PsychU®
Improving mental health care... together®

Impact of Adherence on Individuals with Bipolar I Disorder

March 2022 US.PSY.D.22.00003

Objectives

- Examine barriers and facilitators of medication adherence in individuals with Bipolar I Disorder
- Review approaches for improving medication adherence in Bipolar I Disorder
- Discuss the potential role of long-acting injectables in Bipolar I Disorder

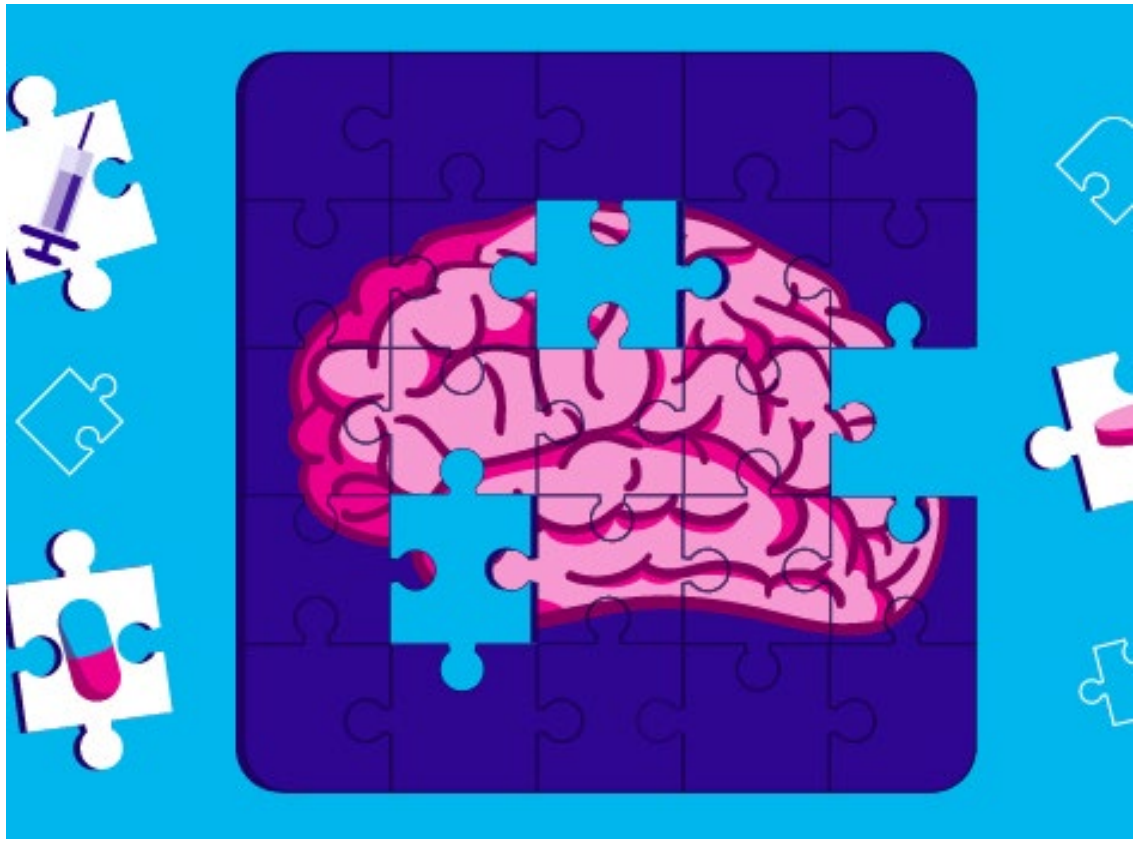
PsychU®
Improving mental health care... together®

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

Expert consensus has defined medication non-adherence as missing 20% or more of prescribed medication[2]

1. Sabate, E., Adherence to long term therapies: evidence for action. Geneva: World Health Organization: 2003..
2. Velligan, D. I., et al. *The Journal of Clinical Psychiatry*, 2009; 70(4): 455.

Medication Non-adherence is Common in Bipolar Disorder



- Estimates of medication non-adherence for BD is approximately 20-60%[1]
  - A prospective cross-sectional study of 140 patients with BD I in a community health center found that 19.3% of patients were non-adherent with medication[2]
  - In a 1-year retrospective cohort analysis of 9,410 Medicaid patients with BD I, an estimated 60% were non-adherent[3]
- 30-40% of people with BD who intend to take their medication are only partially adherent[4]
- Rates of mild or poor adherence are estimated to be ~40% during euthymic periods[5]

BD, Bipolar Disorder.

1. Levin, J. B., et al. *CNS Drugs*, 2016; 30: 819-835.
2. Sajatovic, M., et al. *Compr Psychiatry*, 2009; 50(2): 100-107.
3. Lang, K., et al. *Journal of Medical Economics*, 2011; 14(2): 217-226.
4. El-Mallakh, R. S. *Journal of Psychiatric Practice*, 2007; 13: 79-85.
5. Colom, F., et al. *Journal of Clinical Psychiatry*, 2000; 61(8): 549-555.

Methods for Measuring Medication Adherence

Subjective

- Patient self-report, provider or caregiver report and chart review[1]
- Self-report scales to measure medication non-adherence:
  - 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 one assessment method is recommended[7]

1. Levin, J. B., et al. *CNS Drugs*, 2016; 30: 819-835.
2. Thompson, K., et al. *Schizophrenia Research*, 2000; 42(3): 241-247.
3. Byerly, M. J., et al. *Schizophrenia Research*, 2008; 100(1-3): 60-69.
4. Scott, J., et al. *American Journal of Psychiatry*, 2002; 159(11): 1927-1929.
5. Jonsdottir, H., et al. *Journal of Clinical Psychopharmacology*, 2010; 30(2): 169-175.
6. Byerly, M., et al. *Psychiatry Research*, 2005; 133(2-3): 129-133.
7. Velligan, D. I., et al. *Journal of Clinical Psychiatry*, 2009; 70 (suppl 4): 1-46.

Understanding Adherence Barriers in Bipolar Disorder

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

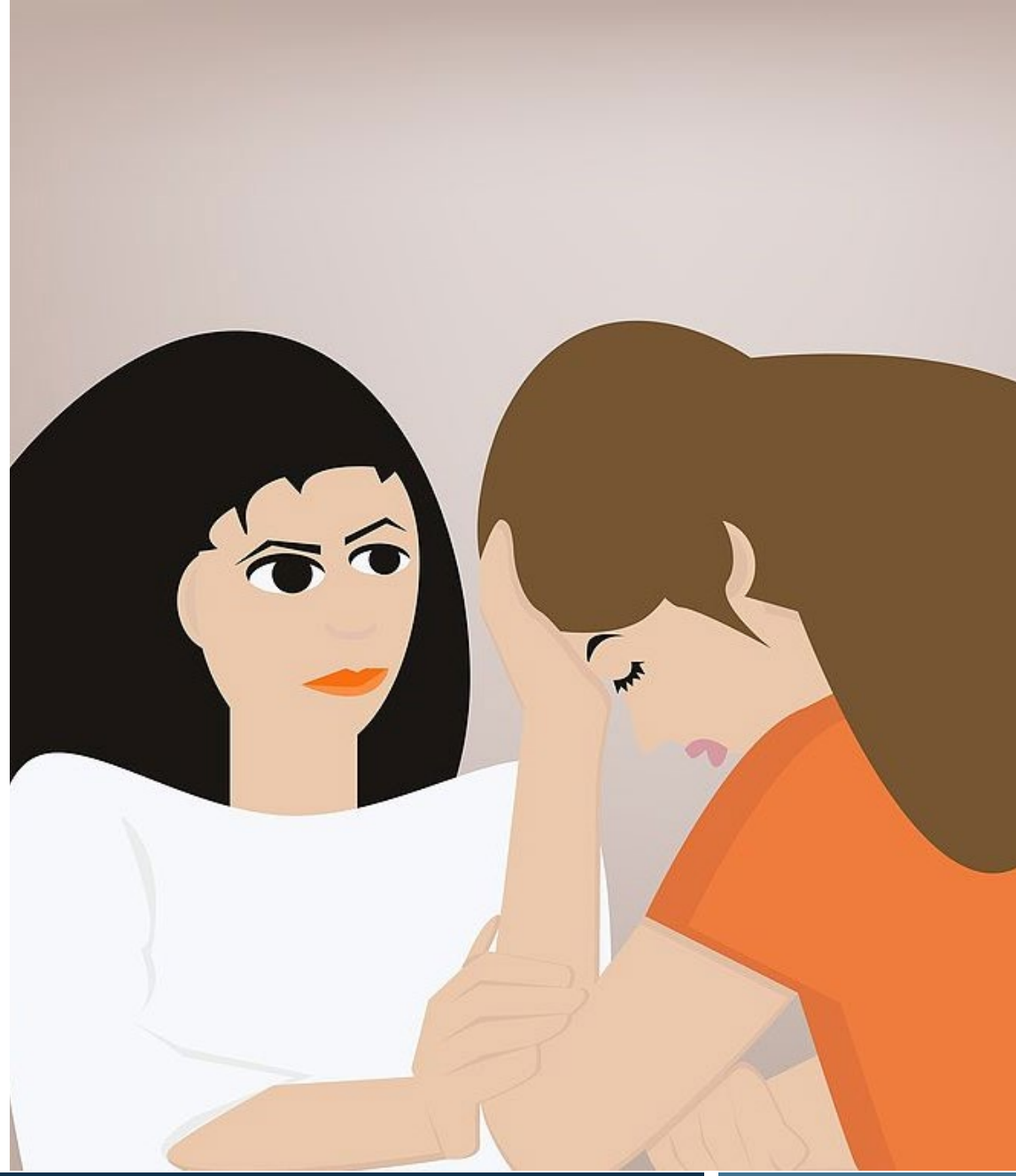
- Access to care
- Medication cost

BD, Bipolar Disorder.

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

Facilitators of Medication Adherence in Bipolar Disorder

- **Treatment alliance and strong social support**
  - Perceived collaboration with, empathy from, and accessibility to providers
  - Strong therapeutic alliance helps change illness and medication attitudes
- **Accepting attitude regarding medication treatment**
  - High levels of treatment necessity beliefs
  - Low levels of concerns regarding treatment
- **Patient medication preferences**
  - Psychiatric advance directives
  - Reassess potential barriers throughout the course of treatment



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

Adherence is a Major Determinant of Prognosis in Bipolar Disorder

Lower frequency of remission & recovery[1]

Increase in BD symptoms & higher frequency of recurrence, relapse, & hospitalization[1]

Suicide attempts, completed suicide, & early mortality[1,2,3]

Increases risks for unstable housing status[4]

Higher risk of arrest & mean number of days of incarceration[5]

Higher system-level & total mental healthcare costs[6]

BD, Bipolar Disorder

1. Hong, J. et al. *Psychiatry Research*, 2011; 190(1): 110-114.
2. Baldessarini, L., et al. *Journal of Clinical Psychiatry*, 2003; 64(5): 44-52.
3. Muller-Oerlinghausen, B., et al. *Acta Psychiatr Scand*., 1996; 94(5): 344-347.
4. Copeland, L. A., et al. *American Journal of Public Heal*th, 2009; 99(5): 871-877.
5. Robertson, A. G., *Psychiatric Services*, 2014; 65(10): 1189-1191.
6. Svarstad, B. L., *Psychiatric Services*, 2001; 52(6): 805-811.

Discontinuing Psychotropic Drug Treatment

- Stopping treatment ≠ Being untreated
- Interruption of ongoing treatment with antipsychotics and mood stabilizers can be followed by:
  - Clinically significant withdrawal reactions within hours or days
  - Increases in relapses or recurrences
- Abrupt/rapid discontinuation is followed by earlier clinical worsening than gradual discontinuation

1. Tondo, L. & Baldessarini, R. J. *BJ Psych Open*, 2020; 6(2): e24.

Approaches to Improve Medication Adherence in BD

- Should consider an individual's needs, knowledge, beliefs, and attitudes[1]
- No single intervention stands out as having sufficient efficacy to recommend it above others[2]
- Reminders may improve the timing of doses[2]
- Effects appear to be durable[1]

Psychoeducation

Motivational Interviewing

Financial Incentives

Cognitive behavioral treatment

BD, Bipolar Disorder

1. MacDonald, L. et al. *Journal of Affective Disorders*, 2016; 194: 202-221.
2. Levin, J. B., et al. *CNS Drugs*, 2016; 30: 819-835.

Making Medications Easier to Remember to Take

Novel drug-delivery systems used in general medicine

- Strategies to simplify dosing (e.g., less frequent administration)[1]
- Blister packaging of medications that include electronic monitoring systems[2]
- Personal programmable pill boxes[3]
- Ingestible digital sensor[4]

Technology-facilitated multi-component adherence-enhancement system[5]

- System components:
  - Automated pill cap with remote monitoring sensor
  - Multimedia adherence-enhancement program
  - Treatment incentive program

Ecological momentary intervention delivered via personal digital assistants[6]

- Two-daily prompts asking patients to report adherence behaviors as well as symptoms

1. van Dulmen, S., et al. *BMC Health Service Research*, 2008; 8: 47.
2. van Onzenoort, H. A., *American Journal of Health System Pharmacy*, 2012; 69(10): 872-879.
3. Berkowitz, A. C., *J Neurosci Nurs*. 2009; 41(2): 115-120.
4. Wong, S., et al. *Med Technol*. 2016; 85(1): 38-40.
5. Sajatovic, M., et al. *Patient Prefer Adherence*. 2015; 9: 753-758.
6. Wenze, S. J., et al. *Behav Modif*. 2014; 38(4): 497-515.

Novel Drug-Delivery Formats[1]

- Long-Acting Injectables
- Oral chewable formulations (e.g., gummies)
- Liquid formulations
- Orally disintegrated tables
- Fast-dissolving sublingual formulations

Expert consensus recommended LAI antipsychotics as first-line[2]

- **For BD pts with assumed treatment adherence:**
  - Patient prefers LAI
  - History of suboptimal adherence to medications
  - Has done well on LAI in the past
  - Frequently misses clinic appointments
- **For BD pts with questionable treatment adherence:**
  - Has failed to respond to lithium or anticonvulsant mood-stabilizing medications
  - Predominant history of manic relapse
  - Patient with whom clinician has a good therapeutic alliance

2013 Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines[3]

- Includes a LAI antipsychotic as a first-line agent for maintenance treatment of BD

LAIs allow the provider to promptly identify & address non-adherence if the injection appointment is missed[4]

BD, Bipolar Disorder; LAI, long-acting injectables; pts, patients.

1. Levin, J. B., et al. *CNS Drugs*, 2016; 30: 819-835.
2. Sajatovic, M., et al. *Neuropsychiatric Disease and Treatment*, 2018; 14: 1463-1474.
3. Yatham, L. N., et al. *Bipolar disorder*, 2013; 15(1): 1-44.
4. Gigante, A. D., et al. *CNS Drugs*, 2012; 26(5): 403-420.

Initiating and Maintaining LAIs in BD

Agreeing to LAI trial

- Discuss risks/benefits with pt & family/care partners
- Obtain pt agreement
- Document discussion with pt
- Provide educational materials

Choosing an agent

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

LAI initiation

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

LAI trial

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

Maintenance treatment

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

BD, Bipolar Disorder; EPS, extrapyramidal symptoms; LAI, long-acting injectables; PI, prescribing information; pt, patient.

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

LAIs May Help Improve Adherence in BD

- Commercial and Medicaid claims dataset
  - Adult patients (≥ 18) with BD (N = 11,344)
  - Either began receiving an LAI (no prior LAI therapy) or changed to a different oral antipsychotic (monotherapy)

- Patients who began receiving LAIs had **5% better medication adherence** and were **19% less likely to discontinue their medication** than those using oral antipsychotics.

	LAI (n =1,672)	**Oral (n =9672)**
Proportion of days covered (PDC), mean (SD)*	.51 (.34)	.45 (.41)
Medication adherence rate (PDC ≥ 0.8), n (%)*	516 (30.9)	2,084 (21.5)
Duration of index treatment without a gap ≥ 60 days, mean (SD) days*	250.9 (240.3)	202 (218.6)
Discontinuation rate, n (%)*	1,136 (67.9)	7484 (77.4)

*, p < .001; BD, Bipolar Disorder; LAI, long-acting injectable

1. Greene, M., et al. *Journal of Medical Economics*, 2018; 21(2); 127-134.

LAI + Customized Adherence Enhancement (CAE)

- 6-month prospective, uncontrolled trial of LAI + CAE in 30 poorly adherent individuals with BD
- CAE intervention was delivered in 7-sessions for 30-60 min and included up to 4 psychosocial treatment modules:
  - Psychoeducation on BD medications
  - Communication with providers
  - Strategies to enhance medication routines
  - Targeting substance use problems with modified motivational enhancement therapy

Primary Outcomes

- Proportion of missed medications in the past week from screen to 24 weeks significantly improved from 50.1% to 16.5%

Secondary Outcomes

- Significant improvements on the BPRS, MADRS, YMRS, CGI, SOFAS, and GAF

BD, bipolar disorder; BPRS, Brief Psychiatric Rating Scale; CAE, customized adherence enhancement; CGI, Clinical Global Impressions; GAF, Global Assessment of Functioning; LAI, long-acting injectable; MADRS, Montgomery-Asberg Depression Rating Scale; SOFAS, Social and Occupational Functioning Assessment Scale; YMRS; Young Mania Rating Scale.

1. Sajatovic, M., et al. *Prim Care Companion CNS Disod.*, 2021; 23(5): 20m02888.

Summary

Medication nonadherence is common and a major determinant of prognosis in Bipolar I Disorder

To address medication adherence in Bipolar I Disorder, both barriers (i.e., patient and external factors) and facilitators must be identified and targeted

Psychosocial interventions can improve adherence in Bipolar I Disorder

- Psychoeducation, motivational interviewing, immediate positive reinforcement in the form of financial incentives, and cognitive behavioral strategies

Alternative drug-delivery formats and technology facilitated approaches are showing promise in adherence promotion

- Long-acting injectables may have a role in improving adherence in Bipolar I Disorder, particularly when used in conjunction with behavioral support