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Clinical and Economic Impact of Bipolar Disorder

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This program is paid for by Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC) and Lundbeck, LLC.

Outline

Overview of Bipolar Disorder Landscape

- Epidemiology
- Features of Bipolar Disorder

Impact of Bipolar Disorder

- Patient outcomes
- Economic considerations

Current Treatment Options & Challenges

- Treatment Challenges
- Current Treatment Options

Defining Features of Bipolar Disorder

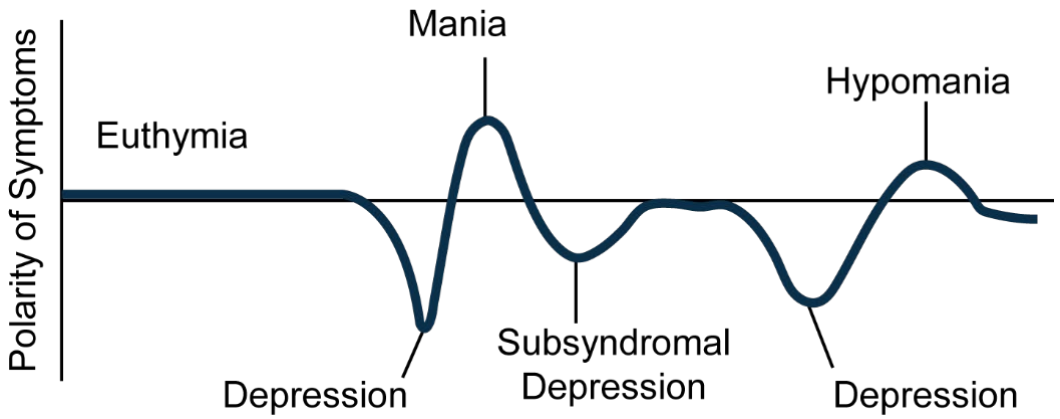


Diagram adapted from Khalife S et al. 2010[3]

Bipolar Disorder is a cyclic disease

- Occurrence of episodes of mania or hypomania which either alternate or occur with depressive episodes[1]
- While episodes are usually separated by periods of recovery, there are high rates of recurrence, and the disease course is not well understood[2]
- Average age of onset is 22.3 years, with onset occurring slightly earlier in women than men[4]
- Patients may experience subsyndromal and/or absence of symptoms in between illness episodes[5,6]
- Delay to first time treatment was associated with higher levels of depression, and higher number of episodes[7]

1. Diagnostic and statistical manual of mental disorders (5th Text Revision ed.). 2013. American Psychiatric Association. Washington, DC.
2. Oswald P et al. *European Neuropsychopharmacology*. 2007; 17(11):687-695.
3. Khalife S et al. Disease Management. Bipolar Disorder. 2010. Cleveland Clinic Medical Education. Available at: http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/psychiatry-psychology/bipolar-disorder/.
4. Blanco C et al. *Journal of Psychiatric Research*. 2017; 84:310-317.
5. Kaya E et al. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2007; 31:1387-1392.
6. Judd LL et al. *Archives of General Psychiatry*. 2002; 59:530-537.
7. Post RM et al. *J Clin Psychiatry*. 2010; 71(7):864-872.

Bipolar I and Bipolar II Disorders

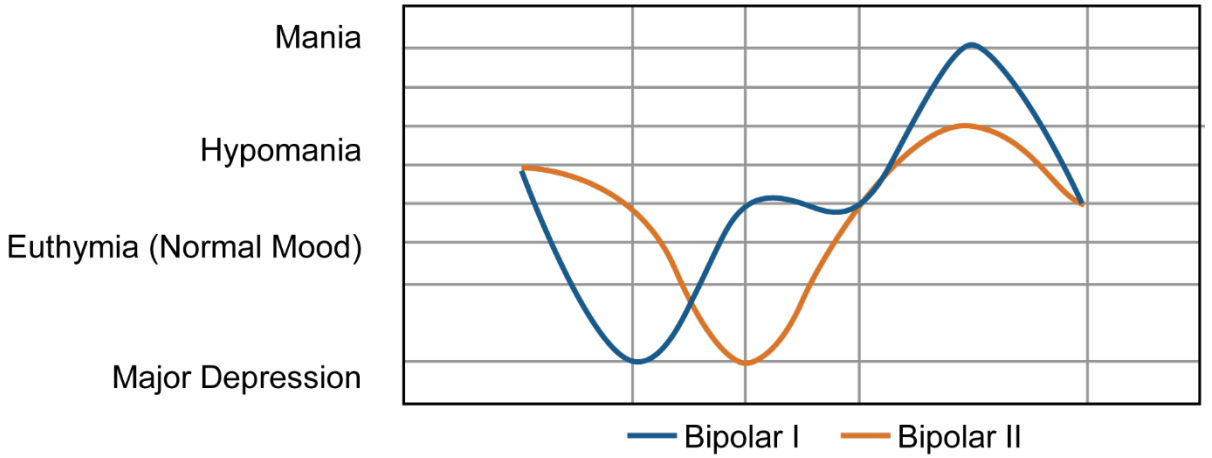
Presentation of Bipolar I and Bipolar II Disorders

Bipolar I Disorder

- Mania or cycling episodes of mania and depression are primary symptoms

Bipolar II Disorder

- Recurring depressive episodes alternating with hypomania (milder state of mania where symptoms are not severe enough to lead to functional impairment/hospitalization)



1. Diagnostic and statistical manual of mental disorders (5th Text Revision ed.). 2013. American Psychiatric Association. Washington, DC.

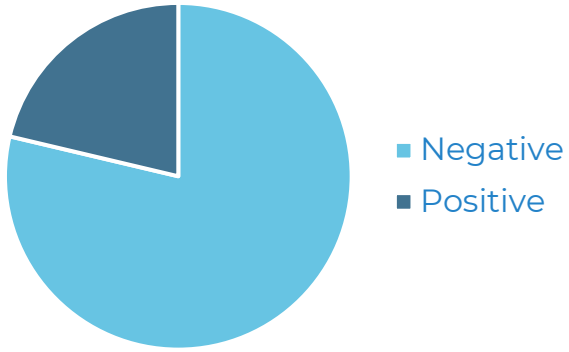
The Scope of Bipolar Disorder

Prevalence of Bipolar Disorder

- In the general US population, 12-month prevalence of BD I is estimated to be 1.5% while lifetime prevalence is 2.1%[1]
  - Prevalence estimates did not differ according to gender
  - BD I was higher among Native Americans, but lower among Blacks, Hispanics, and Asians/Pacific Islanders compared to whites
  - Rates were also lower among younger than older persons, those previously married (vs. currently married) and people with lower education and income relative to higher education and income

Prevalence may be underestimated

Of 649 patients being treated with antidepressants for depression, 21.3% screened positive for bipolar disorder[2]



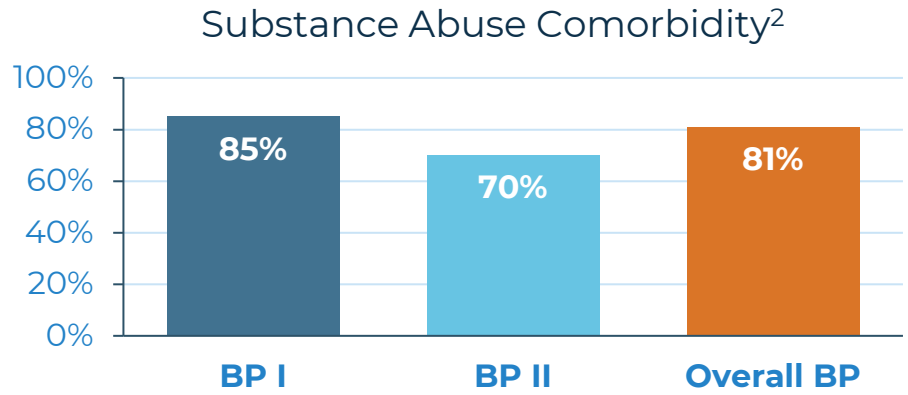
- ~70% to 80% of patients with BD may be misdiagnosed, most commonly with depression[3,4]
- More than one-third of patients may seek help for ≥10 years before being accurately diagnosed[3]
- Patients may receive >3 misdiagnoses and see 4 physicians before a correct diagnosis is made[4]

BD, bipolar disorder.

1. Blanco C et al. *Journal of Psychiatric Research*. 2017; 84:310-317.
2. Hirschfeld RM et al. *J Am Board Fam Pract*. 2005; 18:233-239
3. Hirschfeld RM et al. *J Clin Psychiatry*. 2003; 64(2):161-174.
4. National Depressive and Manic Depressive Associations (NDMDA). "Constituency Survey." Available at: http://www.dbsalliance.org/pdfs/bphowfar1.pdf. Accessed July 7th, 2017.

Bipolar Disorder and Comorbid Psychiatric Conditions

- 12-month and lifetime prevalence of BD I were significantly related to substance use disorders[1]
- Rates of substance abuse were also found to be higher among patients with BD I than those with BD II[2]
  - Lower household income and higher manic severity were predictors of substance use disorders[2]

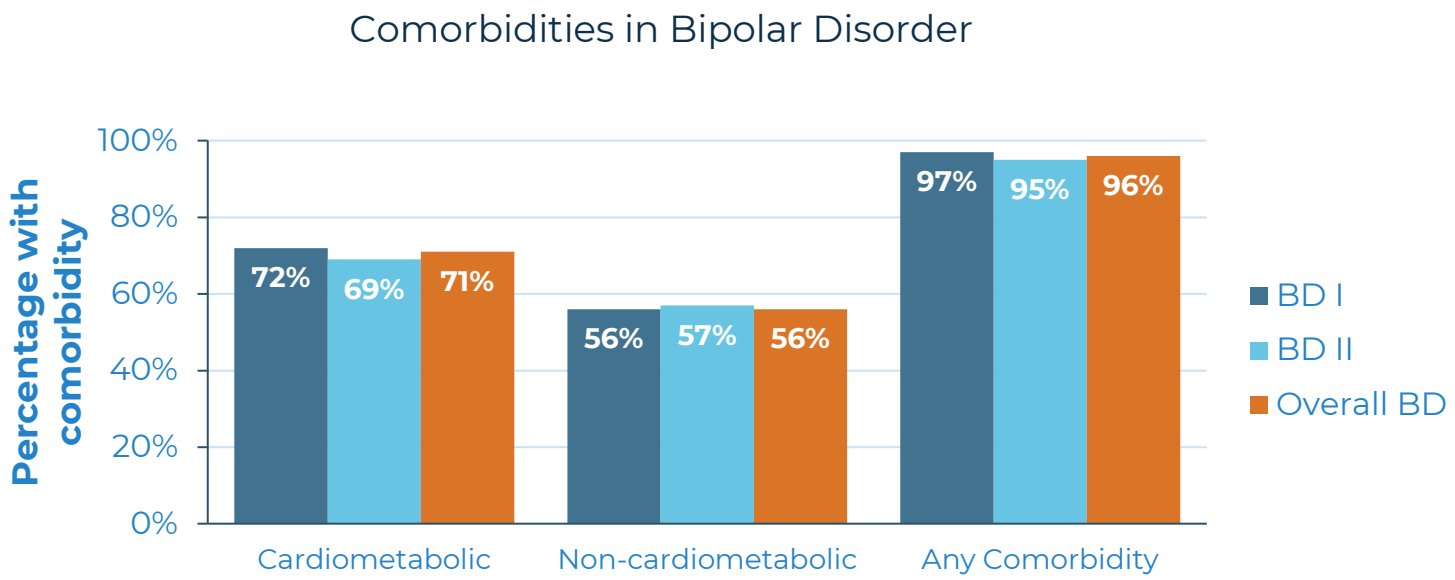


- High prevalence of comorbid OCD was noted among those with bipolar disorder (pooled prevalence = 24.6%), especially BD I[3]
- The lifetime prevalence estimates of anxiety related disorders is high among patients with BD according to a systematic literature review of studies conducted from 1992-2013:[4]
  - Generalized anxiety disorder = 14.4%
  - PTSD = 10.8%
  - Any anxiety disorder = 42.7%
- The presence of psychiatric comorbidities was identified as significant predictors of a longer time to reach remission[5]
- A prospective analysis found comorbid Alzheimer's disease was correlated with lower remission rates through the first year, and higher risk of hospitalization during 24 period[6]

BD, bipolar disorder; OCD, obsessive compulsive disorder; PTSD, post-traumatic stress disorder.

1. Blanco C et al. *Journal of Psychiatric Research*. 2017; 84:310-317.
2. Shelton S et al. *Bipolar Disorders*. 2015; 17:212-223.
3. Amerio A et al. *J Affective Disorders*. 2015; 186: 99-109.
4. Nabavi B et al. *EBioMedicine*. 2014; 2(10):1405-1419.
5. Kora K et al. *Prim Care Companion J Clin Psychiatry*. 2008; 10(2):114-119.
6. Kim SW et al. *J Affective Disorders*. 2014; 166:243-248.

Bipolar Disorder and Comorbid Medical Conditions



More than 50% of those with bipolar disorder have at least one comorbid condition, with higher rates of comorbidities among the BD I cohort

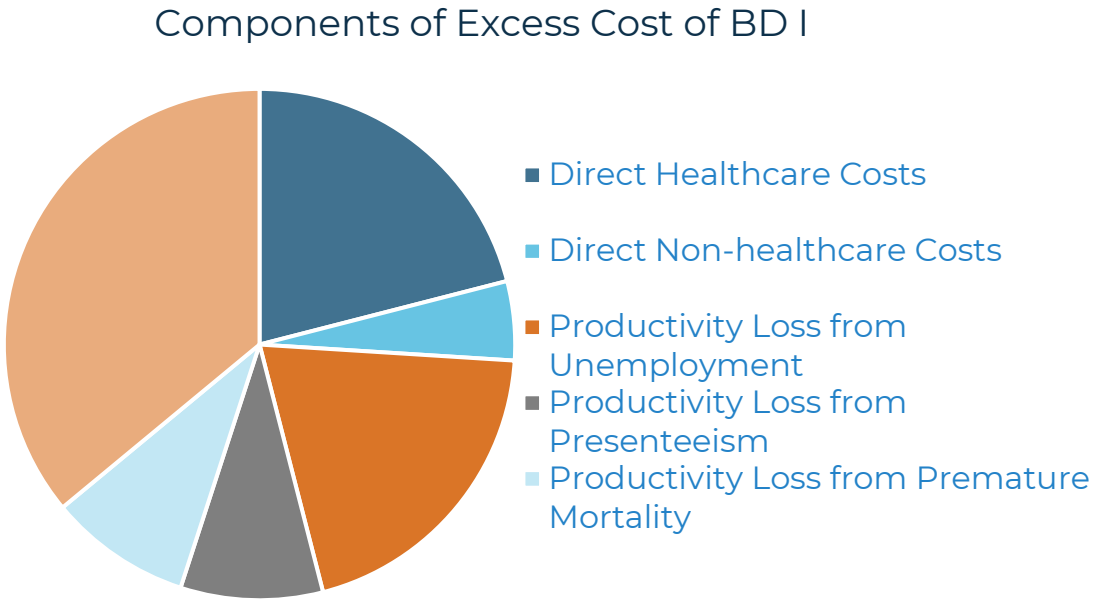
- Predictors of cardiometabolic comorbidities included later age of onset, increased number of depressive symptoms, and fewer manic symptoms at baseline
- Predictors of non-cardiometabolic comorbidities included female gender, larger amount of time spent depressed, younger age of onset, longer duration of illness
- Predictors of substance abuse included race, lower household income, older age, lower educational level, experiencing comorbid anxiety disorder, worse depression and increased illness severity

BD, bipolar disorder.

1. Shelton S et al. *Bipolar Disorders*. 2015; 17:212-223.

Bipolar Disorder is a Costly Disease

- Total costs and excess costs because BD I were calculated for both insured and uninsured individuals:
  - Total costs for individuals with BD I, in direct healthcare, direct non-healthcare costs, and indirect costs in 2015 amounted to $202.1 billion
    - The largest contributors were unemployment costs (36%), caregiving costs (25%) and direct healthcare costs (23%)
  - In comparison to the US general population, this represents an **excess cost** of $119.8 billion



BD, bipolar disorder.

1. DOF HEOR-0003

Bipolar Disorder is Associated with Adverse Workplace Outcomes

- BD impacts work productivity and performance:
  - Employment opportunities are negatively impacted[1,2]
  - Significantly higher rates of absenteeism from work were noted amongst those with BD in comparison to those without BD (18.9 days vs. 7.4 days)[3]
  - Absenteeism due to BD amounted to 27.7 days while presenteeism due to BP totaled 35.3 days[4]
  - The estimated unemployment rate was higher for those with BD I than the US general population: 61.5% versus 41.2%[5]
    - The excess costs associated with productivity loss from unemployment were calculated to be $24.2 billion (2015 USD)[5]
  - Among individuals with BD I who were employed, reduced work productivity was also noted[5]
    - Productivity among employed individuals with BD I was 79.9%, meaning that individuals with BD I were 21.1% less productive than the general population[5]
    - The cost of productivity loss per employed individual with BD I was $9,722 (2015 USD)[5]

BD, bipolar disorder; USD, United States Dollar.

1. Parker G et al. *J Affective Disorders*. 2013; 149:46-55.
2. Marwaha S et al. *Acta Psychiatrica Scandinavica*. 2013; 128:179-193.
3. Gardner HH et al. *J Clin Psychiatry*. 2006; 67(8):1209-1218.
4. Kessler RC et al. *Am J Psychiatry*. 2006; 163(9):1561-1568.
5. DOF HEOR-0003

Bipolar Disorder Also Exacts a Human Toll

- Consumers with BD may experience:
  - Psychotic symptoms and impaired functioning[1]
  - Decreased self-reported HRQoL across all phases of the disease[2,3]
    - In comparison to the general US population, HRQoL was significantly impacted among those with BD[2,3,4]
    - However, treatment has been associated with improved HRQoL[5]
- Suicide is also common in those with BD
  - Suicide has been found to be 10.3 to 16.2 times higher among individuals with BD I[6]
  - Lifetime co-morbid substance abuse disorder has been significantly associated with suicide attempts[7]
  - Other predictors of suicide in the BD population include[8]:
    - History of suicide attempt
    - Subjective rating of the severity of depression
    - Pessimism
    - Aggression/impulsivity factors

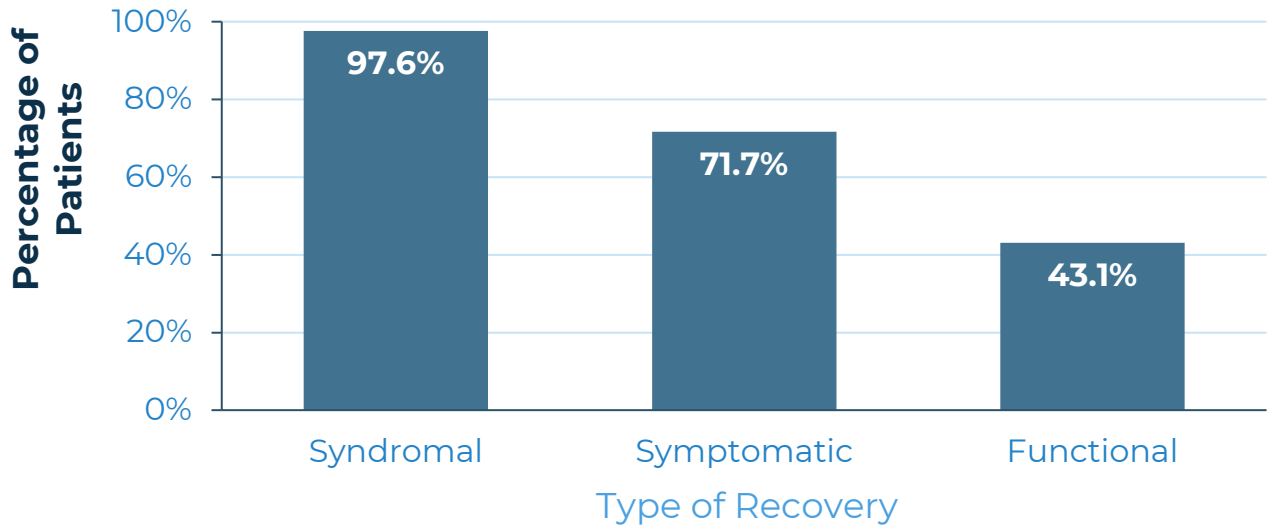
BD, bipolar disorder; HRQoL, health-related quality of life.

1. Geddes JR et al. *Lancet*. 2013; 381.
2. Blanco C et al. *Journal of Psychiatric Research*. 2017; 84:310-317.
3. Miller CJ et al. *J Affective Disorders*. 2013; 146:100-105.
4. Zhang H et al. *Compr Psychiatry*. 2006; 47(3); 161-168.
5. Deckersbach T et al. *J Clin Psychiatry*. 2016; 77(1):100-108.
6. DOF HEOR-0003
7. Dalton JE et al. *Bipolar Disorders*. 2003; 5(1):58-61.
8. Oquendo MA et al. *Am J Psychiatry*. 2004; 161(8):1433-1441.

Functional Recovery in Bipolar Disorder

Fewer patients may experience functional recovery than syndromal or symptomatic recovery

2-Year recovery after index manic of mixed episode in patients with bipolar disorder (N=166) after first hospitalization for manic or mixed episode



Patients with bipolar disorder (N=166) were followed 2-4 years after their first hospitalization for a manic or mixed episode to assess timing and predictors of outcomes. Three aspects of recovery were measured: syndromal (DSM-IV criteria for disorder no longer met), symptomatic (Young Mania Rating Scale score ≤ 5 and Hamilton Depression Rating Scale score ≤ 8), and functional (regaining of premorbid occupational and residential status).

1. Tohen et al. *Am J Psychiatry*. 2003; 160:2099-2107.

Stigma in Bipolar Disorder

- **Types of Stigma encountered:**
  - **External stigma** – Discrimination due to public perceptions associated with mental illness[1]
    - May lead to fewer opportunities and social isolation[1]
  - **Self-stigma** – Internalization of negative perceptions of BD[1]
    - Contributes to lowered self-esteem and feelings of embarrassment/shame[1]
  - **Healthcare Provider Stigma** – Stigma against those with mental illness by healthcare professionals[1]
    - May create barriers to effective communication[1]
- **Stigma and the Impact on Patients**
  - Stigma is one reason that persons with BD do not seek treatment or discontinue treatment[1]
  - Stigma is associated with social withdrawal, concealment of diagnosis and social anxiety. This in turn leads to a decrease in social support networks[2]
  - A lack of social support is associated with relapse and slower recovery[2]

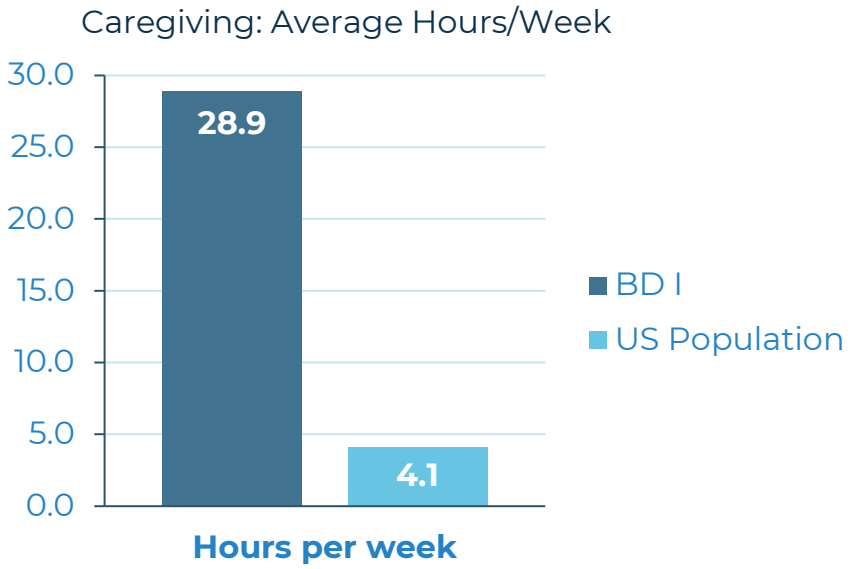
BD, bipolar disorder; HRQoL, health-related quality of life; US, United States.

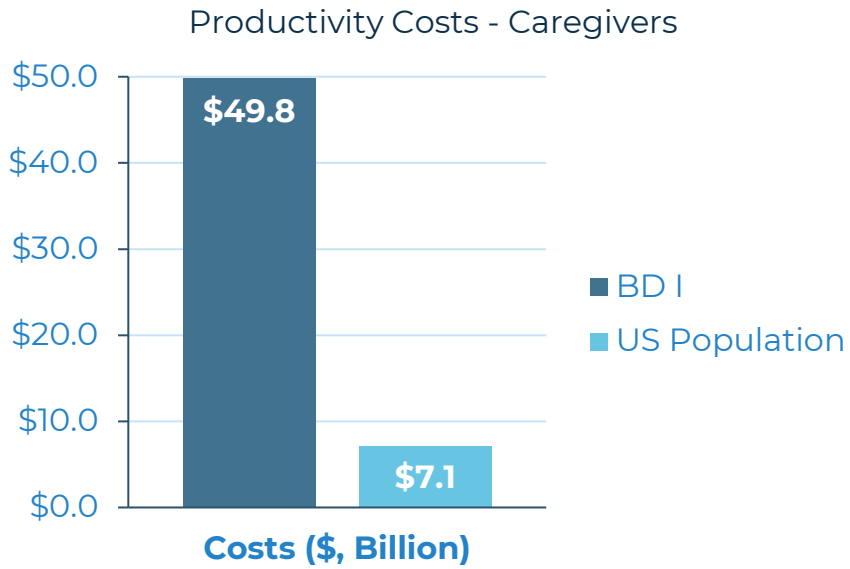
1. Committee on the science of changing behavioral health social norms, Board on behavioral, cognitive and sensory sciences, Division of behavioral and social sciences and education, National Academies of Sciences, Engineering, and Medicine. "Ending discrimination against people with mental and substance use disorders: the evidence for stigma change." 2016.
2. Hawke LD et al. *J Affective Disorders*. 2013; 150(2):181-191.

Caregivers Are Also Affected

The impact of providing care for someone with BD I is significant:

- 57.6% of those with BD I live with a family member
- Those with BD I require more hours of caregiving than the general population and this translates into lost productivity cost among caregivers





Caregivers incur incremental direct healthcare costs of $0.9 billion (2015, USD) due to caregiving

BD, bipolar disorder; US, United States.

1. DOF HEOR-0003

Psychosocial Treatment of Bipolar Disorder

Goal of Therapy: Stabilization of mood (euthymic state) when patients are experiencing either mania or depression[1]

- During phases of recovery, treatment goals focus on relapse prevention, reducing any residual symptoms and improving general functioning[1]
- Targeted psychotherapy has been identified as being crucial to better patient outcomes[1]
- The main goals of psychotherapy for bipolar disorder are[1]:
  - Educate patients and caregivers about stress management
  - Identify early signs of recurrence and follow proper procedures for treatment
  - Help patients understand importance of maintaining a healthy lifestyle
  - Teach patients the importance of consistency with pharmacological treatment
- If psychosocial therapies are used, they should be combined with pharmacotherapy[2]

1. Geddes JR et al. *Lancet*. 2013; 381
2. Hirschfeld RMA, et al. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Bipolar Disorder: Second Edition.

Pharmacotherapy for Bipolar Disorder

Treatment for Manic or Mixed Episodes

Manic or Mixed – First-Line Treatment

- For less ill patients, monotherapy with a mood stabilizer, or an antipsychotic should be sufficient

Severe Manic or Mixed – First-Line Treatment

- **Initiate mood stabilizer + antipsychotic**
  - Atypical antipsychotics may be preferred over typical antipsychotics due to the side effect profiles
- **Severely ill/agitated patients may need short term adjunctive treatment with benzodiazepine**

Failure of first-line treatment at optimal doses

- Add second first-line medication
- Add anticonvultant instead
- Add antipsychotic if not already prescribed
- Change antipsychotic

Antidepressants should be tapered and discontinued if possible.

Initial treatment selection should be guided by factors such as illness severity, associated feature, patient preferences and side effect profiles

1. Hirschfeld RMA, et al. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Bipolar Disorder: Second Edition.

Pharmacotherapy for Bipolar Disorder

Treatment for Depressive Episodes

Bipolar Depression – First-Line Treatments[1]

- Initiate mood stabilizer
- Antidepressant monotherapy generally not recommended
- For severely ill patients, initiation of combination therapy with mood stabilizer + antidepressant
- For patients with suicidal ideation, psychosis, or those experiencing severe depression during pregnancy, electroconvulsive therapy (ECT) is an alternative

- Add second line medications
- Add other antidepressants, includer older generation

Use of atypical antipsychotics have been studied as well with varying results (depending on drug)[2]

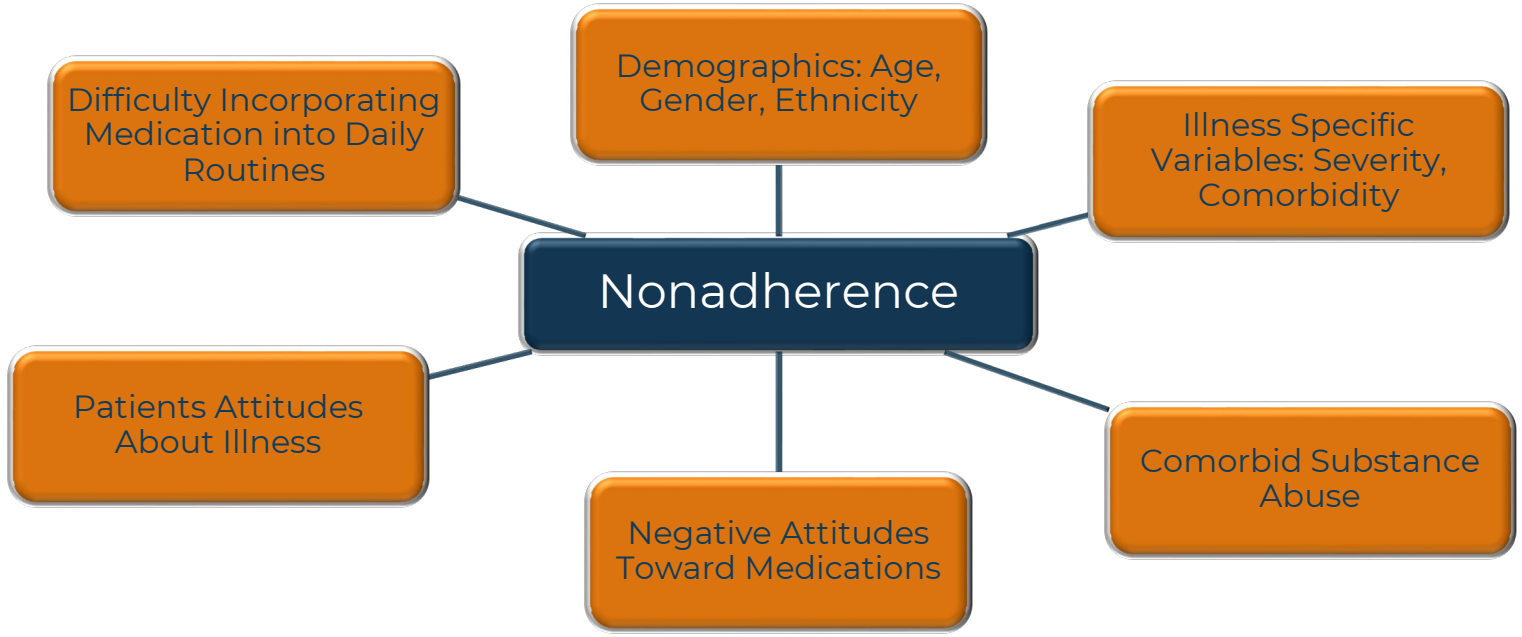
1. Hirschfeld RMA, et al. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Bipolar Disorder: Second Edition.
2. Geddes JR et al. *Lancet.* 2013; 381

Treatment Adherence in Bipolar Disorder

Nonadherence with Treatment is Common in Bipolar Disorder

- Twelve-month and lifetime treatment rates for BD I were estimated to be 46.0% and 72.4% in a sample representative of the US general population[1]
- Up to 40% of patients with mania are either partially or completely nonadherent with their prescribed medications[2]:

Factors Contributing to Medication Nonadherence[2]



BD, bipolar disorder; US, United States.

1. Blanco C et al. *Journal of Psychiatric Research.* 2017; 84:310-317.
2. Sajatovic et al. *Comprehensive Psychiatry.* 2009; 50:100-107.

Impact of Poor Adherence in Bipolar Disorder

Poor adherence can lead to negative consequences

- Effects of nonadherence include not only worsening of symptoms, but also decreased quality of life and potentially suicide in persons with BD[1]
  - Suicidal behaviors were 16 times higher after medication discontinuation in comparison to monotherapy with mood-stabilizers
- Nonadherence is also associated with increased use of health resources, including inpatient hospitalizations[2]
  - Nonadherent patients were found to have significantly higher healthcare costs, especially inpatient, than adherent patients[2]
  - As adherence (measured by MPR) increased, the risk of inpatient hospitalization decreased[3]

Risk of Mental Health Related Hospitalizations[3]

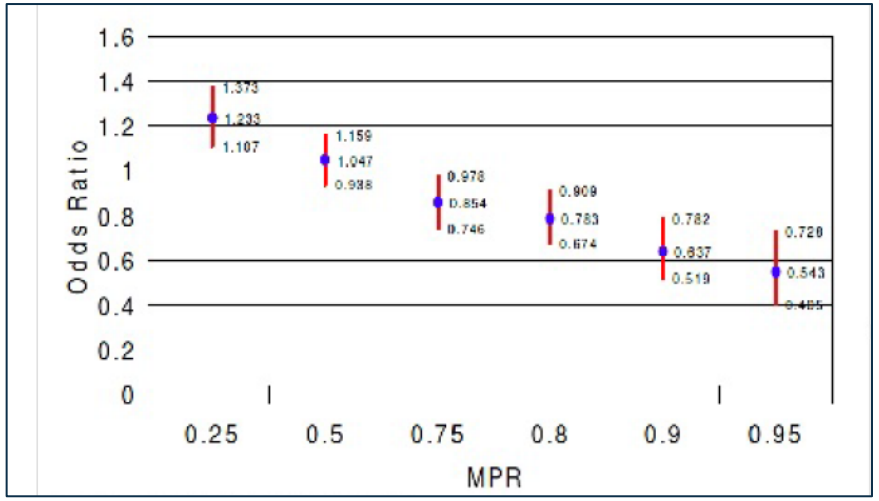


Diagram adapted from Lage and Hassan, 2009.

Increase in adherence (increasing MPR) was associated with decreased risk of hospitalization[3]

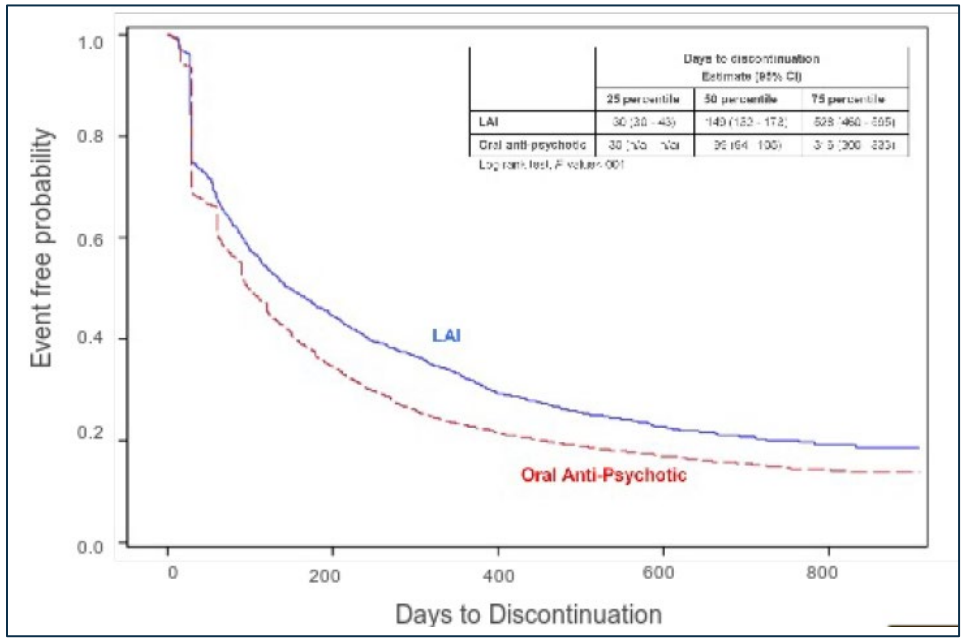
BD, bipolar disorder; MPR, medication possession ratio.

1. Sajatovic et al. *Comprehensive Psychiatry.* 2009; 50:100-107.
2. Hong J et al. *Psychiatry Research.* 2011;190(1):110-114.
3. Lage MJ et al. *Annals of General Psychiatry.* 2009.

A Role for Long-Acting Injectable Antipsychotics

LAIs may improve outcomes in certain patients

- LAIs have demonstrated improved outcomes compared to oral antipsychotics[1,2]
  - Significantly delayed time to recurrence of mood episodes was noted with LAI monotherapy versus placebo among patients with BD I[1]
  - Among patients with BD I who relapse frequently, time to relapse was significantly delayed[2]
- A study using Truven MarketScan data showed patients were likely to continue with LAIs longer in comparison to oral antipsychotics*[3]



*This study was funded by Otsuka Pharmaceutical Development & Commercialization, Inc.
BD, bipolar disorder; LAI, long-acting injectable antipsychotic.

1. Quiroz JA et al. *Biological Psychiatry.* 2010;68(2):156-162.
2. Macfadden W et al. *Bipolar Disorders.* 2009;11:827-839.
3. Yan T et al. "Treatment patterns, healthcare utilization, and costs among bipolar patients treated with oral and long-acting injectable antipsychotics: Analysis of Truven MarketScan commercial and Medicaid claims data." Poster presented at International Society for Pharmacoeconomic and Outcomes Research Annual Meeting, May 20-24, 2017, Boston, MA, USA. 2017.

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