Depressing Thoughts – Understanding the Complexities of Bipolar Depression
Bethany DiPaula, PharmD, BCPP

Home Study Webcast Handout
2 slides per page
Depressing Thoughts - Understanding the Complexities of Bipolar Depression

ACTIVITY DESCRIPTION
JC, a thirty year old male, suffers from bipolar disorder. Unlike many patients, JC spends more of his time in a depressed mood. He doesn’t seem to present other symptoms like mania, hypomania or euthymia to as great an extent. The challenge of treating psychiatric conditions, like bipolar disorder, is that all mood disorders are not alike and each may require unique treatment considerations. The unique and complex nature of bipolar depression requires different treatment approaches than bipolar disorder or depression. Medications that work for one or the other may not be appropriate for bipolar depression. This program will review the FDA approved treatment options for bipolar depression (second generations antipsychotics (SGAs)) and identify the complex challenges associated with taking them (such as weight gain, hyperglycemia, and metabolic syndrome).

TARGET AUDIENCE
The target audience for this activity is pharmacists and nurses in hospital, community, and retail pharmacy settings.

LEARNING OBJECTIVES
After completing this activity, the pharmacist will be able to:

- Differentiate between major depression, bipolar disorder and bipolar depression
- Outline the currently available 2nd generation atypical antipsychotics for the management of bipolar depression to include comorbidities, side effects and adverse events associated with treatment
- Describe steps to open up two way communications with patients with bipolar depression and integrate effective strategies to monitor therapeutic goals and evaluate and concurrently manage or minimize comorbidities and maximize adherence

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ABOUT THE AUTHOR
Dr. DiPaula is a residency trained, board certified psychiatric pharmacist. She is an Associate Professor with the University of Maryland, School of Pharmacy and has served as Director of Pharmacy at state-funded psychiatric hospitals for 16 years. She has acted as a residency preceptor for 16 years and Director of the University of Maryland PGY2 Psychiatric Pharmacy Residency program for 8 years. She currently collaborates with 2 community clinics, providing medication management and direct patient care for individuals with a variety of psychiatric disorders. She also provides medication reviews and consultations at a residential adolescent facility.

Dr. DiPaula has presented at local and national programs and serves as Instructor and/or Coursemanager for several University didactic and experiential courses. She has published articles, continuing education programs, and a book chapter on psychiatric and substance use disorders. Her major area of research and practice interest is in patients with comorbid psychiatric and substance use disorders.

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Objectives

• Differentiate between major depression, bipolar disorder and bipolar depression.

• Outline the currently available 2nd generation antipsychotics for the management of bipolar depression to include comorbidities, side effects and adverse events associated with treatment.
Objectives

• Describe steps to open up two way communications with patients with bipolar depression and integrate effective strategies to monitor therapeutic goals and evaluate and concurrently manage or minimize comorbidities and maximize adherence.

Outline

• Diagnosis
• Epidemiology
• Treatment of Bipolar Disorder
• Treatment of Acute BPD-Depression
• Treatment of BPD-Depression Maintenance
• Comorbidities
DSM-5 Types of Bipolar Disorder

- Bipolar Disorder I—“classic bipolar disorder”
- Bipolar Disorder II—experience more depression

DSM-5 Manic Episode

- Elevated, expansive, or irritable mood and ↑ energy/activity for ≥ 1 week, present most of the day, nearly every day
- ≥3 (4 if mood irritable):
  - ↑ self-esteem, grandiosity
  - ↓ need for sleep
  - Talkative/pressured speech
  - Flight of ideas/racing thoughts
  - Distractibility
  - ↑ activity/psychomotor agitation
  - ↑ activity with negative consequences (buying sprees, sexual promiscuity)
- Symptoms cause significant impairment

DSM-5 Hypomanic Episode

- Elevated, expansive, or irritable mood and ↑ energy/activity for > 4 days, present most of the day, nearly every day
- Doesn’t cause marked impairment but is observable
- > 3 (4 if mood irritable):
  - ↑ self-esteem, grandiosity
  - ↓ need for sleep
  - Talkative/pressured speech
  - Flight of ideas/racing thoughts
  - Distractibility
  - ↑ activity/psychomotor agitation
  - ↑ activity with negative consequences (buying sprees, sexual promiscuity)


DSM-5 Major Depressive Episode

- Depressed mood or loss of interest/pleasure for > 2 weeks
- > 5
  - Weight change
  - Sleep change
  - Psychomotor agitation/retardation
  - ↓ energy
  - Feelings of worthlessness/guilt
  - ↓ concentration
  - Recurrent thoughts of death/suicidal ideation
- Symptoms cause significant impairment

DSM-5 Bipolar Disorder I Criteria

- >1 manic episode usually interspersed with major depressive episodes
- Symptoms not due to another psychiatric disorder


DSM-5 Bipolar Disorder II Criteria

- >1 hypomanic episode and >1 major depressive episode. NO history of manic episode
- Symptoms not due to another psychiatric disorder

Difference between MDD, Bipolar, and Bipolar Depression?

- MDD
  - Depressive Episode

- BPD I
  - Manic Episode
  - Depressive Episode

- BPD II
  - Hypomanic Episode
  - Depressive Episode

Prognosis

- ↑ rates of comorbid medical, psychiatric, and substance abuse disorders
  - ↑ rates of diabetes mellitus, liver and cardiovascular disease compared to the general population
  - Anxiety and substance abuse most common (40-60% lifetime prevalence)

- ↓ life expectancy and quality of life

- 15x> risk for suicide than general population

- Important to screen for medical and psychiatric comorbidities
Consequences of BPD Depression

- > impairment in work, family, social life compared with mania
- > morbidity/mortality associated with BPD
- > lifetime risk for suicide among psychiatric illnesses
- Optimal management of BPD depression is essential to improve LT functioning
  - Treatment can be delayed or suboptimal due to misdiagnosis


Patient Assessment

- > 50% bipolar I and most with bipolar II will initially present with major depressive episode
  - Obtain history of past manic/hypomanic symptoms
- The initial evaluation should rule out
  - Medical: physical exam and lab data
  - Substance abuse
  - Medications: may cause or exacerbate such as antidepressants, stimulants

Connolly, KR. Prim Care Companion CNS Disord. 2011;13(4):doi:10.4088/PCC.10r1097
General Treatment Principles of Bipolar Disorder

• Urgent treatment: acute mania, depression, or mixed states can be associated with psychosis, poor insight, and suicidal ideation
• There are several US and international evidence-based guidelines published, mostly written before 2010
• 1st line pharmacologic treatment differs depending on type of bipolar disorder

General Treatment Principles of Bipolar Disorder

• Treatment is divided into:
  • Management of acute episodes
  • Inter-episode maintenance treatment to prevent reoccurrence
• Mood stabilizers and/or antipsychotics commonly used to manage bipolar disorder
  • Not all agents are equal in their ability to manage or prevent manic or depressive episodes
• Acute treatment may differ from maintenance treatment
  • Regimens should be optimized (↓ #, dose) during maintenance, if possible
Case 1

• CC: “I feel worthless and want to die.”
• HPI: TS is a 29 yo M recently admitted to an inpatient psychiatric unit. The pt is severely agitated and c/o depressed mood, auditory hallucinations telling him that he should kill himself. He also reports sleeping for only a few hours per night and only eating once per day, when he is hungry. He has history of experiencing manic episodes in the past
• Diagnostic Impression: Bipolar Disorder I-Depressive Episode
• What role might antipsychotics play in managing this patient?

Treatment of Acute Depressed Episode with Psychotic Features

• Psychotic symptoms occur with acute manic and depressive episodes
  • More common in mania
• Antipsychotics recommended with psychotic features
Antipsychotics and Bipolar Disorder
(Not all AP are the Same)

- 1\textsuperscript{st} generation antipsychotics (FGA)
  - Beneficial for behavioral control and psychosis
  - No mood stabilizing properties
- 2\textsuperscript{nd} generation antipsychotics (SGA) do produce mood stabilizing effects

First Generation Antipsychotics (FGA)

- Haloperidol (Haldol®)
- Fluphenazine (Prolixin®)
- Trifluoperazine (Stelazine®)
- Perphenazine (Trilafon®)
- Chlorpromazine (Thorazine®)
- Thioridazine (Mellaril®)
- Thiothixene (Navane®)
- Loxapine (Loxitane®)
- Molindone (Moban®)
Side Effects of FGAs

- Movement disorders
  - Extrapyramidal symptoms (EPS): pseudoparkinsonism, dystonia, akathisia
  - Tardive Dyskinesia - patients with mood disorder more susceptible
- Anticholinergic: dry mouth, dry eye, blurred vision, constipation
- Weight gain
- Hyperglycemia/Hyperlipidemia
- Sexual dysfunction
- Gynecomastia/Galactorrhea
- Cognitive Slowing
- Photosensitivity
- Neuroleptic malignant syndrome

Second Generation Antipsychotics (SGA)

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rispeidal®</td>
<td>Risperidone</td>
</tr>
<tr>
<td>Seroquel®</td>
<td>Quetiapine</td>
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<tr>
<td>Zyprexa®</td>
<td>Olanzapine</td>
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<tr>
<td>Geodon®</td>
<td>Ziprasidone</td>
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<td>Abilify®</td>
<td>Aripiprazole</td>
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<tr>
<td>Fanapt®</td>
<td>Iloperidone</td>
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<tr>
<td>Saphris®</td>
<td>Asenapine</td>
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<tr>
<td>Latuda®</td>
<td>Lurasidone</td>
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<tr>
<td>Vraylar®</td>
<td>Cariprazine</td>
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<tr>
<td>Clozaril®</td>
<td>Clozapine</td>
</tr>
</tbody>
</table>
Second Generation Antipsychotics

• SGA=atypical antipsychotics
• Dopamine and serotonin antagonist
• Advantages over FGA in BPD
  • Improved mood and cognition
  • ↓ EPS
• Target and maximum doses for BPD are similar to those used to manage psychosis/schizophrenia

### Medication

<table>
<thead>
<tr>
<th>Medication</th>
<th>SGA FDA Approved Indication in BPD as of July 2016</th>
</tr>
</thead>
</table>
| Aripiprazole                | Bipolar disorder - Psychomotor agitation (IM)  
BPD I manic or mixed episode Monotherapy  
BPD I manic or mixed episode Adjunctive with lithium or valproate |
| Asenapine                   | BPD I manic or mixed episode Monotherapy  
BPD I manic or mixed episode Adjunctive with lithium or valproate |
| Cariprazine                 | BPD I manic or mixed episode |
| Lurasidone                  | BPD I depression Monotherapy  
BPD I depression Adjunctive with lithium or valproate |
| Olanzapine                  | Bipolar disorder - Psychomotor agitation (IM)  
BPD I manic or mixed episode Monotherapy  
BPD I manic or mixed episode Adjunctive with lithium or valproate  
BPD I maintenance therapy |
| Olanzapine/fluoxetine       | BPD I depression |
| Quetiapine                  | BPD I manic or mixed episode Monotherapy  
BPD depression Monotherapy  
BPD I maintenance therapy |
| Risperidone (oral or LAI)   | BPD I manic or mixed episode Monotherapy  
BPD I manic or mixed episode Adjunctive with lithium or valproate |
| Ziprasidone                 | BPD I manic or mixed episode Monotherapy  
BPD I manic or mixed episode Adjunctive with lithium or valproate  
BPD I maintenance therapy Adjunctive with lithium or valproate |
Side Effects of SGA

• Sedation
• ↑ appetite
• “Metabolic Syndrome”
  • Weight gain and abdominal obesity
  • ↑ cholesterol/lipids
  • ↓ insulin sensitivity → hyperglycemia
  • ↑ blood pressure
• ↑ prolactin (gynecomastia, galactorrhea)
• Movement disorders (EPS/TD)
  • < with FGAs
  • ↑ with mood disorder

<table>
<thead>
<tr>
<th>Antipsychotic agent</th>
<th>Notable SGA differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone, Paliperidone</td>
<td>Hyperprolactinemia. Dose-related EPS</td>
</tr>
<tr>
<td>Ziprasidone, Aripiprazole, Lurasidone</td>
<td>Weight neutral, LESS glucose intolerance, LESS hyperlipidemia</td>
</tr>
<tr>
<td>Clozapine, Olanzapine</td>
<td>Greatest risk for weight gain, hyperlipidemia, glucose intolerance, Smoking significantly ↓</td>
</tr>
<tr>
<td>Ziprasidone, Iloperidone</td>
<td>Significant QTc prolongation</td>
</tr>
<tr>
<td>Risperidone, Quetiapine, Ziprasidone, Olanzapine, Aripiprazole</td>
<td>Generic available</td>
</tr>
<tr>
<td>Ziprasidone, Lurasidone</td>
<td>Poor bioavailability when taken on an empty stomach—always give with food!!!</td>
</tr>
<tr>
<td>Asenapine</td>
<td>Poor bioavailability when taken orally—should be taken sublingually!!!</td>
</tr>
</tbody>
</table>
Monitoring Parameters for SGA

- Metabolic: fasting glucose, HgbA1c, lipids
- Weight
- Abnormal involuntary movements
- EKG—at least baseline with ziprasidone

<table>
<thead>
<tr>
<th>Monitoring Parameter</th>
<th>Baseline</th>
<th>1 mo</th>
<th>2 mo</th>
<th>3 mo</th>
<th>6 mo</th>
<th>Annually</th>
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<tbody>
<tr>
<td>HGBA1c</td>
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<tr>
<td>Fasting plasma glucose</td>
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<tr>
<td>Fasting lipid panel</td>
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<tr>
<td>Body Mass Index</td>
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<tr>
<td>Waist Circumference</td>
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10/14/2016

Case 1 wrap up

- Patient diagnosed with acute BPD I depression episode and is experiencing psychotic symptoms and severe agitation
- AP (FGA or SGA) treatment options for acute psychotic symptoms/agitation
- FGA no mood stabilizing effects
Case 2

• HPI: JL is a 24 yo F who presents to her PCP with complaints of worsening depression. She has been receiving lithium but would like to switch to an alternative agent. While the patient is not experiencing any manic symptoms currently, she does have a history of a previous hypomanic episode without psychosis.
• Should her PCP prescribe an antipsychotic to manage her depressive symptoms?

Treatment of Acute Bipolar Depression

• Recommendations vary among guidelines suggesting need for further research
• Treatment response may vary between Bipolar I depression and Bipolar II depression. However, many studies include mixed populations
• Unclear whether to start with mood stabilizer or SGA monotherapy
Treatment of Acute Bipolar Depression

- Mood stabilizers: lithium, lamotrigine
  - Limited data to support use: VPA, CBZ
- SGA: olanzapine, lurasidone, quetiapine
- Antidepressants should not be used as monotherapy!
  - Controversy when combined with mood stabilizer but commonly prescribed
  - AD associated with ↑ switch, suicide, mixed state
  - TCA, SSRI higher risk of switch than bupropion
  - No AD has FDA approval for BPD depression

Acute Bipolar Depression: SGA

- Have rapid onset and can be beneficial
  - Olanzapine, quetiapine within 1 wk
- Guideline conflict as to which if any SGA should be considered 1st line monotherapy
- Data with quetiapine, olanzapine-fluoxetine, olanzapine, lurasidone
  - > data with quetiapine
  - Meta-analysis found efficacy ranking of
    - olanzapine/fluoxetine > quetiapine > lurasidone > olanzapine > aripiprazole
  - Aripiprazole conflicting data. Ziprasidone ineffective
### Case 2 Discussion

- **Should JL’s MD prescribe an antipsychotic to manage her depressive symptoms?**
  - JL is not a candidate for FGA since there is no psychosis
  - SGA (quetiapine, olanzapine/fluoxetine, lurasidone) monotherapy could be used to manage mood symptoms
    - > data with quetiapine

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<table>
<thead>
<tr>
<th>SGA</th>
<th>Weight Gain</th>
<th>Dyslipidemia</th>
<th>Hyperglycemia</th>
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<tbody>
<tr>
<td>Aripiprazole</td>
<td>+/0</td>
<td>+/0</td>
<td>+/0</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>+/0</td>
<td>+/0</td>
<td>+/0</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>++</td>
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Case 3

TS is a 37 yo M who has a history of bipolar disorder and recently experienced an acute depressive episode. He has since been stabilized on lithium 600mg bid and quetiapine 300mg bid. He presents to the pharmacy for refills but would like to know, if he should continue these medications now that he is feeling better.

AP Maintenance of BPD Depression

• Maintenance phase starts after 3 months of mood stability
• Goal to prevent reoccurrence
• FGA not effective in prevention of BPD depression
• Olanzapine, quetiapine may have benefit in preventing relapse
• Safety, tolerability, adherence must be considered with any regimen
Case 3 Discussion

Should TS’s regimen be modified for maintenance treatment?
• Maintain regimen
• Evaluate for efficacy and adverse events over time
• Consider optimizing regimen by ↓ dose/meds

Psychiatric Comorbidities

• More time spent depressed is a predictor of medical comorbidities
• Common psychiatric comorbidities: anxiety, substance use disorder, ADHD
BPD & Metabolic Syndrome

• BPD are particularly at risk for metabolic syndrome.
  • Incidence varies by country
  • Meta-analysis found 37% of BPD patients had metabolic syndrome (2x rate of general population)
• Metabolic syndrome associated with ↑ CV morbidity/mortality
• Metabolic syndrome associated with depressive symptoms putting those with bpd depression at > risk


BPD & Metabolic Syndrome

• Why is metabolic syndrome associated with BPD?
  • Limited access to healthcare
  • ↑ Lifestyle risks (weight gain, physical activity, sleep disturbance, smoking history)
  • Neurobiologic (neurotrophic factors, oxidative stress, and inflammation)
  • Pharmacotherapy

• Management
  • Assess metabolic risk
  • Monitor BMI, waist circumference, lipids, fasting glucose
  • Diet and exercise
  • Manage pharmacotherapy based on metabolic risk
  • Pharmacotherapy for hypertension, hyperglycemia, dyslipidemia

Pharmacist Role

• Understand the differences in presentation and treatment of unipolar and bipolar depression
• Be comfortable asking about acute psychiatric symptoms like suicidal ideation, depressed mood, hallucinations
• Assess for switch to mania, hypomania, rapid cycling, or worsening depression (dysphoria, irritability) which can occur with AD administration in BPD
• Check with patient about benefits of current regimen. Encourage the patient to follow up with his/her provider, if treatment not optimal

Pharmacist Role

• Educate about the importance of adherence and help the patients understand the need for polypharmacy, when relevant
• Recognize and help to manage adverse effects and drug-drug interactions
• Familiarize yourself and educate about medication patient assistance programs
• Discuss preventative health and encourage primary care follow up to manage comorbid illnesses
• Provide information about appropriate diet and exercise to maintain healthy body weight
• Collaborate with the physician to optimize patient’s medication regimen
Conclusion

• Bipolar disorder is a lifelong illness, which requires long term therapy. Polypharmacy is common.
• There are multiple subtypes of BPD.
• Evidenced based pharmacotherapy recommendations are still evolving and further research is necessary to determine the clear hierarchy of pharmacologic treatment, especially with bipolar depression.

Conclusion

• SGA have been shown to be effective monotherapy or adjunctive therapy for acute and maintenance treatment of bipolar mania and depression. However, efficacy varies among SGA and guidelines conflict regarding SGA’s place in therapy.
• ↑ risk for side effects with SGA in BPD, especially with polypharmacy.
Exam Questions:

1. JR is a 28 yo male whose mood fluctuates between manic episodes, major depressive episodes, and euthymia. For which one of the following types of bipolar disorder is JR most likely to meet the DSM 5 criteria?
   a. Bipolar Disorder Type 1
   b. Bipolar Disorder Type 2
   c. Dysthymia
   d. Major Depressive Disorder

2. TS is a 33 yo female whose mood fluctuates between hypomanic episodes, major depressive episodes, and euthymia. For which one of the following types of bipolar disorder is TS most likely to meet the DSM 5 criteria?
   a. Bipolar Disorder Type 1
   b. Bipolar Disorder Type 2
   c. Dysthymia
   d. Major Depressive Disorder

3. A 28 yo Male is being treated with haloperidol 5mg bid to manage his acute psychotic symptoms associated with bipolar disorder. Which one of the following side effects is this patient at greater risk for developing compared with patients without a mood disorder?
   a. Diabetes Mellitus
   b. Hypertension
   c. Tardive Dyskinesia
   d. Hyperthermia

4. A patient with bipolar disorder is experiencing severe agitation associated with auditory hallucinations. Which one of these agents would you recommend to manage the agitation?
   a. Fluphenazine
   b. Quetiapine
   c. Benztropine
   d. A and B
5. Which one of the following second generation antipsychotics has been shown to be beneficial in managing bipolar depression?
   a. Quetiapine
   b. Asenapine
   c. Ziprasidone
   d. Perphenazine

6. Which one of the following antipsychotics is more likely to cause metabolic syndrome in a patient with bipolar disorder?
   a. Aripiprazole
   b. Ziprasidone
   c. Lurasidone
   d. Olanzapine

7. Extrapyramidal side effects are most commonly associated with which one of the following medications?
   a. Quetiapine
   b. Chlorpromazine
   c. Haloperidol
   d. Ziprasidone

8. TL is a 35 yo Female with a history of previous hypomanic episodes. She is currently experiencing a severe depressive episode and presents to the pharmacy with a prescription for sertraline 100mg qam. Which one of the following is evidence based?
   a. Sertraline is the treatment of choice for this patient
   b. Patient should be switched to mirtazapine and monitored for sedation
   c. Patient should be receiving an antipsychotic and monitored for increased risk of extrapyramidal symptoms
   d. Patient should be receiving a medication with mood stabilizing effects and monitored for manic symptoms

9. Which one of the following psychiatric disorders can commonly co-occur with bipolar disorder?
   a. Schizophrenia
   b. Attention Deficit Hyperactivity Disorder
   c. Dissociative Identity Disorder
   d. Autism Spectrum Disorder
10. The pharmacists should recommend that the following medication should be administered with food to improve bioavailability.

   a. Lurasidone
   b. Fluphenazine
   c. Olanzapine
   d. Quetiapine