Clinical Pearls: Depression, Insomnia and Bipolar Disorder

Karrie R. Jones, PharmD, BCPP, BCPS
Clinical Pharmacy Specialist, Mental Health

Navigating the Oceans of Opportunity

Disclosure

□ I do not have a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation

Objectives

□ Identify current management options for bipolar disorder
□ Design a treatment plan for patients with depression
□ Discuss behavioral and pharmacological treatment options for sleep disorders

Depression

Patient Case

CC: “I am not interested in life anymore”

HP:
□ RD is 32 year old female, married
□ Describes feeling down, lack of interest in hobbies, and lack of motivation
□ No history of depression
□ PMH significant for GERD
□ Social history-quit smoking 1 yr ago; does not have health insurance
□ Medications: ranitidine 150mg twice daily

DSM-5

□ Diagnostic and Statistical Manual of Mental Disorders (DSM-5)
□ Published in 2013
□ Most published treatment guidelines contain DSM-IV-TR

DSM-5

Diagnostic and Statistical Manual of Mental Disorders (DSM-5)

Published in 2013
Most published treatment guidelines contain DSM-IV-TR
Common Symptoms

- **SIGECAPS**
  - S—sleep disturbances (insomnia or hypersomnia)
  - I—interest changes
  - G—excessive guilt
  - E—changes in energy
  - C—concentration impairment
  - A—appetite changes
  - P—psychomotor agitation
  - S—suicidal ideations or actions

First line treatment options

- **SSRIs**
  - Citalopram
  - Escitalopram
  - Fluoxetine
  - Paroxetine
  - Sertraline

- **SNRIs**
  - Desvenlafaxine
  - Duloxetine
  - Levomilnacipran
  - Venlafaxine

- **OTHERS**
  - Bupropion
  - Mirtazapine
  - Vilazodone

Non-pharmacological
- Cognitive behavioral therapy (CBT)
- Psychotherapy
- ECT

Antidepressant Selection

- Considerations
  - Patient preference
  - History/prior response
  - Safety and tolerability
  - Adverse effects
  - Comorbid conditions
  - Drug interactions
  - Cost (formulary)

Response to Treatment

- **1st week**
  - Increased activity
  - Sleeping and eating normalize
  - Thought process clears

- **1-3 weeks**
  - Depression subsides
  - Decreased suicidality

- **2-4 weeks**
  - Improvement in appetite

- If not moderate improvement at max tolerated dose by 4-8 weeks, consider adjusting therapy

Response to Treatment

- **Week 4-8: partial or no response**
  - Increase the dose
  - Change to alternate antidepressant
  - Augment with psychotherapy
  - Augment with pharmacotherapy
  - Consider ECT

- **Full response**
  - Continue at same dosage for 4-9 months
  - Relapse with discontinuation is 20-85%

Augmentation

- **Different class of antidepressant**
  - Lithium
    - High adverse effects, 16% remission in STAR-D
  - Thyroid hormone
    - Well tolerated, 25% remission in STAR-D
  - Buspirone
    - Not FDA approved, 30% remission in STAR-D
  - Atypical antipsychotics
  - L-methylfolate (medical food)

APA Practice Guidelines 2010

Trivedi, NEJM 2006; Neirenberg, Am J Psychiatry 2006
Atypical Antipsychotics

- Aripiprazole
  - Adjunctive treatment of depression
- Olanzapine
  - Combination with fluoxetine for treatment-resistant MDD
- Quetiapine
  - XR formulation for adjunctive treatment of depression
- Risperidone
  - Not FDA approved, evidence for use

Bradley. Pharmacotherapy, 2013

DSM-5 Criteria

- A predominant complaint of dissatisfaction with sleep quantity or quality, associated with one or more of the following symptoms:
  - Difficulty initiating sleep
  - Difficulty maintaining sleep, characterized by frequent awakenings or problems returning to sleep
  - Early morning awakening with inability to return to sleep
- The sleep disturbance causes clinically significant distress or impairments in social, occupational, educational, academic, behavioral, or other important areas of functioning
- The sleep difficulty occurs at least 3 nights/week
- The sleep difficulty is present at least 3 months
- The sleep difficulty occurs despite adequate opportunity for sleep

APA. Diagnostic and Statistical Manual of Mental Disorders. 2013.

Sleep Disorders

- Insomnia
- Narcolepsy with cataplexy
- Obstructive sleep apnea
- Restless leg syndrome

Substances and Medications Associated with Insomnia

- Alcohol
- Amphetamines/Stimulants
- Antipsychotics
- Anticholinergics
- Anticonvulsants
- Appetite suppressants
- β-blockers
- Bupropion
- Caffeine
- Cimetidine
- Cocaine
- Corticosteroids
- Decongestants
- Diuretics
- Hormone replacements/OCPs
- Hypnotics (chronic use)
- Interferon Alpha
- Levodopa/methylidopa
- MAOs/TCAs
- Nicotine
- Quetiapine
- Reserpine
- SSRI/SSNRIs
- Theophylline
- Thyroid preparations

Schutte-Rodin, JCSM, 2008

Treatment Options

- First-line (non-pharmacological)
  - Behavioral intervention
- Second-line (initial pharmacological)
  - Short-intermediate acting BZRAs, NBRAs or ramelteon
  - Sedating antidepressants
  - Combined BZRAs or ramelteon with a sedating antidepressant
- Third-line
  - Alternative short-intermediate acting BZRAs or ramelteon
  - Other considerations
    - Sedating agents (limited evidence): gabapentin, flagabazine, quetiapine, olanzapine
  - OTC agents

Schuler/Phade, JCSM, 2009
Non-pharmacological

- Cognitive therapy
- Behavioral therapies
  - Stimulus control
  - Sleep restriction therapy
  - Relaxation therapy
- Good sleep hygiene
- Biofeedback
- Light therapy

Pharmacological Treatment

<table>
<thead>
<tr>
<th>BRZAs (benzodiazepine receptor antagonists)</th>
<th>Melatonin Receptor Agonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-benzodiazepines</td>
<td>Ramelteon</td>
</tr>
<tr>
<td>Eszopiclone</td>
<td></td>
</tr>
<tr>
<td>Zolpidem</td>
<td></td>
</tr>
<tr>
<td>Zaleplon</td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td></td>
</tr>
<tr>
<td>Estazolam</td>
<td></td>
</tr>
<tr>
<td>Flurazepam</td>
<td></td>
</tr>
<tr>
<td>Temazepam</td>
<td></td>
</tr>
<tr>
<td>Triazolam</td>
<td></td>
</tr>
<tr>
<td>TCAs (tricyclic antidepressants)</td>
<td>Doxepin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BRZAs and NBRAs</th>
<th>Decrease time to sleep onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxepin</td>
<td>Decreases wakefulness after sleep onset</td>
</tr>
<tr>
<td></td>
<td>Increases total sleep time</td>
</tr>
<tr>
<td></td>
<td>Decreases REM</td>
</tr>
<tr>
<td>Ramelteon</td>
<td>Decrease time to sleep onset</td>
</tr>
<tr>
<td></td>
<td>Increases total sleep time</td>
</tr>
<tr>
<td></td>
<td>No effect on REM</td>
</tr>
<tr>
<td>Trazodone</td>
<td>No effect on time to sleep onset</td>
</tr>
<tr>
<td></td>
<td>Decreases wakefulness after sleep onset</td>
</tr>
<tr>
<td></td>
<td>Increases total sleep time</td>
</tr>
<tr>
<td></td>
<td>Minimal effect on REM</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Decreases time to sleep onset</td>
</tr>
<tr>
<td></td>
<td>Decreases wakefulness after sleep onset</td>
</tr>
<tr>
<td></td>
<td>Increases total sleep time</td>
</tr>
<tr>
<td></td>
<td>Minimal effect on REM</td>
</tr>
</tbody>
</table>

Treatment Statistics

- Data from 1999-2010 (32,328 community dwelling US adults)
- 3% of people had used a medication for insomnia within the preceding month
- Trazodone and zolpidem were most commonly used
- Use increased overall from 1999 to 2010
- 55% were taking at least one other sedating medication
  - 24% opioids
  - 19% benzodiazepines

Dosing Updates

- **Zolpidem maximum doses**
  - IR and SL: 10 mg
    - Females and elderly: 5 mg
  - SL (indicated for middle of night waking): 3.5 mg
    - Females and elderly: 1.75 mg
  - ER: 12.5 mg
    - Females and elderly: 6.25 mg
- **Eszopiclone**
  - Recommended starting dose of 1 mg/night for everyone
  - Increase up to maximum dose of 3 mg/night

Effect on Quality of Sleep

<table>
<thead>
<tr>
<th>Agent/Class</th>
<th>Effect on Quality of Sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRZAs and NBRAs</td>
<td>Decreases time to sleep onset</td>
</tr>
<tr>
<td>Doxepin</td>
<td>Decreases wakefulness after sleep onset</td>
</tr>
<tr>
<td></td>
<td>Increases total sleep time</td>
</tr>
<tr>
<td></td>
<td>Decreases REM</td>
</tr>
<tr>
<td>Ramelteon</td>
<td>Decrease time to sleep onset</td>
</tr>
<tr>
<td></td>
<td>Increases total sleep time</td>
</tr>
<tr>
<td></td>
<td>No effect on REM</td>
</tr>
<tr>
<td>Trazodone</td>
<td>No effect on time to sleep onset</td>
</tr>
<tr>
<td></td>
<td>Decreases wakefulness after sleep onset</td>
</tr>
<tr>
<td></td>
<td>Increases total sleep time</td>
</tr>
<tr>
<td></td>
<td>Minimal effect on REM</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Decreases time to sleep onset</td>
</tr>
<tr>
<td></td>
<td>Decreases wakefulness after sleep onset</td>
</tr>
<tr>
<td></td>
<td>Increases total sleep time</td>
</tr>
<tr>
<td></td>
<td>Minimal effect on REM</td>
</tr>
</tbody>
</table>

Bipolar Disorder
Bipolar Disorder

**Bipolar I Disorder**
- At least one manic episode, usually interspersed with a major depressive episode
- At least one hypomanic episode and at least one major depressive episode
- No history of manic episodes

**Bipolar II Disorder**
- Two years of numerous periods of hypomanic symptoms (without manic episode) and numerous periods of depressive symptoms (without major depressive episode)

**Cyclothymic Disorder**
- At least one hypomanic episode
- At least one major depressive episode

<table>
<thead>
<tr>
<th>Specifiers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxious distress</td>
</tr>
<tr>
<td>Rapid cycling</td>
</tr>
<tr>
<td>Atypical features</td>
</tr>
<tr>
<td>Catatonia</td>
</tr>
</tbody>
</table>

**Suicide rates**
- 10-20% higher than the general population
- Cardiovascular disease and hypertension ~5 x more prevalent than matched controls

**Comorbid Conditions**
- Endocrine
- Neurologic
- Infectious
- Cardio
- Pulmonary
- Metabolic
- Hematologic
- Personality disorders
- Anxiety
- ADHD
- Substance abuse

**Lithium Drug Interactions**

<table>
<thead>
<tr>
<th>Increase Lithium Levels</th>
<th>Decrease Lithium Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazide diuretics</td>
<td>Caffeine</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Osmotic diuretics</td>
</tr>
<tr>
<td>ARBs</td>
<td>Sodium bicarb antacids</td>
</tr>
<tr>
<td>NSAIDs (less with sulindac)</td>
<td>Theophylline</td>
</tr>
<tr>
<td>Reduced sodium intake</td>
<td>Increased sodium intake</td>
</tr>
</tbody>
</table>

**Adverse Effect Management**

- GI upset
  - Take with food
  - Slow release formulation or divide doses
- Intentional hand tremor
  - Slow release formulation or divide doses
  - Add propranolol
- Weight gain
  - Monitor for high sodium polydipsia
  - Reduce sodium and add thiazide supplement
- Hypothyroidism
  - Continue lithium and add thyroid supplement
- Leukocytosis
  - Continue lithium, monitor for signs and symptoms of infections
- Nephrogenic diabetes insipidus
  - Avoid dehydration, do not fluid restrict
  - Reduce sodium intake, high sodium intakes, or consider midazolam and maintain lithium dosage
- Dermatological
  - May treat with topical antibiotics or retinoic acid
- Cardiac
  - May treat with topical corticosteroids or restrict fluid

**Suicide rates**
- Average of 2.5 comorbid conditions
- Suicide rates are 10-20% higher than the general population

**Mania versus Hypomania**

- **Mania**
  - Abnormally and persistently elevated
  - Expansive
  - Or irritability
  - Lasting at least 7 days
  - Any duration if hospitalization required
  - +/-. psychosis

- **Hypomania**
  - Abnormally and persistently elevated
  - Expansive
  - Or irritability
  - Lasting at least 4 days
  - No hospitalization
  - No psychosis
  - No impairment

**Lithium Drug Interactions**

<table>
<thead>
<tr>
<th>Increase Lithium Levels</th>
<th>Decrease Lithium Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazide diuretics</td>
<td>Caffeine</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Osmotic diuretics</td>
</tr>
<tr>
<td>ARBs</td>
<td>Sodium bicarb antacids</td>
</tr>
<tr>
<td>NSAIDs (less with sulindac)</td>
<td>Theophylline</td>
</tr>
<tr>
<td>Reduced sodium intake</td>
<td>Increased sodium intake</td>
</tr>
</tbody>
</table>

**Adverse Effect Management**

- GI upset
  - Take with food
  - Slow release formulation or divide doses
- Intentional hand tremor
  - Slow release formulation or divide doses
  - Add propranolol
- Weight gain
  - Monitor for high sodium polydipsia
  - Reduce sodium and add thiazide supplement
- Hypothyroidism
  - Continue lithium and add thyroid supplement
- Leukocytosis
  - Continue lithium, monitor for signs and symptoms of infections
- Nephrogenic diabetes insipidus
  - Avoid dehydration, do not fluid restrict
  - Reduce sodium intake, high sodium intakes, or consider midazolam and maintain lithium dosage
- Dermatological
  - May treat with topical antibiotics or retinoic acid
- Cardiac
  - May treat with topical corticosteroids or restrict fluid

**Suicide rates**
- Average of 2.5 comorbid conditions
- Suicide rates are 10-20% higher than the general population

**Mania versus Hypomania**

- **Mania**
  - Abnormally and persistently elevated
  - Expansive
  - Or irritability
  - Lasting at least 7 days
  - Any duration if hospitalization required
  - +/-. psychosis

- **Hypomania**
  - Abnormally and persistently elevated
  - Expansive
  - Or irritability
  - Lasting at least 4 days
  - No hospitalization
  - No psychosis
  - No impairment
FDA Approved Treatments for Bipolar Disorder

<table>
<thead>
<tr>
<th>Indication</th>
<th>Monotherapy</th>
<th>Adjunctive Monotherapy</th>
<th>Adjunctive Mood Stabilizer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maintenance</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Lurasidone
- Olanzapine plus fluoxetine
- Quetiapine

- Lamotrigine
- Divalproex
- Lithium
- Antidepressants

Antidepressant Use

- Controversial topic with inconclusive data available
- Ensure adequate dose of mood stabilizer
- SNRIs and TCAs should generally be avoided due to higher incidence of "switching"
- Should be avoided in patients with recent manic episode, rapid cycling, substance abuse or history of mania from antidepressant
- Consider risk versus benefit in bipolar depression
- Discontinue if not effective or hypomanic/manic episode occurs

Bipolar Depression Treatment

- FDA approved
  - Lurasidone
  - Olanzapine plus fluoxetine
  - Quetiapine

- Not FDA approved
  - Lamotrigine
  - Divalproex
  - Lithium
  - Antidepressants

Questions

Guideline Recommendations

- American Psychiatric Assoc (2005)
  - Monotherapy:
    - Lithium or lamotrigine
  - Severe:
    - Lithium + SSRI
  - With psychotic features:
    - Add atypical antipsychotic

- Canadian Network for Mood and Anxiety Treatments (CANMAT-2013)
  - Lithium
  - Lamotrigine
  - Quetiapine
  - Lithium or VPA + SSRI
  - Olanzapine + SSRI
  - Lithium + VPA
  - Lithium or VPA + bupropion