MOUNTAIN HIGH AND VALLEY LOW
A Pharmacist and Technician Primer for Appropriate Diagnosis and Management of Bipolar Disorder

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Learning Objectives: Pharmacists

- At the completion of this knowledge-based presentation, the pharmacist will be able to:
  - Identify presenting symptoms and DSM-5 diagnostic criteria for manic, depressive, and mixed episodes of bipolar disorder
  - Design a comprehensive pharmacotherapeutic regimen for bipolar disorder taking into account comorbid conditions, concurrent medications, and patient preference
  - Appraise a patient treatment regimen for bipolar disorder for appropriateness of medication indication, dose, and follow-up monitoring
  - Employ effective counseling skills when discussing common bipolar disorder treatments with patients and caregivers to promote optimal medication utilization and minimize adverse effects
  - Discuss the role pharmacists have in routine screening for suicidality in patients with chronic mental health conditions, providing example questions and brief assessments for effective triaging to appropriate mental health care providers.

Learning Objectives: Technicians (AKA – The Miracle Workers)

- At the completion of this knowledge-based presentation, the Pharmacy Technician participant will be able to:
  - Identify concerning symptoms and statements suggesting a current or impending manic or depressive episode in bipolar disorder
  - Utilize and explain the importance of appropriate terminology when discussing the various presentations of bipolar disorder with patients, caregivers, and fellow healthcare providers
  - Discuss briefly the available treatment options for manic, depressive, and mixed episodes in bipolar disorder
  - Recognize appropriate starting and maintenance doses, monitoring parameters, required provider follow-up, and potential adverse effects for common bipolar disorder pharmacotherapies
  - Establish an appreciation for the importance of routine screening for suicidality in patients with chronic mental health conditions.

Conflicts of Interest

- I have no financial connections to any of the herein discussed treatments or procedures.
- I am a current employee of the Veterans' Health Administration of the executive branch of the federal U.S. government.
- I tend to get carried away discussing matters of psychopharmacology and admit a personal positive bias to the subject material discussed herein.
- I have no other disclosures to make at this time.

Psychiatry Diction 101

- Affect – the visually perceived appearance of a person's emotions as judged by the objective rater
- Mood – the self-perceived feeling of one's emotions
- Anhedonia – loss of interest and pleasure in previously enjoyed activities
- Avolition – inability to complete goal-directed tasks
- Mania – an emotional state characterized by excessive excitement or agitation, lack of need for sleep, grandiosity, psychomotor activation, and rapid thought process (flight of ideas)
- Euthymia – neutral state of emotion; neither excessively happy or sad

DEFINING BIPOLAR DISORDER

- MOUNTAIN HIGH
- AND VALLEY LOW
Myths and Facts

■ Bipolar affective disorder (BPAD) is not:
  - Split or multiple personalities
  - Sudden or repetitive mood swings
  - Impulsive mood

■ BPAD is:
  - Prevalent at a rate of approximately 1% in all populations worldwide
  - Accounts for a quarter of all mental health costs in the U.S.
  - Estimated annual cost (direct and indirect) total $65 billion

Making the Diagnosis

■ BPAD (formerly Manic-Depression) is a chronic, and often difficult to treat, mental illness characterized by periods of weeks to years of mania (elated) and euthymic periods with or without the presence of depressive periods.

■ Presence of a full manic period defines BPAD I
  - “A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary).”

■ Presence of a hypomanic period defines BPAD II
  - “A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least 4 consecutive days and present most of the day, nearly every day.”

■ Estimated annual costs (direct and indirect) total $65 billion

Diagnosing Mania

■ “During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms (four if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior:
  - Inflated self-esteem or grandiosity.
  - Decreased need for sleep (e.g., feels rested after only 3 hours of sleep).
  - More talkative than usual or pressure to keep talking.
  - Flight of ideas or subjective experience that thoughts are racing.
  - Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.
  - Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless non-goal directed activity).
  - Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).”

■ Mania
  - “The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.”

■ Hypomania
  - “The episode is associated with an unequivocal change in functioning that is uncharacteristic of the individual when not symptomatic.”
  - “The disturbance in mood and the change in functioning are observable by others.”
  - “The episode is not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization.”
  - “If there are psychotic features, the episode, by definition, manic.”

■ “The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment).”

Diagnosing Depression

■ “Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure:
  - Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, or hopeless) or observation made by others (e.g., observed mood).
  - Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective report or observation).
  - Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.
  - Insomnia or hypersomnia nearly every day.
  - Psychomotor agitation or retardation nearly every day (observable by others).”

Mixed Episodes

■ Now included as a specifier in DSM 5
  - Example: bipolar disorder, most recent episode manic, with mixed features

■ As the name suggests, patients meet criteria for depressed and manic symptoms
  - Patients often appear with hypomanic activation, but irritable and angry, rather than belligerent

■ Treated on a symptom-based approach, most often like manic episodes
TREATMENTS

Basics

- Majority of therapies are used off-label to some extent
  - Example: indication for acute depression, given maintenance of BPAD
- No one treatment guideline is preferred or recognized as superior
  - Veterans’ Affairs/Department of Defense (VA/DoD) Clinical Practice Guideline – 2010
  - American Psychiatric Association (APA) – 2002 (with 2005 updates)
  - British Association for Psychopharmacology (BAP) – 2016
- Treatments should target current symptoms regardless of subtype
- Traditional antidepressants (e.g., SSRIs, SNRIs, TCAs) should be avoided in all subtypes of BPAD, including depressed type, unless the patient has a history of positive response

Lithium

- FDA approved for acute mania in BPAD and maintenance of BPAD
  - Also acts as an agent shown in non-psychotic patients to reduce risk of suicide
- Initiate therapy at 300 mg/day, increase to 150 mg/day after 3 days of therapy
  - Initial choice of formulation (IR vs. SR) makes little difference
  - Obtain plasma concentration 8 to 12 hours post-dose and after 5 days of therapy
  - Average elimination half-life: 20 to 24 hours (5 days = 5 half-lives)
  - Desired concentrations: 0.6 to 1.2 mEq/L
- May titrate dose every 2 to 3 days in acute mania

Lithium – Proposed Mechanisms

- G-protein linked receptor uncoupling
  - Inhibition of inositol monophosphatase
  - Depletion of inositol triphosphate (IP3) and diacylglycerol (DAG)
  - Inhibition of Ca2+ dependent release of NE and DA
  - Mistargeted G-protein uncoupling → adverse effects (polyuria, hypothyroidism)
- Alteration of protein kinase C-mediated signaling
  - Altered gene expression → varied production of neuroplastic proteins

Lithium Side Effects

- Most side effects can be minimized by altering the dose formulation or timing
- Changing therapy is often necessary to completely eliminate side effects

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyuria/polydipsia</td>
<td>Increase fluids, use IR formulation for high peak/lower sustained concentrations; use once daily dosing; possibly add a thiazide diuretic</td>
</tr>
<tr>
<td>Tremor</td>
<td>Use ER/SR formulations to lower Cmax; use twice daily dosing; try adjunctive propranolol or metoprolol; avoid caffeine</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Use IR preparations (earlier GI release for majority of dose); use a lower dose; switch to lithium citrate</td>
</tr>
<tr>
<td>Thyroid abnormalities</td>
<td>Monitor regularly; supplementation if necessary; always verify free T4 before starting treatment</td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>Review for potential drug-drug interactions and alternative causes of renal insult; likely will require change in therapy</td>
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</tbody>
</table>
Lithium Monitoring

<table>
<thead>
<tr>
<th>Test</th>
<th>Baseline</th>
<th>4 weeks</th>
<th>Twice per year</th>
<th>PRN</th>
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<td>X</td>
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<tr>
<td>BMP</td>
<td>X</td>
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<tr>
<td>Thyroid Panel</td>
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<td>ESR</td>
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<tr>
<td>Medical-Hx</td>
<td>X</td>
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<tr>
<td>Med Review</td>
<td>X</td>
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</tr>
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</table>

1. Check for concentration therapy with NSAIDs, ACEi, thiazides
2. Consider checking quarterly if abnormalities noted or reduced renal function

Valproic Acid (VPA)/Divalproex

- FDA-approved for mania in BPAD
- Used off-label for maintenance of BPAD and generalized aggression
- Maintenance – Start 500mg/day and increase as tolerated
- Active Mania – Load with 15 to 20 mg/kg/day, target dose of 20 to 25 mg/kg/day
- IR/DR formulations divide dose out 2 to 3/day
- ER formulation once daily
- Target plasma concentration – 50 to 100mcg/mL
- Protein binding may become saturable with low albumin
  - Increased free fraction available
  - Dose adjustment none needed; metabolic capacity will proportionally increase

VPA – Proposed Mechanisms

- Alteration of inositol and arachidonic acid metabolic pathways
  - Reduced inflammation?
- Gene expression manipulation via inhibition of histone deacetylation
- Possible inhibition of GABA transaminase
- Inhibition of GABA-aminotransferase and succinic semialdehyde dehydrogenase
- Enhancement of postsynaptic GABA signaling
- Inhibition of GABA reuptake
- Reduction of excitatory amino acid (aspartate) signaling

VPA Kinetics

AED Pharmacokinetics

- Linear vs not linear

VPA Formulations

- Valproate sodium (Depacon®)
  - IV solution, 100mg/mL
- Valproic acid (Depakene®)
  - Capsules – 25mg
  - Syrup (raspberry flavor) – 25mg/5mL
- Divalproex sodium (Depakote®)
  - Delayed-release (DR) tablets – 25mg, 50mg, 75mg
  - Extended-release (ER) tablets – 25mg, 50mg, 75mg
  - Sprinkle (IR) capsules – 12.5mg
VPA Monitoring

<table>
<thead>
<tr>
<th>Test</th>
<th>Baseline</th>
<th>4 weeks</th>
<th>8 weeks</th>
<th>12 weeks</th>
<th>Quarterly</th>
<th>Annually</th>
<th>Q 5 years</th>
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<td>CBC</td>
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<td>Medication Review</td>
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<tr>
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VPA Side Effects and Solutions

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Mitigation Strategy</th>
</tr>
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<tbody>
<tr>
<td>Fatigue, dizziness, somnolence, ataxia</td>
<td>Indication of low-grade toxicity, use lower dose</td>
</tr>
<tr>
<td>Tremor</td>
<td>Try propranolol or metoprolol, use lower dose</td>
</tr>
<tr>
<td>Nausea, vomiting, anorexia</td>
<td>Use EBR or OR formulations, take with food</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Monitor for severity; discontinue if clinically warranted</td>
</tr>
<tr>
<td>Hyperammonanemia</td>
<td>Add/replace simazine 5mg/kg/day; may require discontinuation of therapy</td>
</tr>
<tr>
<td>Diplopia, nystagmus</td>
<td>Indication of low-grade toxicity, use lower dose</td>
</tr>
<tr>
<td>Weight gain</td>
<td>Increase activity, dietary counseling, change therapy</td>
</tr>
<tr>
<td>Pancreatitis, hepatitis</td>
<td>Change therapy, supportive care</td>
</tr>
</tbody>
</table>

Atypical Antipsychotic Basics

- Shown effective in acute and maintenance phases for treatment and prevention of mania and/or depression
- Use is not restricted to patients with psychotic features
- Faster onset for acute presentation vs. other mood stabilizers
- Olfactory monitoring or adjunct with lithium, etc.
- Major concern with long-term use is metabolic complications

Antipsychotic Monitoring

<table>
<thead>
<tr>
<th>History</th>
<th>Baseline</th>
<th>4 weeks</th>
<th>8 weeks</th>
<th>12 weeks</th>
<th>Quarterly</th>
<th>Annually</th>
<th>Q 5 years</th>
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<tr>
<td>Weight</td>
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Atypical Antipsychotics for BPAD

<table>
<thead>
<tr>
<th>Atypical Antipsychotic</th>
<th>Dose Range</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>5 to 30mg daily</td>
<td>Ineffective for BPAD depression; may cause/exacerbate mania</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>5 to 40mg daily with a meal of at least 350 Calories</td>
<td>Effective for BPAD depression; may cause/exacerbate mania</td>
</tr>
<tr>
<td>Asenapine</td>
<td>5 to 20mg twice daily</td>
<td>Only available as sublingual tablet; effective and approved only for BPAD mania</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>5 to 30mg twice daily</td>
<td>Effective for BPAD depression; may cause/exacerbate mania</td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>5 to 40mg twice daily</td>
<td>Ineffective for BPAD depression; may cause/exacerbate mania</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>20 to 120mg daily with a meal of at least 350 Calories</td>
<td>Effective for BPAD depression; may cause/exacerbate mania</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>25 to 600mg dosed one to two times daily</td>
<td>Effective for BPAD depression; may cause/exacerbate mania</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>2.5 to 15mg daily</td>
<td>Effective for BPAD depression; may cause/exacerbate mania</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>20 to 80mg twice daily</td>
<td>Ineffective in two RCTs (avoid)</td>
</tr>
</tbody>
</table>

Atypical Antipsychotic Side Effects

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Aripiprazole</th>
<th>Asenapine</th>
<th>Brexpiprazole</th>
<th>Lurasidone</th>
<th>Quetiapine</th>
<th>Olanzapine</th>
<th>Ziprasidone</th>
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<tbody>
<tr>
<td>Hallucinations</td>
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<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>EPS/TD</td>
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<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
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<tr>
<td>Prolactin elevation</td>
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<td>Sedation</td>
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<td>++</td>
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<tr>
<td>Anti-ACh</td>
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<td>++</td>
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</tr>
<tr>
<td>Orthostasis</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
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<td>QTc prolong</td>
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<td>++</td>
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</tr>
</tbody>
</table>

Atypical Antipsychotic Side Effects

- HLD: Hallucinations
- EPS/TD: Extrapyramidal Symptoms/Tardive Dyskinesia
- Orthostasis: Orthostatic Hypotension
- QTc: QT interval corrected

*Table indicates presence of side effect/patient history of obesity, diabetes mellitus, dyslipidemia, hypertension, cardiovascular disease
*No preference for antipsychotic guidelines; not included in the BPAPA easy recommendations.
### Indication

- Depressive episode

### Dose Range

- 400 to 1600 mg

### Miscellaneous Agents

<table>
<thead>
<tr>
<th>Carbamazepine</th>
<th>BDAD</th>
<th>400 to 1600 mg</th>
<th>Strongest evidence for mania</th>
<th>Drug Interactions; Stevens-Johnson, requires lab monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamotrigine</td>
<td>BDAD, maintenance</td>
<td>15 to 45 mg (titration)</td>
<td>Low side effect profile for one of few effective agents for depression</td>
<td>Stevens-Johnson, requires slow titration and frequent monitoring; lacks evidence of benefit to prevent mania</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>None</td>
<td>6 to 12 mg</td>
<td>Less drug interactions than CBZ</td>
<td>No clinical evidence implied from CBZ; SHAD</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>None</td>
<td>Symptom-based, (potentially up to 15 mg/day)</td>
<td>Rapid onset, highly effective</td>
<td>Not for maintenance, fall fracture risk</td>
</tr>
</tbody>
</table>

### Algorithms

**Counseling on BPAD**

And ensuring the best practice standards

### Be the Pharmacist

- Involve family and caregivers as much as possible in counseling and education
- Stress the warning signs of an impending episode
  - Depressive episode – sadness, feeling your setting, increased/decreased in mood
  - Manic episode – spending more than usual, sleeping less, starting, but not completing, overachieving
- Know warning signs of imminent self-harm or suicide
  - Frequent verbal expressions of death or suffering, receiving/returning calls to individuals
- Be straight on substance abuse
  - About 50% of patients diagnosed with a mood disorder (e.g., BDAD) also have a substance abuse disorder
- Don’t miss the meds
  - Highest rate of medication noncompliance among common psychiatric disorders (e.g., psychosis, depression)
- BDAD diagnosed patient rates of noncompliance range from 20 to 40%
- Major source of hospitalization and patient admissions

### And be the Provider

- Teach the basics of class of medication, purpose in therapy
- Find work-arounds for barriers to acceptance or compliance
- Mitigate side effects and more common adverse effects
- Obtain monitoring parameters – review/order lab work, EKGs for necessary medications
- Assess tolerability risks – anticonvulsants, lithium
- Know effective non-pharmacologic alternatives exist (e.g., psychotherapy, electroconvulsive therapy)
CASE

DC is a 59-year-old male with a history of BPAD, CAD, seasonal allergic rhinitis, osteoarthritis, sleep apnea, HTN, and BPH who presents to the emergency department in the company of his wife and daughter who report that for the past 2 weeks DC has been increasingly agitated and energetic. He’s spent long hours at night in the garage reportedly working on a machine to communicate with radioactive ghosts living within the produce department at the grocery store. In the last week, they haven’t seen him sleep more than 30 minutes per night. DC’s wife states that he’s accepted his usual medications from her as she normally manages them, but she’s suspicious he may not be swallowing the medications.

When you encounter him in the ED he’s mumbling to himself before you and the attending physician approach him. He denies any audio or visual hallucinations and reports that he’s been 100% compliant with his meds and denies acting at all out of his usual self besides needing to sleep slightly less. He says he acquired a new energy from the ghosts at the grocery store that keeps him active 23 and a half hours a day. His vitals show an elevated HR of 116 and a BP of 157/92. His lithium level returned as undetectable. His labs, vitals, and ROS are otherwise WNL. The attending physician decides to admit him voluntarily to acute psychiatry for medication optimization and psychiatric stabilization.

Medication History

Current Medications
- Lithium 1,200mg at bedtime
- ASA 81mg at bedtime
- Cetirizine 10mg at bedtime
- Etodolac 50mg qid as needed for joint pain
- Terazosin 5mg at bedtime
- Losartan 50mg at bedtime
- Fluticasone NS 50mcg 2 sprays in each nostril at bedtime
- Trazodone 100mg at bedtime for insomnia

Past Medication Trials
- Divalproex ER – caused weight gain and hyperammonemia
- Lithium – reported to you tonight that he hates that it causes him to shake so much
- Haloperidol – caused restlessness
- Olanzapine – stopped by general medicine after diagnosis of CAD; effective for many years prior

Importance for all Professionals

- All health care professionals have a responsibility to ask
- Screening does NOT require specialized psychiatric training
- Full risk assessment is much more difficult
- Know where to refer for full risk assessment
- Best to be blunt
  - “Are you having thoughts of harming or killing yourself?”
  - “How would you kill yourself?”
- Normalize the situation with facts
  - About 1 in 10 people will contemplate suicide in their lifetime
- If you’re uncomfortable, you’re doing a good job.


