acute bipolar depression
  - Efficacy = tolerability (ie, “balanced”) priority (non-urgent care, outpatient)
  - Lamotrigine, ADs (RCT’s suggest particularly limited AD efficacy)
  - Efficacy > tolerability priority (urgent care, inpatient)
  - Lithoside (monotherapy or added to lithium/divalproex)

- **Bipolar maintenance**
  - Efficacy = tolerability (ie, “balanced”) priority (non-urgent care, outpatient)
  - Prior effective acute treatment (with dose adjustment(s) for tolerability)
  - Lamotrigine (esp. depression prevention)/lithium (esp. elevation prevention)

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Non-urgent Care (Outpatient) Acute Hypo/mania Treatments

**Monotherapies (and selected combination therapies)**

- **First-line**
  - Lithium/divalproex (not carbamazepine/lamotrigine) monotherapy
    - ie, Li/DVPX monotherapy
  - Second-line
    - Carbamazepine monotherapy (not lamotrigine)
    - Newer approved SGA monotherapy
    - ie, ARIZP/APSN/CAR monotherapy
  - Third-line
    - Older approved SGA monotherapy
    - ie, OLZO/QTP/RSP monotherapy
  - Urgent care (inpatient) acute mania combination treatments (next slide)
  - Fourth-line
    - FGA monotherapy
    - eg, haloperidol
    - Lithium + anticonvulsant
    - ie, Li + DVPX, or Li + CBZ, (but not Li + LGT)

**Combination therapies**

- **First-line**
  - Lithium/divalproex + newer approved SGA
  - eg, Li/DVPX + ARI/AS
- **Second-line**
  - Lithium/divalproex + older SGA + newer SGA
  - eg, Li/DVPX + OLZO/QTP/RSP + ARI/AS
- **Third-line**
  - Lithium/divalproex + FGA + older SGA + newer SGA
  - eg, Li/DVPX + haloperidol + OLZO/QTP/RSP + ARI/AS

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Urgent Care (Inpatient) Acute Mania Treatments

- **First-line**
  - Lithium/divalproex ± FGA ± older SGA + newer SGA
  - eg, Li/DVPX + haloperidol + OLZO/QTP/RSP + ARI/AS
  - Electroconvulsive therapy (commonly + SGA/FGA)

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Overview of 25 Acute Mania Registration Studies
Numbers Needed to Treat for Response, Rates

<table>
<thead>
<tr>
<th>Therapy Studies</th>
<th>Monotherapy</th>
<th>Combination Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>20 Monotherapy Studies</strong></td>
<td><strong>SGA + Li/DVPX</strong></td>
<td><strong>5 Combination Studies</strong></td>
</tr>
<tr>
<td>Responders (%) (≥ 50% Mania Rating Decrease)</td>
<td>59.4%</td>
<td>51.5%</td>
</tr>
<tr>
<td>Includes First-Line (non-urgent)</td>
<td><strong>2886</strong></td>
<td><strong>2227</strong></td>
</tr>
<tr>
<td>Includes First-Line (urgent)</td>
<td><strong>862</strong></td>
<td><strong>646</strong></td>
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</table>

**Adjuvant SGA Therapy vs Monotherapy Increases Response Rate ≈ 18%**

Non-urgent Care (Outpatient)
Acute Bipolar Depression Treatments

- **Monotherapies (and selected combination therapies)**
  - **“First-line”**
    - Lamotrigine monotherapy
    - AD ± lithium/divalproex (AD monotherapy in certain BD-II, but not BD-I)
    - RCTs suggest particularly limited antidepressant efficacy
  - **Second-line**
    - Lithium ± lamotrigine
    - Adjunctive psychotherapy (CBT, FFT, IPSRT)
    - Urgent care (inpatient) acute bipolar depression monotherapies (next slide)
  - **Third-line**
    - divalproex/carbamazepine
    - Urgent care (inpatient) acute bipolar depression combination therapies (next slide)
  - **Fourth-line**
    - Novel agents/adjunctive therapies

Urgent Care (Inpatient)
Acute Bipolar Depression Treatments

- **Monotherapies and selected combination therapies**
  - **First-line**
    - Newer approved SGA
      - eg, LUR (monotherapy or added to Li/DVPX)
  - **Second-line**
    - Older approved SGA monotherapy
  - **Third-line**
    - Older approved SGA + antidepressant combination
  - **Fourth-line**
    - Adjunctive neuromodulation

Initial Treatment for Bipolar Disorder Patients in the United States in 2002–2003

Tolerability-Prioritized Unapproved Bipolar Depression Rx Benefits and Harms
NNT and NNH, Response and Adverse Effect Rates
Antidepressant-Induced Mania More Common in Bipolar II Compared to Unipolar Depression

Meta-Analysis from Clinical Trials

Unipolar Depression Bipolar II Depression

Switching to Mania (%)

Statistical Significance: TCA vs SSR = PBO

Peet M. Br J Psychiatry. 1994;164(4):549-553

Newer Efficacy-Prioritized Approved Bipolar Depression Rx

Benefits and Harms

NNT and NNH, Response and Adverse Effect Rates

Older Efficacy-Prioritized Approved Bipolar Depression Rx

Benefits and Harms

NNT and NNH, Response and Adverse Effect Rates

Comparative Evaluation of Quetiapine plus Lamotrigine vs Quetiapine in Bipolar Depression (CEQUEL)

NNTs and Remission Rates

Increased Switching with Adjunctive Venlafaxine Compared to Bupropion and Sertraline in Bipolar Depression

Harm (NNH) Mood Switch

YMRs > 13

CGI-M Increase ≥ 2

YMRs > 13 or CGI-M ≥ 3

Adjuvant venlafaxine (compared to sertraline, bupropion) yielded more switching.
Efficacy-Tolerability Balanced Bipolar Maintenance Treatments

Monotherapies and selected combination therapies

- **First-line**
  - Prior effective acute treatment(s) (with dose adjustment(s) for tolerability)
  - Lamotrigine (esp. depression prev/lithium (esp. elevation prev.)

- **Second-line**
  - Adjunctive psychotherapy (PE, CBT, FFT, IPSRT)
  - Depression monotherapy

- **Third-line**
  - Approved SGA monotherapy

- **Fourth-line**
  - Carbamazepine monotherapy; Lithium monotherapy/adjunctive therapy

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

Overview of Bipolar Monotherapy Maintenance Studies Numbers Needed to Treat for Relapse/Recurrence Prevention, Rates

Contemporary Registration Studies

Overview of Bipolar Monotherapy Maintenance Studies Numbers Needed to Treat for Relapse/Recurrence Prevention, Rates

Contemporary Manualized Intensive Psychotherapy Studies
Overview of Adjunctive Pharmacotherapy Bipolar Preventive Studies

Numbers Needed to Treat for Relapse/Recurrence Prevention, Rates

Contemporary Registration Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>NNT</th>
<th>Relapse/Recurrence (%)</th>
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</thead>
<tbody>
<tr>
<td>Contemporary</td>
<td>Adjunctive Risperidone vs Adjunctive Placebo</td>
<td>5</td>
<td>19.3%</td>
</tr>
<tr>
<td>Registration</td>
<td>Adjunctive Quetiapine vs Adjunctive Placebo</td>
<td>4</td>
<td>23.1%</td>
</tr>
<tr>
<td>Studies</td>
<td>Adjunctive Ziprasidone vs Adjunctive Placebo</td>
<td>8</td>
<td>45.8%</td>
</tr>
<tr>
<td></td>
<td>Adjunctive Aripiprazole vs Adjunctive Placebo</td>
<td>10</td>
<td>23.1%</td>
</tr>
</tbody>
</table>

Meta-Analysis of Antidepressants in Bipolar Maintenance

Benefit (NNT) vs Harm (NNH)

Antidepressant Continuation Beneficial in Some (15%?) Bipolar Patients

Prospective 1-year follow-up
Remission of MDE with AD added to mood stabilizer
Enriched sample – 15.3% (94/549) of patients responded and tolerated AD ≥ 2 months
Continuation: AD > 6 months
Discontinuation: AD < 6 months

Seeking Functional Recovery
(Thinking Beyond Medications and Not Settling for Sustained Clinical Remission)

Bipolar Disorders Symptoms are Chronic and Predominantly Depressive

146 BD-I Patients followed 12.8 years
62.7% Depressed
31.9% Elevated
5.9% Cycling / mixed
Percent of Weeks Asymptomatic: 21.1%
Depressed: 31.9%
Elevated: 31.9%
Cycling / mixed: 15.9%

86 BD-II Patients followed 13.4 years
73.7% Depressed
26.3% Elevated
5.7% Cycling / mixed
Percent of Weeks Asymptomatic: 27.4%
Depressed: 73.7%
Elevated: 26.3%
Cycling / mixed: 5.7%

Illness Transition Points
(The 5 Rs, borrowed from MDD)

- Response
  - Clinically significant (eg, ≥ 50%) improvement
  - Partially suppressed index episode still present
- Remission
  - Virtual absence of symptoms < 2 months
  - Fully suppressed index episode still present
- Recovery
  - Virtual absence of symptoms ≥ 2 months
  - Index episode ended (ie, no episode present)
- Relapse
  - Index episode returns after Response or Remission
- Recurrence
  - New episode emerges after Recovery

Mood Disorder Recovery Definitions Focus on Symptom Control


**Recovery in Bipolar Disorder vs Schizophrenia: Definitions and Studies**

- **Narrower Definition**
  - **Bipolar Disorder** (Clinical; Shorter duration)¹
    - ≤ 2 threshold-level depressive/mood elevation symptoms
    - ≥ 8 weeks
  - **Schizophrenia** (Clinical & Functional; Longer Duration)²
    - ≤ mild symptoms
    - ≤ mild relationship/employment deficits
    - ≥ 2 years

- **Fewer Psychosocial Treatment Studies**
  - **Bipolar Disorder**
    - Limited studies³
  - **Schizophrenia**
    - Multiple studies⁴
    - Cognitive Remediation, Social Cognition Training . . .


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**Symptomatic Much More Than Functional Recovery in Bipolar Disorder**

- 6 Months after Hospitalization
- Symptomatic: 78% (33/42)
- Functionally: 21% (9/42)

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**Case – Ms. A: Bipolar I Depression**

- **Demographics**
  - 21-year-old Asian single female undergraduate senior
- **Chief complaints**
  - Persistent depression, anxiety/panic, and insomnia
- **History of present illness**
  - Recently self-discontinued lurasidone due to akathisia
- **Past psychiatric history**
  - Recurrent MDEs since age 12
  - Paranoid referential delusions (when depressed) since age 15
  - Recurrent delusional mixed episodes since age 17
  - Hospitalized at age 21 for mixed episode with S/A by overdose
  - Prior pharmacotherapy
    - SGAs (3 prior SGAs self-discontinued due to side effects)
      - Lurasidone, Aripiprazole = akathisia, Quetiapine = sedation
      - Never had – Olanzapine, Ziprasidone, Risperidone, Clozapine
    - Never had – Mood stabilizers, Antidepressants, Benzodiazepines, ECT
  - No alcohol/substance use disorder
  - Current therapy
  - No pharmacotherapy (self-discontinued lurasidone due to akathisia)
  - No psychotherapy
- **Medical history**
  - Noncontributory (no obesity, diabetes, dyslipidemia)
  - Weight – 120 lbs; Height – 5 feet, 6 inches; BMI 19.4 kg/m²
- **Family history**
  - Sister (younger) with depression, ADHD, and panic disorder
  - Maternal aunt hospitalized for bipolar disorder
  - Maternal family history not available
- **Social history**
  - College IT/philosophy senior (graduating in 9 months)
  - Already had good job offer in NYC
  - Lived in dorm on campus, with parents between terms
Case – Ms. A: Outpatient Visit

• **Current depressive symptoms**
  - Sadness, anhedonia, insomnia (4–6 hours)
  - Feelings of guilt, psychomotor agitation, distractibility
  - Passive suicidal ideation without intent, preparation, or plans

• **Current psychotic symptoms**
  - Subthreshold paranoid delusions (vs severe anxiety)

• **Current mood elevation symptoms**
  - Distractibility, psychomotor agitation
  - Don’t count towards DSM-5 mixed depression

• **Current anxiety symptoms**
  - Panic attacks (2 in prior week, academic stress triggers)
  - Generalized anxiety (daily)

• **Current attitude towards medication**
  - Asking for treatment for depression, anxiety, and insomnia

Case – Ms. A

**Question 1: Current Advisability of Antidepressants**

1. **Worth considering**
   - Effective for unipolar MDD and anxiety
   - Generally adequate somatic tolerability
   - **But**
     - May exacerbate depression, destabilize mood
     - Akathisia, suicidality, sexual dysfunction risks

2. **Avoid (probably)**
   - Inefficacy risk (likely also need antipsychotic)
   - May exacerbate depression, destabilize mood
   - Suicidality, sexual dysfunction, akathisia risks
   - **But**
     - Effective for unipolar MDD and anxiety
     - Generally adequate somatic tolerability

**Question 2: Current Advisability of Benzodiazepines**

1. **Worth considering (probably)**
   - Prominent panic/anxiety/insomnia/psychomotor agitation
   - Generally adequate tolerability
   - Limited sedation risk; can attenuate (rather than trigger) akathisia
   - Limited utility of other agents
   - Mood stabilizers have at best most modest anxiolytic effects
   - Antidepressants might destabilize mood
   - 3 SGAs already overly sedating/activating
   - No personal/family history of alcohol/substance use disorder
   - May ultimately prove necessary to attenuate akathisia
   - **But**
     - Addiction potential (not extreme in this patient)
     - Unlikely to relieve “psychosis” (unless actually severe anxiety)
     - May exacerbate depression (?)

2. **Avoid (probably not)**
   - Addiction potential (not extreme in this patient)
   - Might exacerbate depression (?)

Case – Ms. A

**Follow-up Visits 2 and 3**

- Started weekly individual psychotherapy
- Lorazepam 0.5 mg twice daily
  - Adequately tolerated
  - Modestly attenuated anxiety/panic, insomnia, subthreshold psychosis
  - No improvement in depression
- Lorazepam 0.5 mg each morning + 1 mg each bedtime
  - Inadequately tolerated (sedation)
  - No additional attenuation of anxiety/panic, insomnia, subthreshold psychosis
  - Patient self-discontinued due to sedation and poorer academic productivity
Question 3: Current Advisability of Mood Stabilizers vs SGAs

1. Certain mood stabilizers
   - Lithium, divalproex, carbamazepine, lamotrigine
   - At best, only modest antidepressant, anxiolytic, and antipsychotic effects

2. Certain SGAs
   - History of prominent psychotic symptoms
     - Olanzapine + fluoxetine, quetiapine, lurasidone – approved for bipolar depression
   - Generally more side effects than mood stabilizers
   - Already failed quetiapine, lurasidone, and aripiprazole

Question 4: Choice of SGA

1. Olanzapine (with fluoxetine)
   - Established efficacy for bipolar depression/anxiety
   - Limited akathisia risk
   - But
     - Weight gain/metabolic > sedation/somnolence risks

2. Ziprasidone
   - Inefficacy risk; akathisia risk
   - But
     - Weight neutral

3. Risperidone
   - Inefficacy risk; akathisia, other EPS, hyperprolactinemia risks
   - But
     - Potent antipsychotic effect; as adjunct may help rapid cycling

4. Clozapine
   - Side effects risks (agranulosytosis/sedation/weight gain/metabolic)
   - Inefficacy risk (very limited antidepressant benefit)
   - But
     - May attenuate insomnia/anxiety; minimal akathisia risk

Unapproved SGAs in Bipolar Depression

- Efficacy vs intolerability concerns
  - Olanzapine (monotherapy)

- Inefficacy and tolerability concerns
  - Risperidone (no published placebo-controlled depression trials)

- Inefficacy concerns
  - Aripiprazole, ziprasidone (no published controlled trials)
  - ± Cariprazine (limited controlled data)

Olanzapine plus fluoxetine
- Titrated to
  - Olanzapine 7.5 mg at bedtime
  - Fluoxetine 20 mg each morning

- Good efficacy, with substantially attenuated
  - Anxiety/panic and insomnia
  - Depression

- Good tolerability
  - No akathisia, minimal sedation
  - Weight gain – 5 lbs at 12 weeks (BMI 19.4 → 20.2 kg/m²)

- Good academic function
  - All “A”s last term
### Conclusions
**Treatment-Resistant Bipolar Disorder**

- **Candidates for beyond first-line interventions**
  - Inadequate efficacy, safety/tolerability, feasibility
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- **Clinical circumstances important**
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  - Illness phase (acute mania/depression, maintenance)
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  - Efficacy need (urgent vs non-urgent care)
  - Primary priority (efficacy vs tolerability)
- **Beyond first-line intervention options include**
  - Switching (no efficacy and/or inadequate tolerability)
  - Augmenting (partial efficacy and adequate tolerability)
  - Adjunctive psychosocial treatments

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### Practical Take-Aways
**Treatment-Resistant Bipolar Disorder**

- **Treatment resistance risks**
  - Bipolar depression, mixed episodes
  - Comorbid disorders, rapid cycling
- **Treatment options (commonly combination therapy)**
  - SGAs (± mood stabilizers, antidepressants, anxiolytics)
  - Caution with antidepressants (± SGA/MS counter-balance)
  - Novel adjuncts occasionally beneficial
    - Thyroid, pramipexole, topiramate, nutriceuticals, sleep dep, light Rx
  - Adjunctive psychosocial interventions
    - Try to move from symptomatic to functional recovery