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Strategies to Optimize Patient Outcomes in Bipolar-I Disorder

Role of Long-Acting Injectable Antipsychotics

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Bipolar-1 Disorder

Epidemiology & Unmet Need

Mood Episode Recurrence

Management of Bipolar-I Disorder

Pharmacokinetics

Bipolar Disorder (BD) Is Characterized by Episodes of Elevated and Depressed Mood

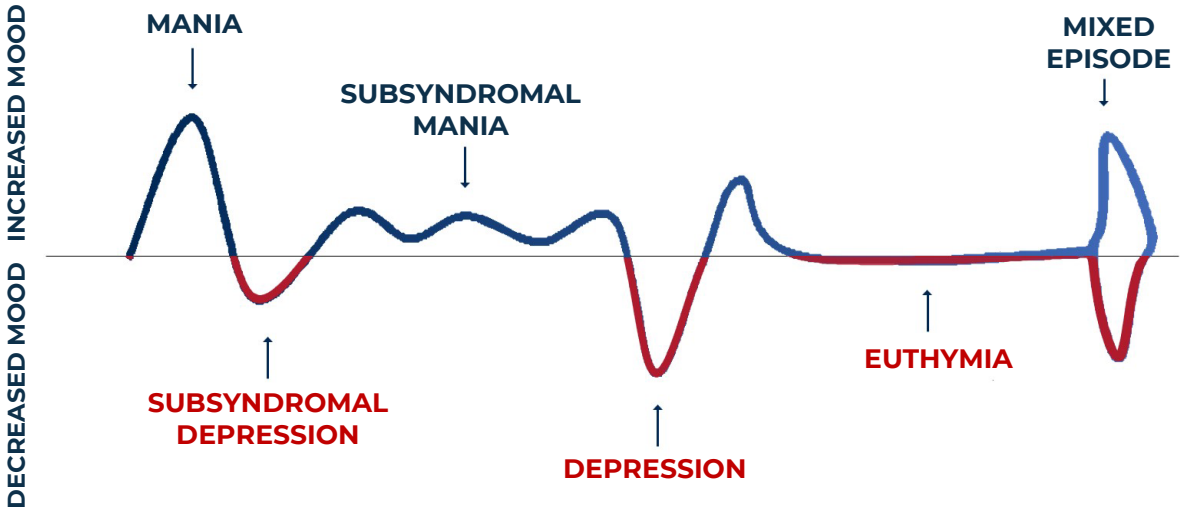
BD is a chronic, neuroprogressive and severe mental illness with **high rates of mood episode recurrence** even when periods of euthymia (stable mood) occur between mood episodes[1-3]

BP-I Disorder (BP-1)

- Must have ≥ 1 manic episode
- Hypomanic and depressive episodes are common but not required

BP-II Disorder (BP-II)[4]

- Must have ≥ 1 hypomanic episode
- Must have ≥ 1 major depressive episode



Many patients with BP-I experience recurrent mood episodes

The average prodrome preceding an initial mood episode lasts 27 months, providing ample time to intervene if symptoms are identified early[5]

50% of patients with BP-I experience a mood episode recurrence within the first year after recovery from the first manic episode[6]

Mood episode recurrence in BP-I impacts short-term and long-term clinical outcomes and cognitive functioning

BP, bipolar disorder; BP-I, bipolar I disorder; BP-II, bipolar II disorder.

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC; 2013. 2. Oswald P, et al. *Eur Neuropsychopharmacol*. 2017;17(11):687-695. 3. Lisy ME, etal. *Bipolar Disord*. 2011;13(4):396-405. 4. NIMH. *Bipolar Disorder*. https://www.nimh.nih.gov/health/topics/bipolar-disorder#part_2261 Accessed March 2, 2023. 5. Van Meter AR, et al. *J Am Acad Child Adolesc Psychiatry*. 2016;55(7):543-555. 6. Yatham LN, et al. *Can J Psychiatry*. 2009;54(2):105-112.

Epidemiology

BP-I in the US

- **1.5%** of patients have had a BP-I diagnosis within the past 12 months, and **2.1%** will have a BP-I diagnosis in their lifetime[1]
- The prevalence of BP may be underestimated due to **high rates** of **misdiagnosis**[2]
  - Misdiagnosis is common among patients with BP, most **commonly with depression**[3]
- **Delay** in the time from symptom onset to diagnosis can be up to **10 years**[3]
- Delay to 1st treatment (either depression or mania) was more than twice as long in the **US vs Europe**[4]
- Mean age of onset is 7 years earlier in the **US vs Europe**[4]

Screening tools

- The Rapid Mood Screener and Mood Disorder Questionnaire **can help identify BP-I and assess the severity of mood episodes**[5,6]

- Psychiatric and medical comorbidities are common in patients with BP[3,7]

BP, bipolar disorder; BP-I, bipolar I disorder.

1. Blanco C, et al. *J Psychiatr Res*. 2017;84:310-317. 2. Hirschfeld RM, et al. *J Am Board Fam Pract*. 2005;18:233-239. 3. Yatham LN, et al. *Can J Psychiatry*: 2009;54(2):105-112. 4. Post R, et al. *Psych Res*. 2020; https://doi.org/10.1016/j.psychres.2020.113274. 5. MyIntyre RS, et al. *Curr Med Res Opin*;.2021; 37(1):135-144. 6. Hirschfeld RM, et al. *Am J Psychiatry*. 2000;157:1873-1875. 7. Sylvia LG, et al. *Bipolar Disord*. 2014;17(2):212-223.

Epidemiology & Unmet Need

Burden of BP-I Disease is multifaceted

PATIENTS

SUICIDE RATES MAY BE

~10–16x

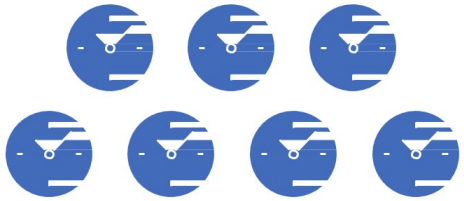
HIGHER IN PATIENTS WITH BP-I[1]

SUBSTANCE USE DISORDERS ARE COMMON IN PATIENTS WITH BP-I[2]

38.3%
SUBSTANCE ABUSE

33.1%
ALCOHOL ABUSE

CAREGIVERS



~7x

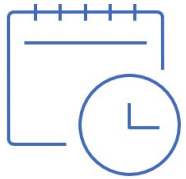
- MORE HOURS PER WEEK CAREGIVING FOR PATIENTS WITH BP-1
- LOSS IN PRODUCTIVITY COSTS[1]

SOCIETY

BD NEGATIVELY AFFECTS WORK PERFORMANCE DUE TO INCREASED ABSENTEEISM AND PRESENTEEISM[3]

65.5

ANNUAL WORKDAYS LOST PER WORKER WITH BP-1[4]



ECONOMIC COSTS

THE LARGEST CONTRIBUTERS TO EXCESS COSTS (~120 B*) FOR PATIENTS WITH BP-1 WERE[1]:

20%
UNEMPLOYMENT

36%
CAREGIVING

21%
DIRECT HEALTHCARE COSTS

BD, bipolar disorder; BP-I, bipolar I disorder.
*In 2015 US dollars.

1. Cloutier M, et al. *J Aff Disord*. 2018;226:45-51. 2. Post RM, et al. *Int J Bipolar Disord*. 2021;9(1):13. 3. Dominiak M, et al. *Front Psychiatry*. 2022;13:951008. 4. Yatham LN, et al. *Can J Psychiatry*. 2009;54(2):105-112.

Epidemiology & Unmet Need - Summary

1. BP is a chronic, progressive, and severe mental illness[1-3]
2. 50% of patients with BP-I experience a mood episode recurrence within the first year after recovery from the first manic episode[4]
3. BP has a significant impact on cognition and function[5]
4. Delay to 1st treatment is greater than twice as long and disease onset is earlier in the US vs Europe than was previously recognized[6]

Home

BP, bipolar disorder; BP-I, bipolar I disorder.

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington, DC; 2013. 2. Oswald P, et al. *Eur Neuropsychopharmacol*. 2017;17(11):687-695.
3. Lisy ME, et al. *Bipolar Disord*. 2011;13(4):396-405. 4. Yatham LN. et al. *Can J Psychiatry*: 2009;54(2):105-112. 5. Sanches M, et al. *Am J Ther*. 2015;22(6):477-486.6. Post R, et al *Psych Res* 2020; 292: https://doi.org/10.1016/j.psychres.2020.113274.

Mood Episode Recurrence

Treatment adherence is the degree to which a patient's behavior matches agreed-upon recommendations from a prescribing clinician[1,2]

Expert consensus has defined **medication nonadherence** as missing 20% or more of prescribed medication[2]

1. Jawad I, et al. *Ther Adv Psychopharmacol*. 2018;8(12):349-363. 2. Lam WY and Fresco P. *Biomed Res Int*. 2015;2015:217047.

Nonadherence Is a Major Factor Implicating Clinical Outcomes in BD

PATIENTS WITH BD HAVE HIGHER RATES OF MEDICATION NONADHERENCE

Up to 79%

Nonadherent with maintenance medication[1a]

~40%

Nonadherent during euthymic periods[2]

Nonadherence is particularly common during mania in the month before hospitalization[3]

NONADHERENCE IS ASSOCIATED WITH:

- Mood episode recurrence[4]
- Decreased likelihood of remission and recovery[4,5]
- Subsyndromal symptoms[6]
- Accelerated mood episode cycling[7]
- Mood symptoms severity[6]
- Suicidality[4,5]

NONADHERENCE IS ASSOCIATED WITH INCREASED RISK OF AND LONGER DURATION OF PSYCHIATRIC HOSPITALIZATION[4,5,8,9]

BD, bipolar disorder.

[a]In a retrospective claims-based study, ~79% of patients with bipolar disorder took antipsychotic medications less than 75% of the time.

1. Lage MJ and Hassan MK,. *Annals Gen Psych*, 2009;8:7 doi: 10.1186/1744-859X-8-7. 2. Colom F, et al. *J Clin Psychiatry.* 2000;61(8):549-555. 3. Vieta E, et al. *World J Biol Psychiatry.* 2008;9(3):219-224. 4. Levin JB, et al. *CNS Drugs.* 2016;30(9):819-835. 5. Hong J, et al. *Psychiatry Res.* 2011;190(1):110-114. 6. Montes J, et al. *Patient Prefer Adherence.* 2013;7:89-94. 7. Perlis RH, et al. *J Clin Psychiatry.* 2010;71(3):296-303. 8. Lage MJ, et al. *Ann Gen Psychiatry.* 2009;8:7. 9. Jiang Y, et al. *Pharmacotherapy.* 2015;35(9):813-822.

Adherence is a Major Determinant of Prognosis in BD

- Suicide attempts, completed suicide, & early mortality[1-3]
- Increases risks for unstable housing status[4]
- Higher risk of arrest & mean number of days of incarceration[5]
- Higher system-level & total mental health care costs[6]

BD, bipolar disorder.

1. Hong J,. et al. *Psych Rese*, 2011;190(1):110-114. 2. Baldessarini L., et al. *J Clin Psych*. 2003;64(5):44-52. 3. Muller-Oerlinghausen B, et al. *Acta Psychiatr Scand*. 1996;94(5):344-347. 4. Copeland LA, et al. *Am J Public Heal*th. 2009;99(5):871-877. 5. Robertson AG, *Psychiatric Services*. 2014; 65(10):1189-1191. 6. Svarstad, BL, *Psychiatric Services*, 2001;52(6):805-811.

Methods for Measuring Medication Adherence

Subjective

- Patient self-report, provider or caregiver report, and chart review[1]
- Self-report scales to measure medication nonadherence:
  - Medication Adherence Report[2]
  - Brief Adherence Ratings Scale[3]
  - Tablets routine questionnaire[4]

Objective[1]

- Pill count
- Serum drug levels
- Pharmacy refill records
- Microchip placement on tablets that indicate when medication is taken
- Computerized pill caps that record openings
- Electronic monitoring packs

Patient self-report (86.3% vs. 61.6% based on blood levels),[5] clinician prediction (50%-60% accuracies),[4,6] and objective methods all have potential inaccuracies; therefore, use of more than 1 assessment method is recommended[7]

1. Levin JB, et al. *CNS Drugs*, 2016; 30: 819-835. 2. Thompson K., et al. *Schizophrenia Research*. 2000;42(3):241-247. 3. Byerly MJ, et al. *Schizophrenia Research*. 2008;100(1-3):60-69. 4. Scott J, et al. *Am J Psychiatry*. 2002;159(11):1927-1929. 5. Jonsdottir H, et al. *J Clin Psychopharm*.2010;30(2):169-175. 6. Byerly M., et al. *Psychiatry Research*. 2005;133(2-3):129-133. 7. Velligan DI, et al. *J Clin Psych*. 2009;70(suppl 4):1-46.

Understanding Adherence Barriers in BD

Patient-Level Barriers

Sociodemographic

- Age
- Marital status
- Race/ethnicity
- Social support

Clinical & Illness Characteristics

- BD type, episode & symptom characteristics/severity
- Comorbidities
- Suicidality

Psychological

- Treatment, medication, & illness beliefs
- Personal & influential beliefs of others

External Barriers

Treatment related

- Side effects
- Treatment complexity
- Class of medication
- Quality of clinician-patient relationship

Systems related

- Access to care
- Medication cost

BD, bipolar disorder.

1Levin JB, et al. *CNS Drugs.* 2016;30:819-835.

Health Equity in BD

Sociodemographic

- In the US, bipolar disorder is more often diagnosed in White individuals than in those of Black/African American, Latino, or Asian race/ethnicity[1,2]
  - Compared with White individuals with bipolar disorder, those of African American ancestry have higher rates of trauma and substance use[3,4]
  - In Black/African American people, the underdiagnosis of bipolar disorder may be due to an unconscious clinician bias that contributes to an overdiagnosis of schizophrenia in this group[2]

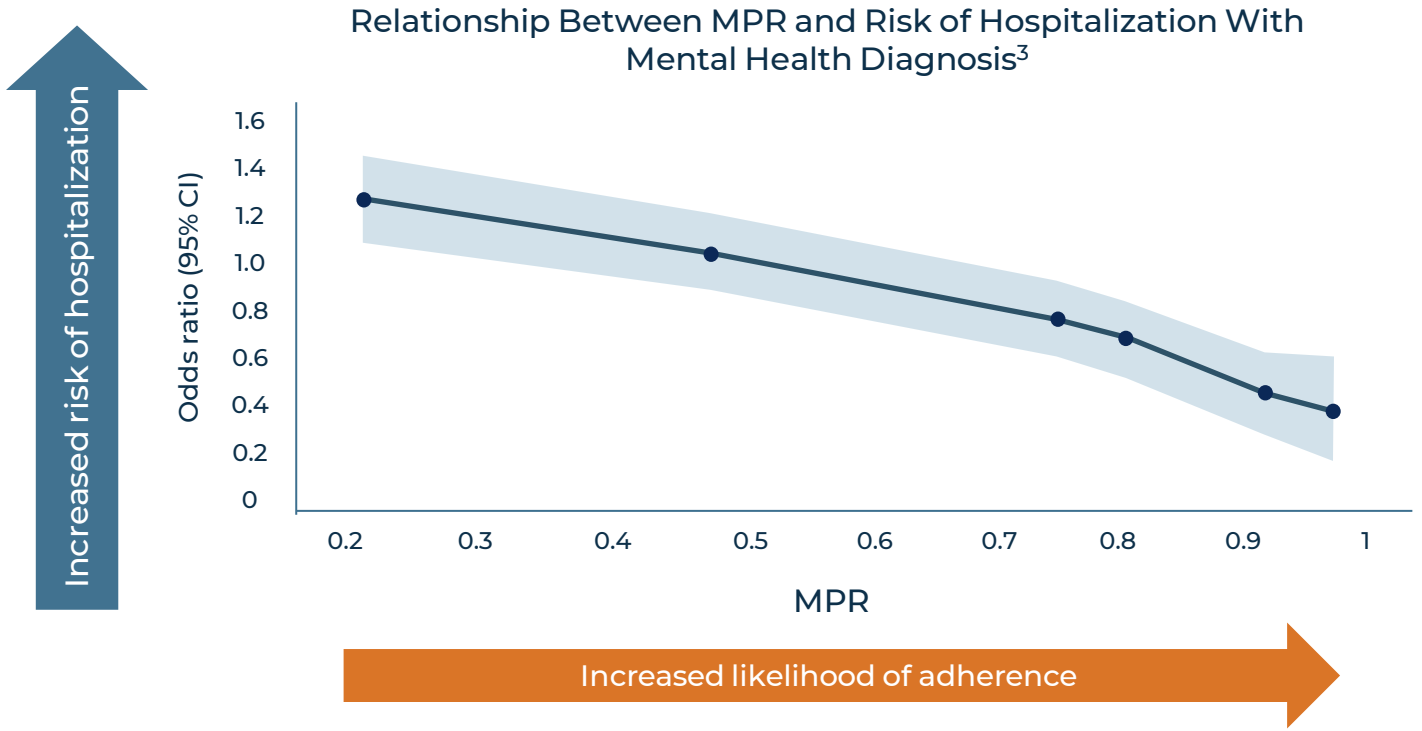
Clinical & Illness Characteristics

- People with bipolar disorder are more likely to complete suicide attempts compared with the general population[5,6]
  - 1 in 3 attempts are successful in those with bipolar disorder, compared with 1 in 20 to 40 in the general population[7]
  - A history of suicide attempts in people with bipolar disorder is more common in females versus males

BD, bipolar disorder.

1. Minsky S, et al., *Arch Gen Psychiatry.* 2003;60(6):637-644. 2. Barnes A. *Soc Work.* 2008;53(1):77-83. 3. Kilbourne AM, et al., *Bipolar Disord.* 2005;7(1):89-97. 4. Taylor-Desir et al., *J Racial Ethn Health Disparities.* 2023;10(1):367-372. 5. Kawa et al., *Bipolar Disord.* 2005;(7)2:119-125. 6. Baldassano, *J Clin Psychiatry.* 2006;67(Suppl 11):8-11.. 7. Miller S, et al. *J Affect Disord.* 2014;169:S3–S11

Nonadherence Is Associated With Increased Risk of Psychiatric Hospitilization[1-4]



NONADHERENCE IS ALSO ASSOCIATED WITH LONGER DURATION OF HOSPITALIZATION INCLUDING OTHER NEGATIVE CONSEQUENCES AND GREATER HEALTH CARE COSTS[1,2]

MPR, medication possession ratio.

1. Hong J, et al. *Psychiatry Res*. 2011;190(1):110-114. 2. Levin JB, et al. *CNS Drugs*. 2016;30(9):819-835. 3. Lage MJ, et al. *Ann Gen Psychiatry*. 2009;8:7. 4. Jiang Y, et al. *Pharmacotherapy*. 2015;35(9):813-822.

Impact & Risk Factors Associated with Mood Episode Recurrence in BP-I

>90%
of patients who have a single manic episode will have future episodes[1,2]

~15%
of patients will have more than 10 episodes in their lifetime[2]

>30%
of patients meet the criteria for rapid cycling[3]

Psychosocial outcomes[4,*]
- Occupational status
- History of ≥1 previous episode
- Residential status
- History of alcoholism
- Psychotic features during index episode
- Male sex

1

Syndromal recovery[5]
- Shorter hospitalization for index episode
- Female sex
- Age
- Lower baseline depression ratings
- Marital status

2

Functional recovery[5]
- Increasing age
- Race
- Shorter hospitalization for index episode
- Marital status

3

Time to relapse[4]
- History of alcoholism
- Psychotic features during index episode
- Occupational status
- Depressive symptoms during index episode

4

Mania recurrence[5]
- Initial mood-congruent psychosis
- Lower premorbid occupational status
- Initial manic presentation

5

Depression onset[5]
- Occupational status
- Initial mixed presentation
- Comorbidities

6

Nonadherence[6]
- Attitudes/beliefs
- Medication type
- Comorbidities
- Access to care

7

***Psychosocial outcomes include occupational and residential status.**

BP-I, bipolar I disorder.

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington, DC; 2013. 2. Müller-Oerlinghausen B, et al. *Lancet*. 2002;359:241-247. 3. Lee S, et al. *Br J Psychiatry*. 2010;196:217-225. 4. Tohen M, et al. *Arch Gen Psychiatry*. 1990;47(12):1106-1111. 5. Tohen M, et al. *Am J Psychiatry*. 2003;160(12):2099-2107. 6. Levin JB, et al. *CNS Drugs*. 2016;30(9):819-835.

Subsyndromal Symptoms Can Predict Mood Recurrence & Decreased Adherence

SUBSYNDROMAL SYMPTOMS ARE COMMON

>50%

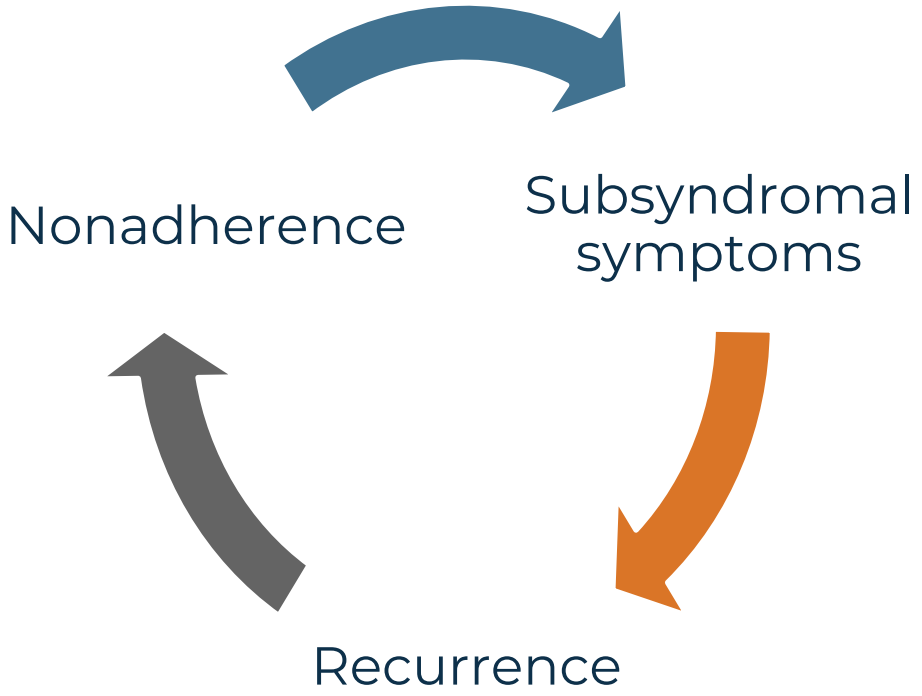
of patients with BP-I may have residual symptoms after a mood episode[1]

~3-fold

Increased risk for recurrence[2]

~40%

of patients with suboptimal adherence can have subsyndromal symptoms[2]



RESIDUAL MANIC SYMPTOMS ARE ASSOCIATED WITH GREATER RISK OF MANIC OR MIXED MOOD EPISODE RECURRENCE[3]

Medication adherence is reportedly the strongest independent predictor of 1- and 2-year mood episode recurrence rates[4]

BP-I, bipolar I disorder.

1. Marangell LB, et al. *J Clin Psychiatry.* 2004;65(suppl 10):24-27. 2. Judd LL, et al. *Arch Gen Psychiatry.* 2008;65(4):386-394. 3. Perlis RH, et al. *Am J Psychiatry.* 2006;163(2):217-224.. 4. Levin JB, et al. *CNS Drugs.* 2016;30(9):819-835.

Mood Episode Recurrence - Summary

1. Subsyndromal symptoms contribute to mood episode recurrence and nonadherence[1-3]
2. Non-adherence is a major factor implicating clinical outcomes, as well as nonclinical outcomes (eg, suicide, housing status, arrest, cost of care)[4-9]
3. Many factors contribute to adherence barriers, including sociodemographic, clinical characteristics, psychological, and treatment-/systems-related[4]

Home

1. Marangell LB, et al. *J Clin Psychiatry.* 2004;65(suppl 10):24-27. 2. Judd LL, et al. *Arch Gen Psychiatry.* 2008;65(4):386-394. 3. Perlis RH, et al. *Am J Psychiatry.* 2006;163(2):217-224. 4. Levin JB, et al. *CNS Drugs.* 2016;30(9):819-835. 5. Hong, J. et al. *Psychiatry Research*, 2011; 190(1): 110-114. 6. Baldessarini, L., et al. *Journal of Clinical Psychiatry*, 2003; 64(5): 44-52. 7. Copeland, L. A., et al. *American Journal of Public Health*, 2009; 99(5): 871-877. 8. Robertson, A. G., *Psychiatric Services*, 2014; 65(10): 1189-1191. 9. Svarstad, B. L., *Psychiatric Services*, 2001; 52(6): 805-811.

Treatment Guidelines for Management of BP-I

Clinical Guidelines Recommend Maintenance Treatment for BP-I and Include Mood Stabilizers, Anticonvulsants, Oral SGAs or SGA LAIs

GOALS FOR MANAGEMENT OF BP-I[1-3]

- Prevent relapse or mood recurrence
- Reduce cycling frequency and mood instability
- Improve long-term outcomes and quality of life
- Reduce subthreshold symptoms
- Reduce suicidal ideation and suicide risk

AVAILABLE MEDICATIONS & FORMULATIONS FOR TREATMENT OF BP-I[4]

- Mood stabilizers
- Second-generation antipsychotics (SGAs)
- SGA long-acting injectables (LAIs)

2019-2020 Florida Best Practice Guidelines[5]

- Recommend SGAs as first-line monotherapies or as first-line treatments adjunctive to mood stabilizers
- Recommend SGA LAIs with “level 1A established efficacy”

2018 CANMAT and ISBD Guidelines[2]

- Recommend SGA LAIs as first- and second-line monotherapies
- Recommend certain combinations of SGAs and mood stabilizers as first- and second-line combination therapies
- Recommend SGA LAIs with “level 2 evidence”

2017 CINP Guidelines[6]

- Recommend SGA monotherapy as the first-line treatment choice
- SGA combination therapy with additional adjunctive agents recommended for second-line and beyond treatment
- Recommend SGA LAIs with “level 1 evidence”

BP-I, bipolar I disorder; CANMAT, Canadian Network for Mood and Anxiety Treatments; CINP, International College of Neuropsychopharmacology; ISBD, International Society for Bipolar Disorders; LAI, long-acting injectable.

1. American Psychiatric Association Working Group on Bipolar Disorder. 2nd ed. American Psychiatric Association; 2010. Accessed June 16, 2022. https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/bipolar.pdf 2. Yatham LN, et al. Bipolar Disord. 2018;20(2):97-170. 3. Ostacher MJ, et al. J Clin Psychiatry. 2016;77(7):920-926. 4. Levin JB, et al. CNS Drugs. 2016:30(9):819-835. 5. Florida Center for Behavioral Health Improvements and Solutions. 2019–2020 Florida Best Practice Psychotherapeutic Medication Guidelines for Adults. Published January 1, 2020. Accessed August 29, 2022. https://floridabhcenter.org/wp-contentuploads/2021/04/2019-Psychotherapeutic-Medication-Guidelines-for-Adults-with-References_06-04-20.pdf. 6. Tohen M, et al. Intl J Neuropsychopharmacol. 2017;20(2):180-195.

Challenges in Maintenance Treatment of BP-I

Maintenance treatment reduces frequency and severity of mood episodes and addresses subsyndromal symptoms[1,2]

Establishing an effective maintenance treatment plan requires a combination of effective patient-provider communication, patient education and appropriate medication selection using shared decision-making[3]

PATIENT CONSIDERATIONS

- Insight
- Understanding of treatment options
- Social support systems
- Access to care

MEDICATION CONSIDERATIONS

- Efficacy
- Tolerability
- Regimen complexity
- Cost

TREATMENT ADHERENCE

BP-I, bipolar 1 disorder.

1. Tohen M, et al. *J Clin Psychiatry.* 2020;81(4):OT19046AH1. 2. Gitlin M, et al. *Bipolar Disord*. 2012;14(suppl 2):51-65. 3. Prajapati AR, et al. *Psychol Med*. 2021;51(7):1082-1098.

LAIs Can Delay Mood Episode Recurrence and Improve Clinical Outcomes

Demonstrated efficacy and continued treatment

- LAIs have demonstrated efficacy in patients with BP-I previously treated with oral antipsychotics, including those with ≥4 mood episodes in the prior year[1,2]
- Patient may continue treatment with LAIs longer than with oral antipsychotics[3]
- LAIs lower inpatient, ED use, and non-medication costs[4]

Comparable safety profile with oral antipsychotics

- Meta-analysis data suggests that LAI AEs, including metabolic dysregulation and EPS, occur at similar rates as with oral antipsychotics[5]

Delayed mood episode recurrence

- LAIs have increased the time to mood episode recurrence in patients with BP-I with a history of frequent mood episode relapse[2]
- May help with intentional and unintentional barriers to adherence[6]
- Lower risk of relapse leading to psychiatric and all-cause hospitalization[7]

Improved pharmacokinetics

- LAIs ensure more consistent serum levels via bypassing first-pass metabolism[8,9]
- Consistent dose delivery[10,11]
- Provide a longer duration of pharmacological coverage[9,12]

AE, adverse event; BP-I, bipolar I disorder; EPS, extrapyramidal symptoms; LAI, long-acting injectable; SGA, second-generation antipsychotic.

1. Quiroz JA, et al. *Biol Psychiatry.* 2010;68(2):156-162. 2. Macfadden W, et al. *Bipolar Disord*. 2009;11(8):827-839. 3. Shah A, et al. *Adv Ther*. 2018;35(11):1994-2014. 4. 5. Misawa F, et al. *Schizophrenia Res*. 2016;176(2-3):220-230 . 6. Levin JB, et al. *CNS Drugs*. 2016;30(9):819-835. 7. Calabrese JR, et al. *J Clin Psychiatry*. 2017;78(3):324-331. 8. Kane JM, et al. *Eur Neuropsychopharmacol*. 1998;8(1):55-66. 9. Keramatian K, et al. *CNS Drugs*. 2019;33(5):431-456. 10. Tohen M, et al. *J Clin Psychiatry*. 2020;81(4):OT19046AH1. 11. El-Mallakh PL, et al. *Curr Drug Deliv*. 2013;10(6):706-712. 12. Greene M, et al. *J Med Econ*. 2018;21(2):127-134.

Advantages and Disadvantages in Oral and LAI Formulations

Oral: Advantages

- Effective[1]
- Many generics available[2]
- Extensive clinical experience[1]
- Flexibility[3]
- Short duration of action[3]

Oral: Disadvantages

- Daily administration[4]
- Potential for misuse[3]
- Influenced by first-pass metabolism[5]
- Adherence rates can be inaccurate[6]

LAI: Advantages

- Transparency of adherence[7]
- Ease of administration[8]
- Reduced peak-trough plasma levels[7]
- Improved patient outcomes[7]
- Improved patient and physician satisfaction[7]
- Lowered relapse rate[5,7]
- Decreased rehospitalizations[9]

LAI: Disadvantages

- Concerns regarding potential pain of injection[10]
- Slow dose titration and longer time to reach steady state[8]
- May prolong side effects[8]
- Difficult to adjust small doses[10]
- Potential for small amount to leak into subcutaneous tissue[8]
- Association with involuntary hospitalization and related trauma[11]
- Perception that treatment is punitive or forced by clinicians without consideration of patient feelings or rights[12]

BP-I, bipolar I disorder; LAI, long-acting injectable.

1. Citrome L., et al. *Expert Opin Pharmacother.* 2012;13(11):1545-1573. 2. Albright B. et al. https://www.psychcongress.com/article/three-key-antipsychotics-lose-patent-protection. Accessed June 28, 2022. 3. Burton N. 2nd ed. *Wiley-Blackwell*; 2010. 4. Bera RB, et al. *J Clin Psychiatry.* 2014;75(suppl 2):30-33. 5. Zhornitsky S, et al. *Schizophr Res Treatment.* 2012;2012:407171. 6. Velligan DI, et al. *Schizophr Res.* 2020;215:17-24. 7. Geerts P, et al. *BMC Psychiatry.* 2013;13:58. 8. Agid O, et al. *Expert Opin Pharmacother.* 2010;11(14):2301-2317. 9. Lafeuille MH, et al. *BMC Psychiatry.* 2013;13:221. 10. Jeong HG, et al. *Clin Psychopharmacol Neurosci.* 2013;11(1):1-6. 11. Iyer S, et al. *Can J Psychiatry.* 2013;58(5 suppl 1):14S-22S. 12. Brissos S, et al. *Ther Adv Psychopharmacol.* 2014;4(5):198-219.

Overcoming Barriers to Positive Behavioral Change

Barriers to or facilitators of positive behavioral change in patients with BD may be modified when identified and specifically addressed[1]

BARRIERS[1]

- Denial of illness
- Not understanding the need for maintenance treatment
- Forgetfulness/carelessness

- Absence of shared decision-making
- Family or friends discouraging/ stigmatizing medication adherence

FACILITATORS[1]

- Acceptance of illness
- Being well-informed about the disorder and its treatment
- Establishing a medication-taking routine

- Belief that healthcare provider has provided choices and options
- Regular contact with mental health team

BD, bipolar disorder; BP-I, bipolar I disorder.

1. Prajapati AR, et al. *Psychol Med*. 2021;51(7):1082-1098.

Initiating & Maintaining LAIs in Patients with BD

- Discuss risk/benefits with patient and family/care partners
- Obtain patient agreement
- Document discussion with patient
- Provide educational materials

- Previous response to specific antipsychotics, including side effects
- Out-of-pocket expense and formulary restrictions
- Clinician's expectation of good tolerability and efficacy for specific LAIs
- Availability of formulations with varying dosing intervals and injection sites

- Sufficient tolerability of oral version
- Follow PI directions for concomitant oral antipsychotic initiation
- Start with intended maintenance dose
- 2nd injection should be given accordingly to schedule in PI, unless symptoms increase before the end of dosing interval

- Should allow achievement of steady state or 1-2 cycles after steady state
- Measure treatment response based on psychotic, manic/hypomanic, and/or mixed symptoms and functional status
- If manic symptoms persist add or switch to a different mood stabilizer; no first-line consensus for depressive or psychotic symptoms

- Support continued through appointment reminders and LAI administration in the home by a mental health professional
- Address side effects
- Monitor metabolic parameters, EPS, liver function, prolactin and blood pressure

BD, bipolar disorder; BP-I, bipolar I disorder; EPS, extrapyramidal symptoms; LAI, long-acting injectable; PI, prescribing information.

Sajatovic, M, et al. *Neuropsychiatric Disease and Treatment*, 2018; 14: 1475-1492.

Management of BP-I - Summary

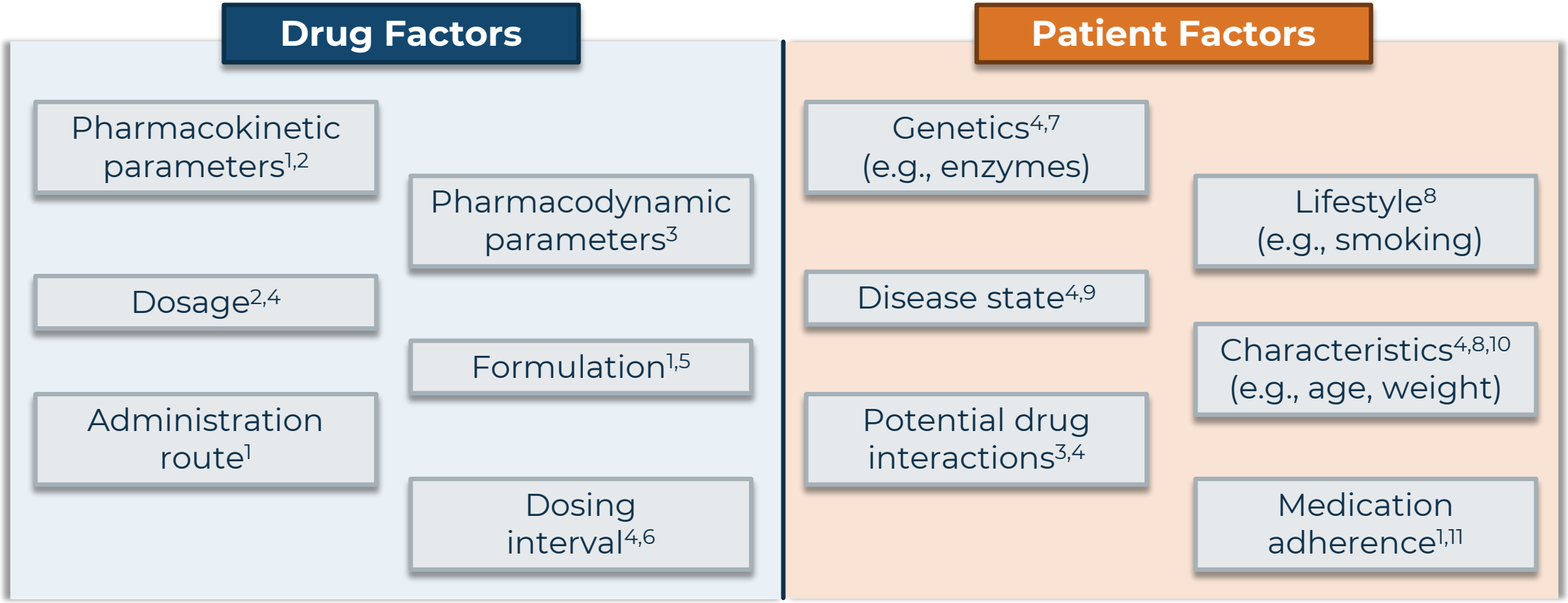
1. BD requires a collaborative/customized treatment approach[1-3]
2. To address medication adherence, both barriers and facilitators must be identified and targeted[1-3]
3. Alternative drug-delivery formats and technology facilitated approaches are showing promise in adherence promotion[4]
4. LAIs may optimize maintenance treatment by reducing mood episode recurrence, minimizing nonadherence, and improving quality of life[5-7]
5. The goal of treatment is to improve patient outcome and adherence[1-3]

Home

BP, bipolar disorder; LAI, long-acting injectable.

1. Yatham LN, et al. *Bipolar Disord*. 2018;20(2):97-170. 2. Ostacher MJ, et al. *J Clin Psychiatry*. 2016;77(7):920-926. 3. Prajapati AR, et al. *Psychol Med*. 2021;51(7):1082-1098. 4. Levin JB, et al. *CNS Drugs*. 2016:30(9):819-835. 5. Tohen M, et al. *J Clin Psychiatry*. 2020;81(4):OT19046AH1. 6. Macfadden W, et al. *Bipolar Disord*. 2009;11(8):827-839. 7. Quiroz JA, et al. *Biol Psychiatry*. 2010;68(2):156-162.

What Factors Determine Drug Effect?

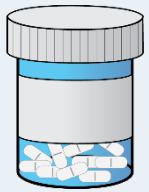


1. Correll CU, et al. *CNS Drugs*. 2021;35(1):39-59. 2. Currie GM. *J Nucl Med Technol*. 2018;46(3):221-230. 3. Currie GM. *J Nucl Med Technol*. 2018;46(2):81-86. 4. Alomar MJ. *Saudi Pharm J*. 2014;22(2):83-94. 5. Chow SC. *Wiley Interdiscip Rev Comput Stat*. 2014;6(4):304-312. 6. Alavijeh MS, et al. *NeuroRx*. 2005;2(4):554-571. 7. Roden DM, et al. *Lancet*. 2019;394(10197):521-532. 8. Niederberger E, et al. *Int J Mol Sci*. 2021;22(14):7692. 9. Staudinger JL. *Pharm Res*. 2013;30(9):2171-2173. 10. Mangoni AA, et al. *Br J Clin Pharmacol*. 2004;57(1):6-14. 11. Levin JB, et al. *CNS Drugs*. 2016;30(9):819-835.

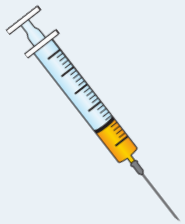
Drug Formulation Impact on PK

Administration

Different dosing interval and administration route[1,2]



Oral

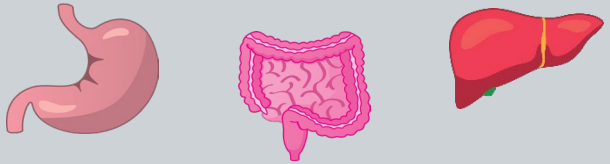


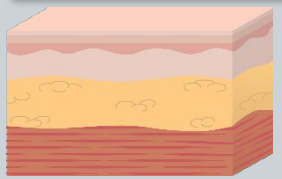
LAI

Absorption[2]

Rate and location affect time to maximal plasma concentration (t_{max})

Absorbed in GI tract
t_{max}: hours[3]





Subcutaneous
or
Intramuscular

Steady slow absorption[2]
t_{max}: days[3]

Metabolism[2]

Whether first-pass metabolism occurs affects bioavailability

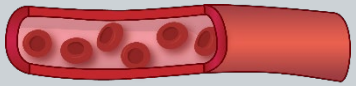
First-pass metabolism lowers bioavailability[2,4]

No first-pass metabolism[2,4]

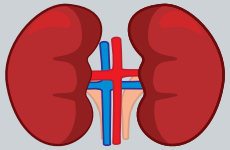
- Less interpatient variability in bioavailability[5]

Distribution and elimination

Once the drug is fully absorbed, these processes are relatively similar[2]



Complete elimination is extended due to slow absorption rate[2]



GI, gastrointestinal tract; LAI, long-acting injectable; PK, pharmacokinetics.

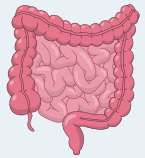
1. Hard ML, et al. *CNS Drugs*. 2017:31(7):617-624. 2. Correll CU, et al. *CNS Drugs*. 2021;35(1):39-59. 3. Sheehan JJ, et al. *Innov Clin Neurosci*. 2012;9(7-8):17-23. 4. Currie GM. *J Nucl Med Technol*. 2018;46(3):221-230.
5. Kane JM, et al. *J Clin Epidemiol*. 2013;66(8 Suppl):S37-S41.

Clinical Relevance of PK

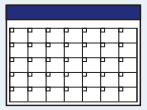
Desired drug effect is related to plasma concentration staying within therapeutic range[1]

Understanding PK of drug formulations

Absorption[2-4]
- Extended drug exposure
- Less frequent doses required



Metabolism[1,5]
- Lower bioavailability
- Higher dose may be required



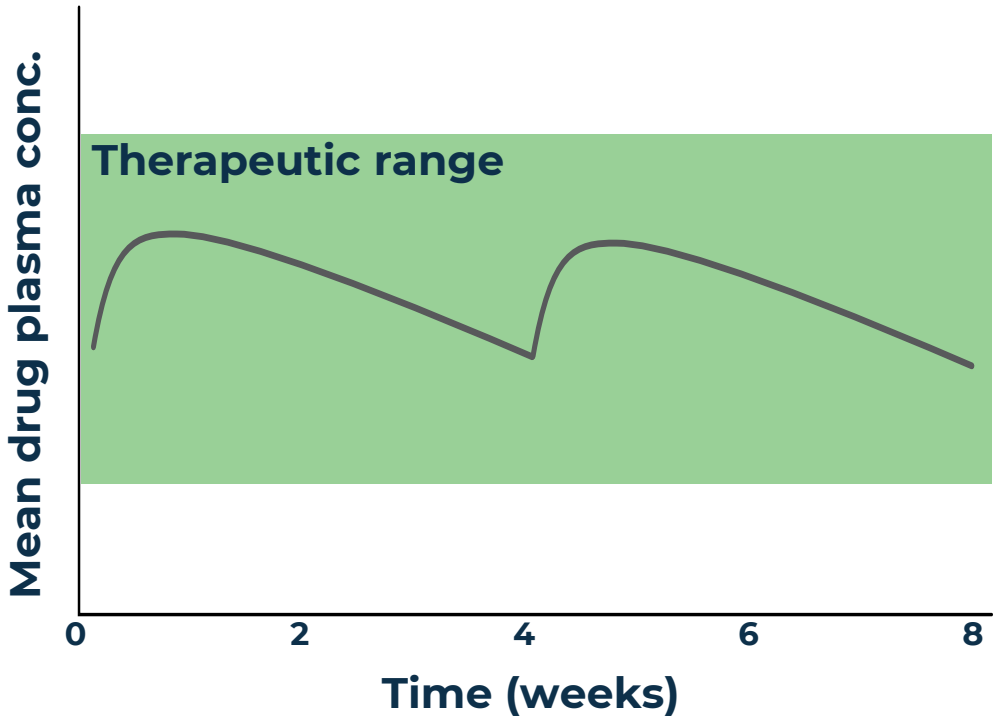
Half-life[4]
- Length of drug exposure
- Frequency of doses required

Understanding the variables (eg, age,[6] genetics[7]) that affect PK is important for adjusting treatment regimens

PK, pharmacokinetics.

1. Currie GM. *J Nucl Med Technol*. 2018;46(3):221-230. 2. Correll CU, et al. *CNS Drugs*. 2021;35(1):39-59. 3. Alavijeh MS, et al. *NeuroRx*. 2005;2(4):554-571. 4. Andrade C. *J Clin Psychiatry*. 2022;83(4):22f14584.
5. Price G, et al. *StatPearls*. Accessed September 12, 2022. https://www.ncbi.nlm.nih.gov/books/NBK557852/ 6. Mangoni AA, et al. *Br J Clin Pharmacol*. 2004;57(1):6-14. 7. Roden DM, et al. *Lancet*. 2019;394(10197):521-532.

Importance of Therapeutic Plasma Concentrations



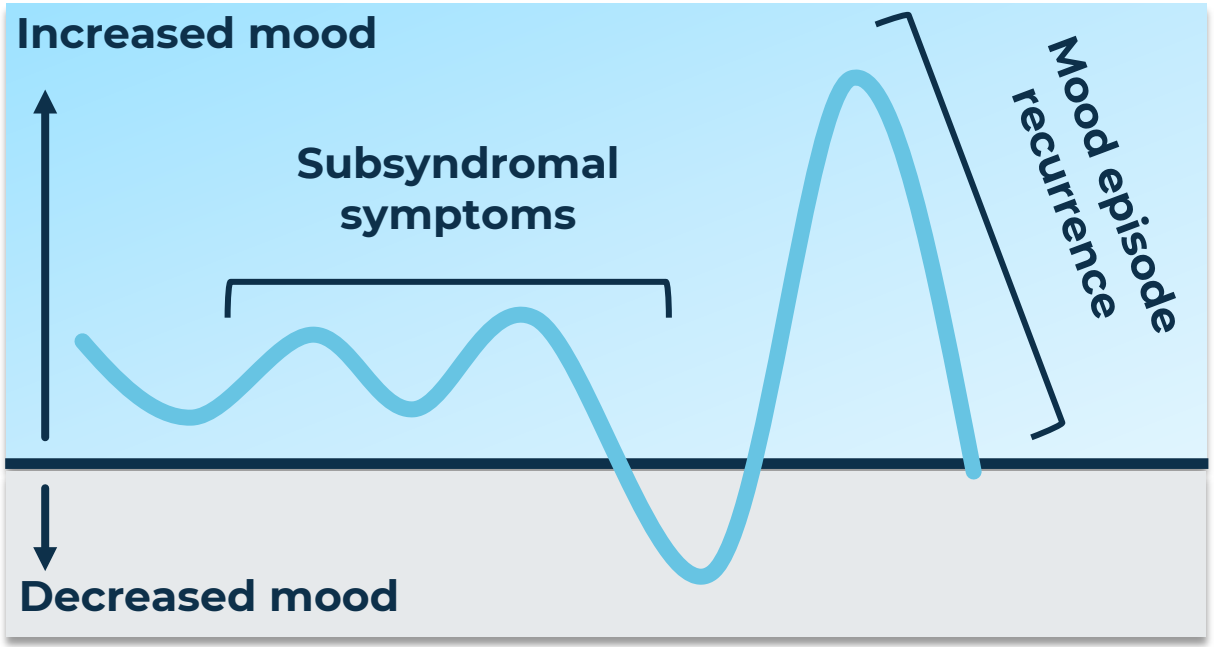
Efficacy[1,2]	Stabilized within established range for therapeutic effect
Safety[1,2]	Maintained within safe range to avoid adverse effects
Variability[3-6]	Individual characteristics can impact PK data (eg, age,[3] genetics,[4] drug-drug interactions[5]) • Possible dose adjustments[6]
Consistency[6,7]	Stabilized plasma concentration is important for maintaining efficacy (eg, symptom control)

PK, pharmacokinetics.

1. Currie GM. *J Nucl Med Technol*. 2018;46(3):221-230. 2. Cooney L, et al. *BMC Med Res Methodol*. 2017;17(1):84. 3. Mangoni AA, et al. *Br J Clin Pharmacol*. 2004;57(1):6-14. 4. Roden DM, et al. *Lancet*. 2019;394(10197):521-532.
5. Currie GM. *J Nucl Med Technol*. 2018;46(2):81-86. 6. Correll CU, et al. *CNS Drugs*. 2021;35(1):39-59. 7. Hughes DA. *Br J Clin Pharmacol*. 2008;65(6):871-878.

Example of Clinical Relevance: BD

BD is characterized by episodes of elevated and depressed mood[1]



Goals of treatment[2]

Mood stabilization

- Returns patient with mania or depression back to stable mood

Maintenance

- Aims to prevent relapse events
- Reduces subsyndromal symptoms
- Enhances social and occupational functioning

Important factors

- Efficacy is dependent on maintaining drug plasma concentration within therapeutic window[3,4,5]
  - Maintain stable plasma concentration[6]
- Continuous treatment[5-7]

BD, bipolar disorder.

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington, DC; 2013. 2. Geddes JR, et al. *Lancet*. 2013;381(9878):1672-1682. 3. Currie GM. *J Nucl Med Technol*. 2018;46(3):221-230. 4. Cooney L, et al. *BMC Med Res Methodol*. 2017;17(1):84. 5. Wakamatsu A, et al. *Innov Clin Neurosci*. 2013;10(3):23-30. 6. Correll CU, et al. *CNS Drugs*. 2021;35(1):39-59. 7. Chakrabarti S. *World J Psychiatry*. 2016;6(4):399-409.

Pharmacokinetic Effects in Nonadherent Patients With BD

Reasons for nonadherence

- Adverse side effects[1]
- Complex drug regimens[1]
- Financial cost[1]
- Attitude toward medication[1]
- Forgetting[1]
- Unclear instructions[1,2]
- Lack of illness understanding[2]

Consequences of nonadherence

- Increased risk of:
  - Relapse[1]
  - Mood episode recurrence[3]
    - Number of episodes is a moderator of brain changes and associated with neurocognitive decline[4]
  - Suicidality[3,5]
  - Subsyndromal symptoms[6]
  - Hospitalization[1]
- Decreased likelihood of recovery and remission[3,5]
- Treatment costs[1]

EFFECTS ON PHARMACOKINETICS

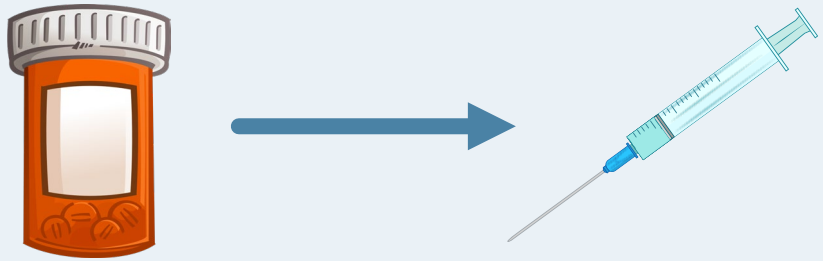
- **MISSED DOSES TYPICALLY PRODUCE REDUCED AND PROLONGED TROUGH (C_{MIN}) CONCENTRATIONS[7]**
- **POTENTIAL LOSS OF DRUG EFFECT[7]**

BD, bipolar disorder; C_{min}, minimum concentration.

1. Jawad I, et al. *Ther Adv Psychopharmacol*. 2018;8(12):349-363. 2. Hajda M, et al. *Neuropsychiatr Dis Treat*. 2016;12:1561-1570. 3. Levin JB, et al. *CNS Drugs*. 2016;30(9):819-835. 4. Kapczinski NS, et al. *Expert Rev Neurother*. 2017;17(3):277-285. 5. Hong J, et al. *Psychiatry Res*. 2011;190(1):110-114. 6. Montes JM, et al. *Patient Prefer Adherence*. 2013;7:89-94. 7. Hughes DA. *Br J Clin Pharmacol*. 2008;65(6):871-878.

LAIs May Offer a Solution to Nonadherence: Improved PK

LAIs were developed to overcome nonadherence with oral antipsychotics[1]



Improved pharmacokinetics

- LAIs ensure more consistent plasma levels via bypassing first-pass metabolism[2,3]
- Consistent dose delivery[1,4]
- Provide longer duration of pharmacological coverage[3,5]
- Missed dose does not decrease plasma concentration as rapidly as oral medications[6]

Clinical impact

- Delay time to mood episode recurrence in patients with BP-I[7]
- May help with intentional and unintentional barriers to adherence[8]
- More time to intervene after missed dose[6]

BP-I, bipolar I disorder; LAI, long-acting injectable; PK, pharmacokinetics.

1. Tohen M, et al. *J Clin Psychiatry*. 2020;81(4):OT19046AH1. 2. Kane JM, et al. *Eur Neuropsychopharmacol*. 1998;8(1):55-66. 3. Keramatian K, et al. *CNS Drugs*. 2019;33(5):431-456. 4. El-Mallakh PL, et al. *Curr Drug Deliv*.2013;10(6):706-712. 5. Correll CU, et al. *CNS Drugs*. 2021;35(1):39-59. 6. Kane JM, et al. *J Clin Epidemiol*. 2013;66(8 Suppl):S37-S41. 7. Macfadden W, et al. *Bipolar Disord*. 2009;11(8):827-839. 8. Levin JB, et al. *CNS Drugs*. 2016;30(9):819-835.

Pharmacokinetics - Summary

1. There are various drug and patient factors that determine drug effect for BD patients, including dosing and administration route (oral vs LAI)[1]
2. LAIs offer sustained plasma concentration over time because they are absorbed steadily and slowly with a longer half-life and low peak-to-trough ratio[1-3]
3. The sustained plasma concentration of LAIs allows for consistent dose delivery and longer duration of pharmacological coverage[1,4-6]
4. Efficacy of BD treatment is dependent on maintaining stable plasma concentration within the therapeutic window[1, 7-9]
5. LAIs may offer a solution to nonadherence in BD by providing improved PK[4]

BD, bipolar disorder; LAI, long-acting injectable; PK, pharmacokinetics.

1. Correll CU, et al. *CNS Drugs*. 2021;35(1):39-59. 2. Sheehan JJ, et al. *Innov Clin Neurosci*. 2012;9(7-8):17-23. 3. Andrade C. *J Clin Psychiatry*. 2022;83(4):22f14584. 4. Tohen M, et al. *J Clin Psychiatry*. 2020;81(4):OT19046AH1. 5. El-Mallakh PL, et al. *Curr Drug Deliv*. 2013;10(6):706-712. 6. Keramatian K, et al. *CNS Drugs*. 2019;33(5):431-456. 7. Currie GM. *J Nucl Med Technol*. 2018;46(3):221-230. 8. Cooney L, et al. *BMC Med Res Methodol*. 2017;17(1):84. 9. Wakamatsu A, et al. *Innov Clin Neurosci*. 2013;10(3):23-30.

Summary

BP-I is a neuroprogressive disease with frequent symptom relapse that has a significant impact on cognition and function[1-3]

Adherence is a major determinant of prognosis in BP-I[4]

Subsyndromal symptoms are common in BP-I and contribute to mood episode recurrence and nonadherence[5]

BP-I requires a collaborative/ customized treatment approach with a goal of improving patient outcomes and adherence[6-8]

LAIs may offer a solution to nonadherence in BP-I by providing improved PK[9]

Home

BP-I, bipolar I disorder; LAI, long-acting injectable; PK, pharmacokinetics.

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington, DC; 2013. 2. Oswald P. et al. *Eur Neuropsychopharmacol*. 2017;17(11):687-695.
3. 3. Lisy ME. etal. *Bipolar Disord*. 2011;13(4):396-405. 4. Levin JB, et al. *CNS Drugs*. 2016;30(9):819-835. 5. Marangell LB, et al. *J Clin Psychiatry*. 2004;65(suppl 10):24-27. 6. Yatham LN, et al. *Bipolar Disord*. 2018;20(2):97-170.
7. Ostacher MJ, et al. *J Clin Psychiatry*. 2016;77(7):920-926. 8. Prajapati AR, et al. *Psychol Med*. 2021;51(7):1082-1098. 9. Tohen M, et al. *J Clin Psychiatry*. 2020;81(4):OT19046AH1.