The Pharmacist’s Role in Treating Bipolar Disorder

(Diagnosis, Treatment Options, and Outcomes)

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Speaker Disclosure: Dr. Montagnese has no actual or potential conflicts of interest in relation to this program.

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Program Overview: Pharmacists can play a proactive role in the treatment of bipolar disorder and the adherence problems associated with the illness. Pharmacists must understand the underlying condition, potential of currently available treatment options (along with their probable results and possible side effects) and understand the need to educate patients and family members on drug treatment strategies and the long-term medication and adherence problems commonly encountered with bipolar patients.

Objectives:
1. Identify the importance of long-term maintenance treatment for bipolar disorder and economic impact of poor therapy adherence on the healthcare system.
2. Describe the lifestyle changes and pharmaceutical strategies (including the modes of action, efficacy, and contraindications of currently available therapeutic agents) available for managing bipolar disorder.
3. Review the pharmacist’s role in counseling patients on the lifestyle changes, drug treatment strategies and medication adherence to improve the quality of life and long-term maintenance of bipolar patients.

What is bipolar disorder?

- Julia - a 28 year old female seeks treatment at the request of her parents for depression, impulsive decisions and out of control anger.
- Nickii - an 8 year girl with uncontrollable rage and psychotic symptoms.
- Jake - a 52 year old male with multiple hospitalizations for depression and mania.
What is bipolar or “manic depression”?
- Unipolar depression: all lows
- Bipolar is both ends of the spectrum
- Severe mood swings
- Classic form: periods of extreme depression to periods of exaggerated happiness or euphoria
- Many shades of the illness in between the extremes
- Episodic nature, chronic, variable course

What are the forms of bipolar disorder?
- Bipolar I Disorder
- Bipolar II Disorder
- Bipolar Disorder NOS
- Cyclothymic Disorder
- Differential: Medical and Substance-Induced

DSM Criteria for Bipolar I D.O.
- Must have or had at least one episode of mania
- Some patients have had or will have a major depression
- Episodes can be depressive, manic or mixed

What is Mania?
The DSM Criteria:
- Period of abnormally elevated, expansive or irritable mood
- Lasts at least one week or less if hospitalized
- Inflated self esteem, grandiosity
- Decreased need for sleep
- More talkative, pressured speech
- Flight of ideas, racing thoughts
- Distractibility
- Increased goal-directed activity or psychomotor agitation
- Increased pleasure seeking with high potential for negative consequences
### What is a Major Depressive Event?

- Depressed mood (irritable in children) and SIG-E-CAPS criteria
- S: suicidal ideation
- I: decreased interests
- G: excessive guilt (worthlessness, hopelessness)
- E: decreased energy
- C: decreased concentration
- A: appetite
- P: psychomotor retardation or agitation
- S: sleep disturbance

### Bipolar Disorder and Psychosis

- Psychosis may be part of mania or depression
- Catatonia

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### What is Major Depressive Episode?

- Must last at least 2 weeks
- At least 5 of criteria with one including depressed mood or decreased interests

### What is Bipolar II D.O.?

- Must have or had one or more episodes of MDD
- Must have or had at least one episode of hypomania
- Never had a manic episode
What is Hypomania?

- Like mania, just less severe
- Period of elevated, expansive or irritable mood
- At least 4 days
- Not severe enough to cause marked impairment or require hospitalization, no psychotic features

What is Cyclothymic D. O.?

- 2 years minimum (1 year in children)
- Numerous periods of hypomania
- Numerous periods of depression but not MDD

Differences in Disorders

<table>
<thead>
<tr>
<th>Bipolar I</th>
<th>Bipolar II</th>
<th>Cyclothymia</th>
<th>Bipolar NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manic Episode</td>
<td>Hypomanic Episode</td>
<td>Symptoms don’t meet full criteria for depressive, manic, or mixed state</td>
<td>Symptoms don’t meet criteria for any specific bipolar disorder</td>
</tr>
<tr>
<td>Mixed Episode</td>
<td>Depressed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressed with history of mania</td>
<td>Never had a manic or mixed episode</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Task Force Recommendations

- International team of experts
- Expanding diagnostic criteria for several subtypes
- Add pediatric category
- Bipolar II: not “soft bipolar”
- Add ultra-rapid cycling specifier
- Not over diagnosed
- A spectrum disorder with sub threshold symptoms
- Use of diagnostic tools increase accuracy of diagnosis
Epidemiology

- Bipolar I: 0.8%, M=F (All forms: 2.6%)
- Bipolar II: 0.5%, F>M
- Across cultures, races
- Age of onset: 21 years
- M: first episode likely to be mania
- W: first episode likely to be depression
- 2/3 affected have close family member affected
- One parent: risk to child 15-30%
- Two parents: risk to child 50-75%

Course of Disease

- First episode may be mania, hypomania, depressive or mixed.
- First episode may be followed by symptom-free years
- Associated with substance abuse, truancy, recklessness, impulsivity, antisocial behavior
- Variability is hallmark of illness
- Chronic illness
- No cure
- Very treatable
- Suicide completion rate is high: 1 in 5 (M>F)

Misdiagnosis in Bipolar Disorder

- For adequate treatment, correct diagnosis is paramount
- NDMDA: 60% initially misdiagnosed
- Most commonly with MDD (50%)
- Triad of anxiety, alcohol and depression

Avoiding Misdiagnosis

- Obtain diagnostic info from collateral sources: family, significant others
- Ask about prior response to antidepressants
- Half of individuals with Bipolar are initially treated with antidepressants
- Other half are treated with mood stabilizers or antipsychotics
### Comorbid Conditions
- Substance abuse
- Anxiety Disorders: OCD and Panic Disorder
- ADHD

### When Unipolar Depression may be Bipolar Depression
- Earlier onset <25 y. o.
- 5 or more spells of MDD
- Family Hx of Bipolar
- Atypical depressive symptoms
- Postpartum mood disorder
- Severe anhedonia
- Catatonia or psychosis
- Pharmacologically induced mania or hypomania
- Recurrent, brief episodes of depression
- Seasonal component

### Cost of Bipolar Disorders
- $45 billion annually: direct and indirect costs
- Bipolar pt/yr: $3415
- Diabetes pt/yr: $2570
- General medical outpatient/yr: $1462
- Unemployment rate: up to 60%
- Delay in diagnosis increases costs
- 5th leading cause of disability in world

### Leading Causes of Years Lost to Disability Worldwide, 15-44 y.o.

<table>
<thead>
<tr>
<th>Rank</th>
<th>Disease or Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Unipolar Depression</td>
</tr>
<tr>
<td>2.</td>
<td>Alcohol Use Disorders</td>
</tr>
<tr>
<td>3.</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>4.</td>
<td>Iron-deficiency anemia</td>
</tr>
<tr>
<td>5.</td>
<td>Bipolar Depression</td>
</tr>
<tr>
<td>6.</td>
<td>Hearing loss, adult onset</td>
</tr>
<tr>
<td>7.</td>
<td>HIV/AIDS</td>
</tr>
<tr>
<td>8.</td>
<td>Chronic Obstructive Pulmonary Disease</td>
</tr>
<tr>
<td>9.</td>
<td>Osteoarthritis</td>
</tr>
<tr>
<td>10.</td>
<td>Road Traffic Accidents</td>
</tr>
</tbody>
</table>

WHO, March 2007
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Treatment Approaches

Acute phase:
- Hospitalization at times
- Medication
- Education: patient and family
- Psychotherapy

Preventative/maintenance phase:
- Noncompliance is common
- Two or more episodes mania/depression=life long medication
- Maintain regular sleep and daily patterns
- Do not use drugs/alcohol
- Reduce stress
- Recognize early warning signs
- Don’t abruptly stop meds-talk to your doctor
- Enlist support of family/friends

Treatment Goals

- Assess and treat acute exacerbations
- Decrease distress
- Improve functioning between episodes
- Prevent recurrences
- Provide support and insight to patient and family

Pharmacists’ Role in Mental Health

- Frontline providers
- Communicate with PCPs/Psychiatrists
- Patient Education
- Simplifying dosing regimens/medication reminders
- Monitor for polypharmacy
- May be first to see side effects
- Case management/benefits management
### Now, let’s get to the meds

| Lithium: antimanic effects discovered in 1949, used extensively since 1960’s |
| Anticonvulsants: effects discovered in 1970’s |
| Antipsychotics: atypicals and typicals |
| Clozapine |

### Lithium (Eskalith, Lithobid)

- Generic available
- 900-2400 mg/day
- QD or BID
- Check serum levels: 0.6-1.5 mEq/L
- Check serum levels: Day 3-4, 1 mos, 3-6 mos, dose change
- Labs: CBC, renal, lytes, U/A, TSH, pregnancy test, ECG

### Side effects:
- Acne
- Renal dysfunction
- Cognition
- Diarrhea, GI distress
- Hypothyroidism
- Polyuria, polydipsia
- Tremor
- Weight gain
- Sedation

### Drug interactions:
- ACE inhibitors
- Diuretics
- NSAIDs
- Theophylline
- Caffeine

### Valproate (Depakote)

- 750-2000mg/day
- Q hs or BID
- Labs: LFTs, CBC, Cr, BUN, pregnancy test
- Check serum levels: 50-150mcg/ml
- Check serum levels: 1-2 weeks, then 3-6 months, dosage change

### Drug interactions:
- B-blockers
- Diuretics
- Beta-blockers
- Caffeine
- Cytostatics
- Anticoagulants
### Valproate (Depakote)

**Side effects:**
- Alopecia
- Ataxia, tremor
- Cognitive impairment
- Dizziness
- GI upset
- Liver and platelet dysfunction
- PCO
- Weight gain
- Sedation
- Rash

**Drug interactions:**
- Antipsychotics
- Benzodiazepines
- Carbamazepine
- Lamotrigine
- Lithium
- MAOIs
- Phenytoin
- TCAs
- Warfarin

### Carbamazepine (Tegretol)

- Generic available
- 400-1600mg/day
- BID or TID
- Labs: CBC, LFTs, pregnancy test
- Check serum levels: 4-12 mcg/ml
- Check serum levels: day 5-7, weekly ‘til stable, 3-6 months

### Carbamazepine (Tegretol)

**Side effects:**
- Ataxia
- Diplopia, nystagmus
- Dizziness
- Dysarthria
- GI upset
- Hyponatremia
- Leukopenia
- Rash
- Sedation

**Drug interactions:**
- Induces own metabolism
- Antipsychotics
- Benzodiazepines
- Cimetidine
- Corticosteroids
- Valproate
- Erythromycin
- Lamotrigine
- OCP
- TCA
- Warfarin

### Lamotrigine

- Generic available
- 200mg/day
- Titrate slowly
- QD or BID
- Labs: renal, LFTs, pregnancy test
Lamotrigine

Side effects:
- Ataxia
- Dizziness
- Headache
- Nausea
- Serious rash-Stevens Johnson Syndrome
- Sedation

Drug interactions:
- Carbamazepine
- Valproate

Recent Advisory for Mood Stabilizers

- All current antiepileptics pose increase risk of suicidality
- Patients should be warned
- No black box advisory
- Included carbamazepine, oxcarbazepine, valproate among others

Risperidone (Risperdal)

- 1993
- 1-8mg daily
- Only depot form of atypical
- Depot form q 2 weeks
- Weight gain, sedation and high prolactin most common
- Above 6 mg daily - EPS

Olanzapine (Zyprexa)

- 5-20mg daily
- Very sedating
- Excessive weight gain
- Metabolic syndrome
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Quetiapine (Seroquel)
- 300-800 mg daily
- Moderate for weight gain
- Slit lamp eye exam recommended-cataracts, not often done
- Very sedating

Ziprasidone (Geodon)
- 40-160mg daily
- 2001
- Short acting injectable available
- Can be used for acute agitation
- More weight neutral than other atypicals
- Lower incidence of metabolic syndrome

Aripiprazole (Abilify)
- 10-30mg daily
- “Dopamine stabilizer”
- Agonist in areas of low activity
- More weight neutral
- Low incidence of metabolic syndrome

Clozapine (Clozaril)
- 25-900mg daily
- 1989
- Weight gain
- Agranulocytosis- serious, fatal
- Weekly WBC count
- Specific protocol-complex to manage
- Used in refractory cases
- Seizures
- Excessive salivation
Atypical Antipsychotics

- How we choose:
  - Side effect profile - make them work for patient
  - Any absolute contraindications or medical risks
  - Other meds: drug-drug interactions
  - Cost!!
  - Insurance
  - Patient/family perceptions
  - Doctor’s own perceptions about meds

General Side Effects of Atypical

- Less likely to cause EPS or TD
- Prolactin elevation - galactorhoea, gynecomastia
- Sedation
- Anticholinergic
- Weight gain
- Also seen with typicals

Are Atypical Worth It?

- CATIE-Sept 2005
- NIMH study in NEJM
- Ground breaking
- Outcome stated typicals=atypicals in efficacy
- Cost of atypicals may not always be justified
- Patients stopped both meds at a high rate

Texas Implementation of Medication Algorithms (TIMA)

- Facilitate clinical decision making
- Using latest data, updated 2004
- Provide systematic guidance on possible treatment options
- Reduce side effects
- Provide flexibility in treatment choices
- Goal is full remission, improved functioning, relapse prevention
- Increase compliance, patient education
### Treatment for Bipolar Mania/Mixed

**Stage One**

<table>
<thead>
<tr>
<th>Euphoria</th>
<th>Mixed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li</td>
<td>Valproate</td>
</tr>
<tr>
<td>Valproate</td>
<td>Aripiprazole</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Risperidone</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Ziprasidone</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Ziprasidone</td>
</tr>
</tbody>
</table>

**Nonresponders**: try alternate monotherapy

**Partial response + good tolerability**: move to combo treatment

**Note**: Olanzapine and carbamazepine are 2nd tier due to side effect profile

### Stage Two (Combo therapy)

- Add lithium, valproate, atypical antipsychotic
- Pick 2
- Not 2 atypicals
- Not clozapine (no data)
- Not aripiprazole (no data)
- Nonresponders or partial responders: stage 3

### Stage Three (Combo therapy)

- Combinations of 2 different drugs from more choices
- Lithium, valproate, atypicals, carbamazepine, aripiprazole, oxcarbamazepine, typicals
- Not 2 atypicals
- Not clozapine
- Nonresponders/partial responders go to stage 4

### Stage Four

- ECT
- Add clozapine (to lithium and/or anticonvulsant)
<table>
<thead>
<tr>
<th>Treatment for Bipolar Depressed</th>
<th>Stage Two</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage One</strong></td>
<td></td>
</tr>
<tr>
<td>- Optimize current mood stabilizer</td>
<td></td>
</tr>
<tr>
<td>- No response, add lamotrigine</td>
<td></td>
</tr>
<tr>
<td>- No antimanic, no history of mania: start with lamotrigine</td>
<td></td>
</tr>
<tr>
<td>- No antimanic with severe hx, follow 1st protocol for mixed/mania</td>
<td></td>
</tr>
<tr>
<td>- Partial/nonresponders go to stage two.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Try quetiapine monotherapy</td>
</tr>
<tr>
<td></td>
<td>Or olanzapine/fluoxetine combo</td>
</tr>
<tr>
<td></td>
<td>Partial/nonresponders go to stage three</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage Three</th>
<th>Stage Four</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Combination of any two:</td>
<td>- ECT</td>
</tr>
<tr>
<td>- Lithium</td>
<td></td>
</tr>
<tr>
<td>- Lamotrigine</td>
<td></td>
</tr>
<tr>
<td>- Quetiapine</td>
<td></td>
</tr>
<tr>
<td>- Olanzapine/fluoxetine combo</td>
<td></td>
</tr>
<tr>
<td>- Not 2 atypicals</td>
<td></td>
</tr>
<tr>
<td>- Partial/nonresponders go to stage four</td>
<td></td>
</tr>
<tr>
<td>- Lithium, quetiapine, lamotrigine, olanzapine/fluoxetine PLUS</td>
<td></td>
</tr>
<tr>
<td>- Venlafaxine or</td>
<td></td>
</tr>
<tr>
<td>- Bupropion or</td>
<td></td>
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<tr>
<td>- SSRI</td>
<td></td>
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<tr>
<td>- Can induce mania</td>
<td></td>
</tr>
<tr>
<td>- Partial/nonresponders go to stage five</td>
<td></td>
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</tbody>
</table>
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Stage Five

- Limited empirical support
- Adverse effects
- MAO-I s
- TCAs
- Stimulants
- Thyroid supplementation
- Oxcarbamazepine
- Inositol
- Never 2 SSRIs, 2 TCAs, 2 AAP

Bipolar Knows No Boundaries

- Kurt Cobain
- Jane Pauley
- Sinead O’Connor
- Winston Churchill
- Handel
- Keats
- Van Gogh
- Patty Duke
- Teddy Roosevelt
- Ted Turner
- Charles Dickens

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Notes