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Antipsychotic Treatment Options in Schizophrenia

May 2020 MRC2.PSY.D.00100

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Objectives

- Review evolution of antipsychotic treatments
- Discuss definitions of adherence and possible reasons for nonadherence
- Compare evidence supporting oral and long-acting injectable antipsychotics
- Discuss potential communication strategies for patients and providers

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Evolution of Antipsychotic Treatments

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Typical and Atypical APs Have Been Studied for >70 Years

Introduction of typical APs 1950s

- Phenothiazines first used in clinical practice[1]
- Allowed patient discharge; shift from custodial care[2]

Additional typical APs and introduction of atypical APs 1960s-1990s

- Additional typical APs introduced[3]
- First LAI introduced[2]
- Molecular targets of pharmacological agents expanded to DA, 5-HT, and NE[1]
- First atypical AP approved in Europe in 1989[4] and in the United States in 1990[3]

Addition of new formulations and treatment modalities 1990s-present

- Additional oral atypical APs introduced[3]
- First atypical LAI introduced[5]
- Development of novel formulations, including oral disintegrating, sublingual, transdermal APs,[6] subcutaneous LAI injections,[7] and digital medicine[8]

AP, antipsychotic; DA, dopamine; 5-HT, serotonin; LAI, long-acting injectable; NE, norepinephrine.

1. Lehmann and Ban. *Can J Psychiatry*. 1997;42:152-162. 2. Johnson. *Br J Psychiatry Suppl*. 2009;195:S7-S12. 3. Tandon. *J Clin Psychiatry*. 2011;72(suppl 1):4-8. 4. Ayano. *J Schizophr Res.* 2016;3:1027. 5. Patel et al. *Br J Psychiatry Suppl*. 2009;52:S1-S4. 6. Citrome et al. *J Clin Psychiatry*. 2019;80:18nr12554. 7. Karas et al. *P.T.* 2019;44:460-466. 8. Papola et al. *Epidemiol Psychiatr Sci*. 2018;27:227-229.

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Comparison of Typical and Atypical APs

	Typical AP medications (first generation)	Atypical AP medications (second generation)
 Mechanism	• D_2-receptor antagonism[1]	• D_2-receptor antagonism[1] • D_2-receptor partial agonism[1] • 5-HT_{2A} antagonism[1] • 5-HT_{1A} partial agonism[1]
 Benefits	• Reduce frequency and severity of psychotic episodes[2] • Improve functional capacity[2]	• Reduce frequency and severity of psychotic episodes[2] • Improve functional capacity[2] • Reduce risk of tardive dyskinesia[3] • Improve relapse prevention[4] and treatment adherence[5]
 Limitations	• Adverse events (eg, extrapyramidal symptoms)[2]	• Adverse events (eg, weight gain, sedation, agranulocytosis[6])

AP, antipsychotic; D_2, dopamine receptor 2; 5-HT, serotonin.

1. Horacek et al. *CNS Drugs.* 2006;20:389-409. 2. Haller et al. *F1000 Prime Rep*. 2014;6:57. 3. Carbon et al. *World Psychiatry*. 2018;17:330-340. 4. Kishimoto et al. *Mol Psychiatry*. 2013;18:53-66. 5. Dolder et al. *Am J Psychiatry.* 2002;151:103-108. 6. Lehman et al. *Practice Guideline for the Treatment of Patients With Schizophrenia Second Edition*. 2010.

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AP Efficacy Must Be Balanced With Side Effects

Examples of clinical benefits

Efficacious for positive, negative, and cognitive symptoms[1]

Reduces risk of relapse[2]

Improves stability[3]

Improves quality of life[4]

Examples of side effects*

EPS (eg, akathisia, tardive dyskinesia)[5-7]

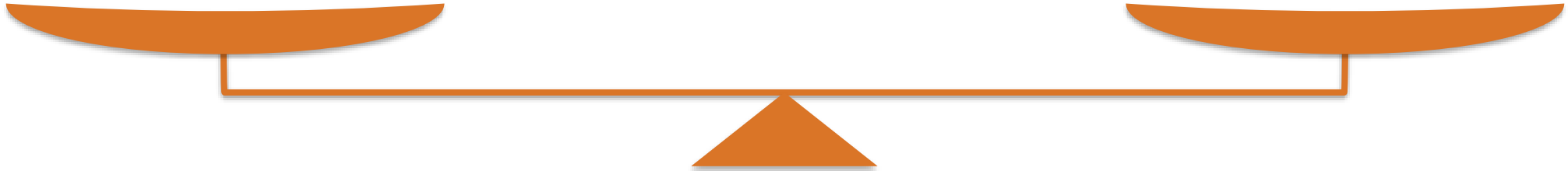
Sedation[5]

Weight gain[5]

Metabolic effects[5]

Hyperprolactinemia[5]

Sexual side effects[5]



Because APs vary in both clinical efficacy and side-effect profiles,[5] treatment decisions may need to change based on disease stage as well as tolerability[6]

AP, antipsychotic; EPS, extrapyramidal symptoms.

*Prevalence depends on class of AP being used.[5]

1. Naber et al. *Schizophr Res.* 2001;50:79-88. 2. Csernansky et al. *CNS Drugs.* 2002;16:473-484. 3. Kay and Lindenmayer. *Comp Psychiatry.* 1991;32:28-35. 4. Briggs et al. *Health Qual Life Outcomes.* 2008;6:105. 5. Leucht et al. *Lancet*. 2013;382:951-962. 6. Lehman et al. *Practice Guideline for the Treatment of Patients With Schizophrenia Second Edition*. 2010. 7. Carbon et al. *World Psychiatry*. 2018;17:330-340.

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Factors Influencing Adherence

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Different Terminology Indicates Extent of Patient Medication Use and Agreement

Persistence refers to patient taking any amount of medication for the prescribed duration of time[1]

Compliance refers to patient taking medication according to HCP recommendation for timing, dosing, and frequency[1]; patient agreement not required[2]

Adherence or **concordance** refers to patient behavior (eg, taking medication, lifestyle changes) according to HCP recommendation; patient agreement required[2]

Systematic review of clinical studies reported that a range of **67% to 90%** was used to define adherence to oral APs, despite expert consensus that **80%** should be the defining threshold of adherence[3]

AP, antipsychotic; HCP, healthcare provider.

1. Cramer et al. *Value Health*. 2008;11:44-47. 2. World Health Organization. http://www.who.int/chp/knowledge/publications/adherence_full_report.pdf. Accessed March 3, 2020. 3. Velligan et al. *Schizophr Res*. 2020;215:17-24.

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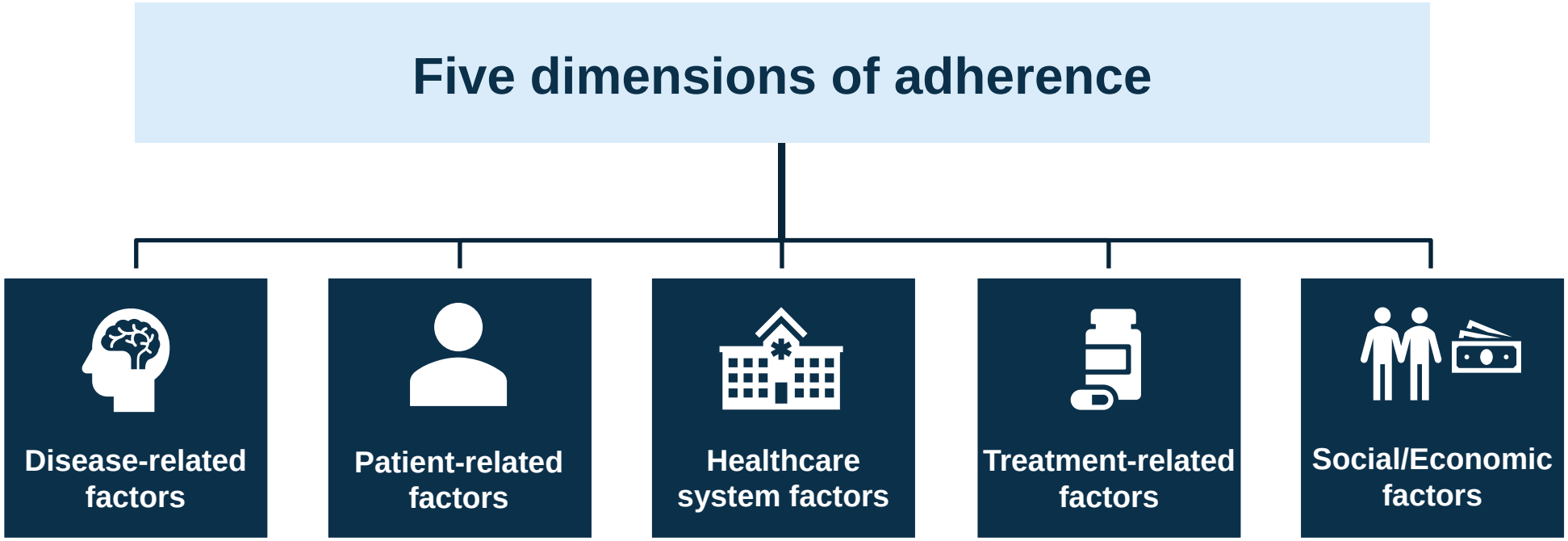
Adherence Is a Multidimensional Phenomenon



World Health Organization. http://www.who.int/chp/knowledge/publications/adherence_full_report.pdf. Accessed March 3, 2020.

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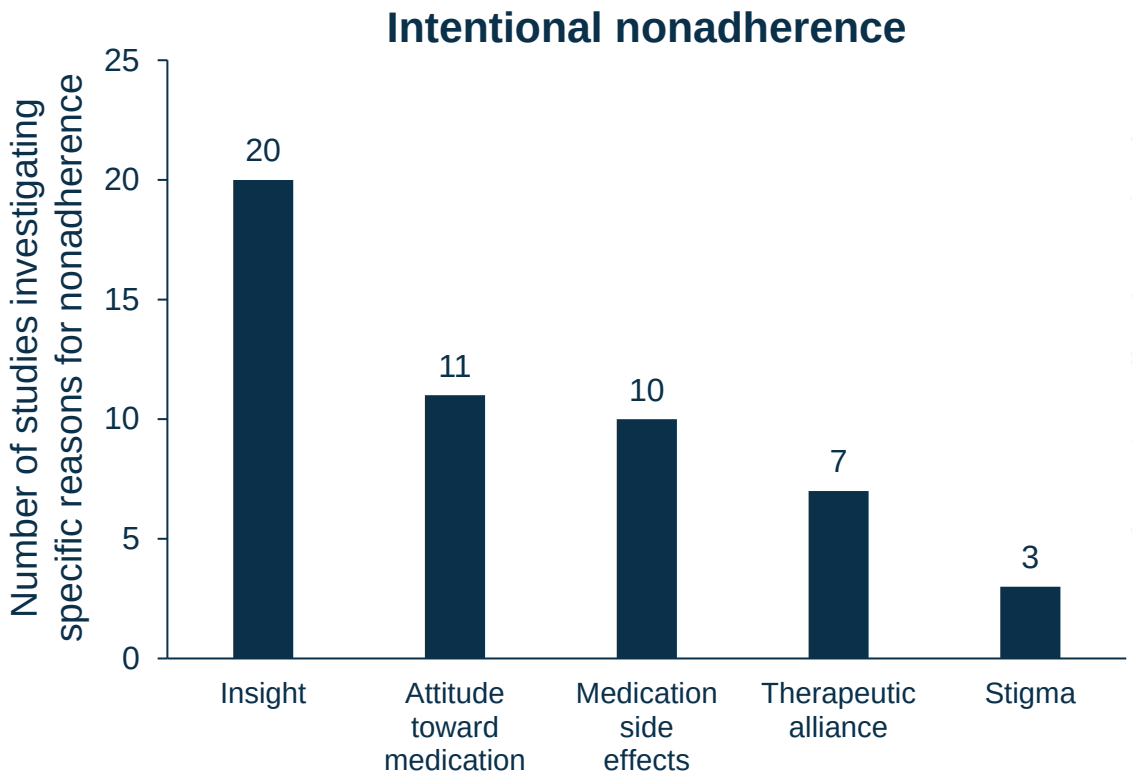
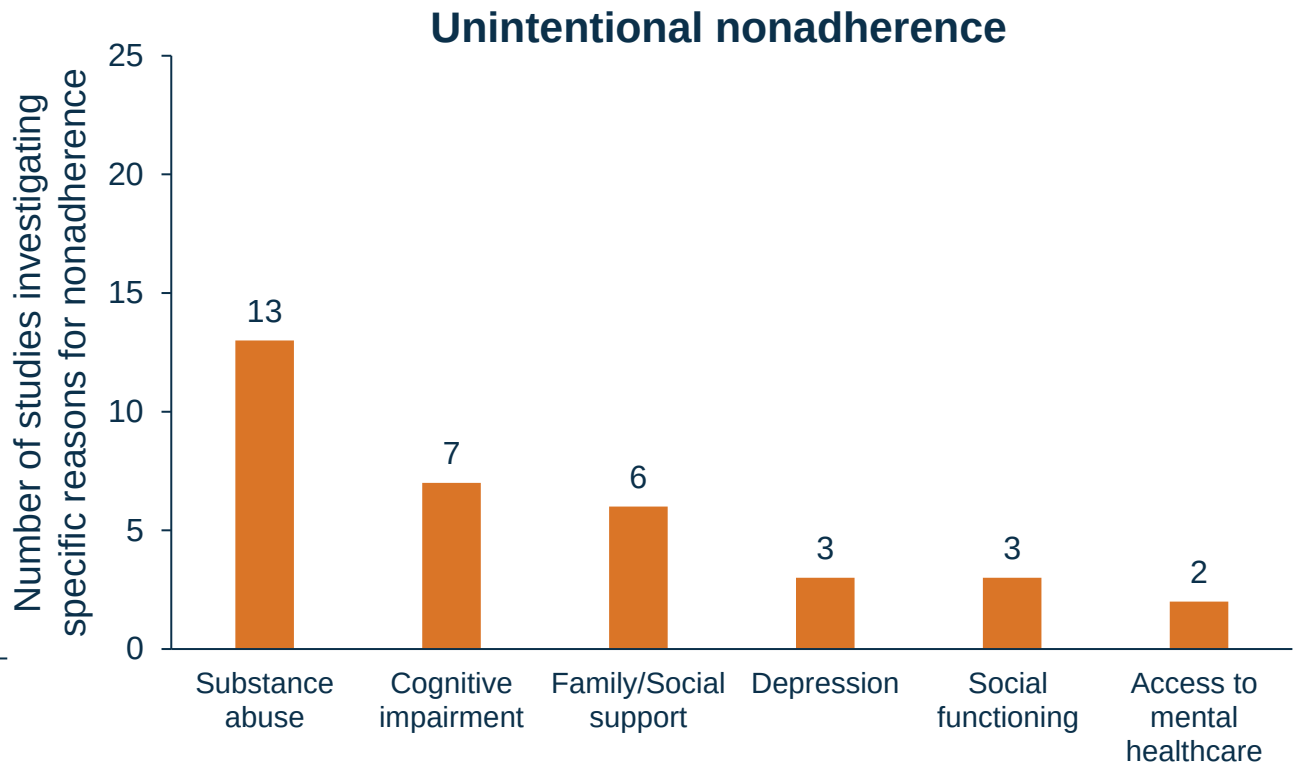
Leading Causes of Nonadherence in Patients With Serious Mental Illness

Reported causes of modifiable reasons for nonadherence to AP medication in patients with serious mental illness (N=36 articles)





AP, antipsychotic.

Velligan et al. *Patient Prefer Adherence*. 2017;11:449-468.

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Poor Adherence May Lead to Poor Patient Outcomes

Up to 75% of patients are nonadherent within 2 years of discharge[1]

Findings from clinical studies and systematic reviews

- Nonadherent patients were almost **twice as likely to undergo psychiatric hospitalization** compared with adherent patients[2]
- Nonadherence increased length of hospital stay **by 9 days**[3]
- Nonadherent patients were **10 times more likely to relapse** compared with adherent patients[4]
- Nonadherent patients were **at 4 to 7 times greater risk of suicide** compared with adherent patients[5]
- Nonadherent patients are **less than half as likely to achieve** remission compared with adherent patients[6]

1. Velligan et al. *J Clin Psychiatry*. 2009;70(suppl 4):1-46. 2. Ascher-Svanum et al. *BMC Res Notes*. 2009;2:6. 3. Sun et al. *Curr Med Res Opin*. 2007;23:2305-2312. 4. Morken et al. *BMC Psychiatry*. 2008;8:32. 5. Higashi et al. *Ther Adv Psychopharmacol.* 2013;3:200-218. 6. Novick et al. *Schizophr Res*. 2009;108:223-230.

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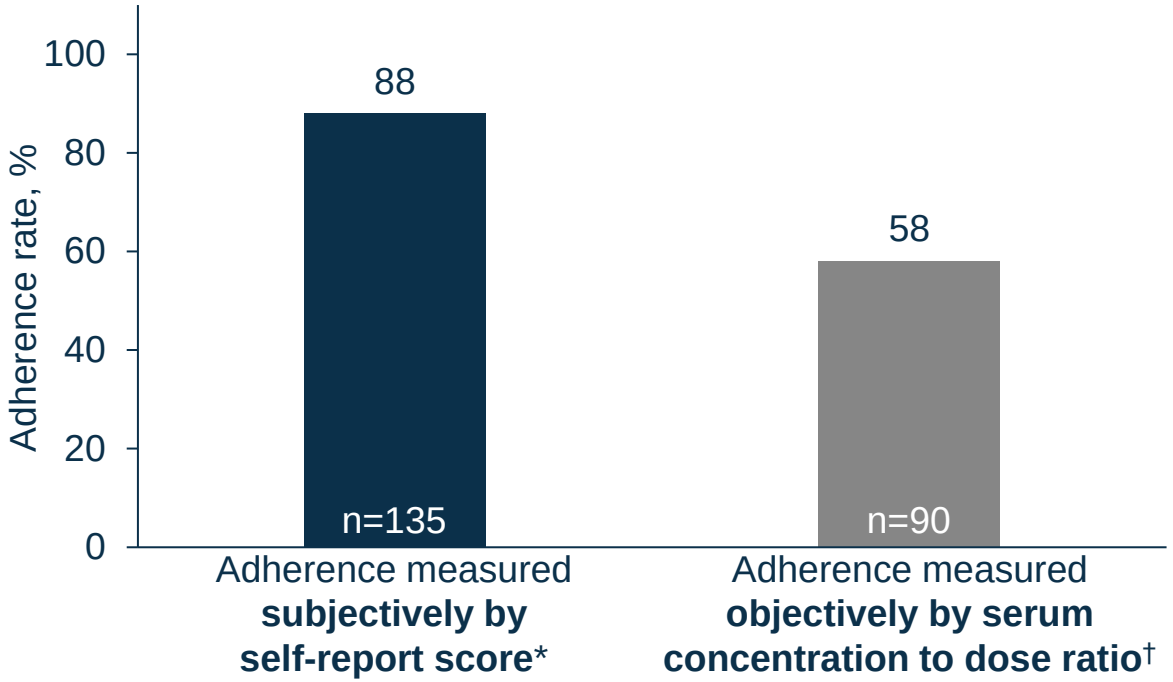
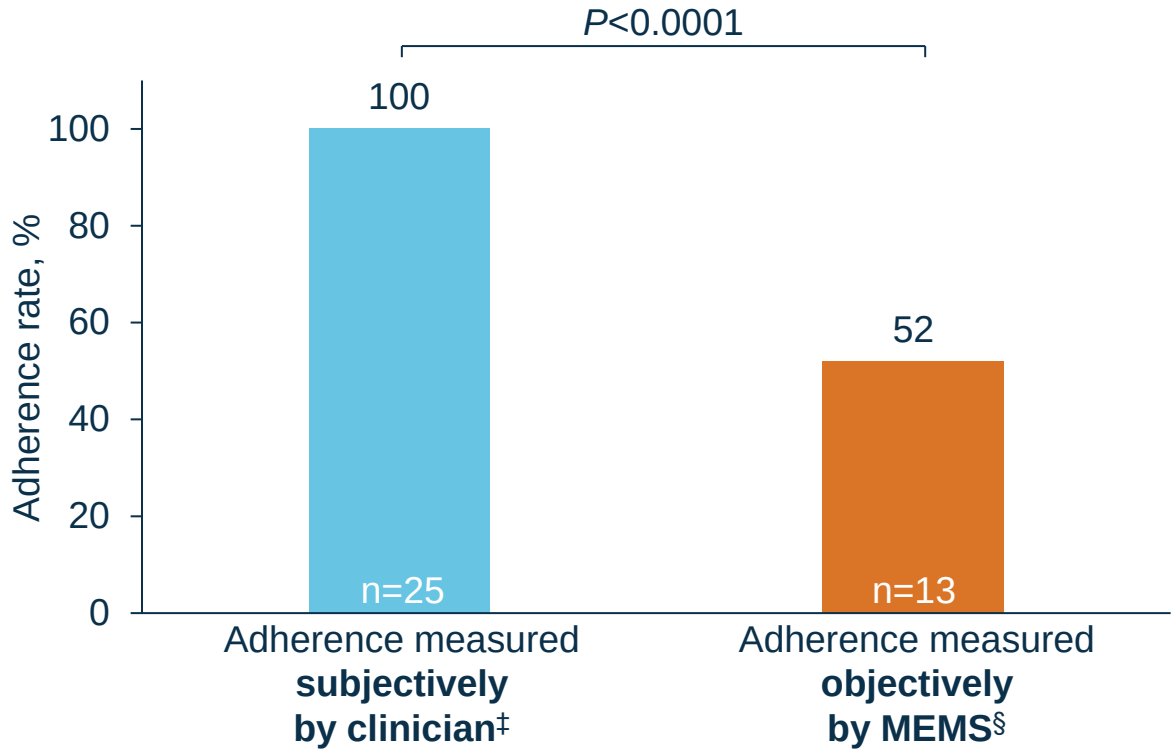
Subjective Measurements of Adherence Can Be Higher Than Objective Measurements

Differences in adherence based on self-report measures vs laboratory assessment



Differences in adherence based on clinician assessment vs medication monitoring



MEMS, Medication Event Monitoring System.

*Self-report adherence was measured via patient questionnaire with patients rating their adherence from 0%-100%, and adherence was defined as >75%. †Serum concentration was measured via blood sampling, and adherence was defined as the reference range for each drug. ‡Clinician-reported adherence was defined as a score of >4 on a scale of 1-7 with 1 indicating total refusal of medication and 7 indicating active participation and willingness to take medication. §Adherence using the MEMS system was defined as patients opening their medication bottle according to the prescribed regimen ≥70% of the time during any 1 of the 3 monthly evaluation periods.

1. Jónsdóttir et al. *J Clin Psychopharmacol*. 2010;30:169-175. 2. Byerly et al. *Psychiatry Res*. 2005;133(2-3):129-133.

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Comparing Evidence Supporting Oral and Long-Acting Injectable Antipsychotics

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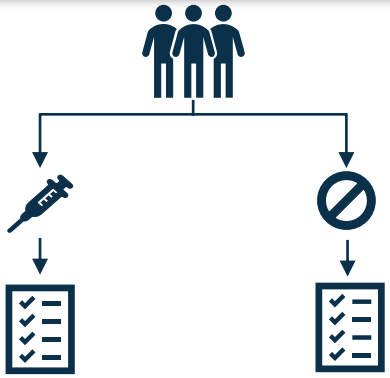
Evidence Supporting Use of Oral or LAI AP Medication Depends on Study Design

RCTs[1]



Compare data from patients receiving investigational therapy vs placebo/active control

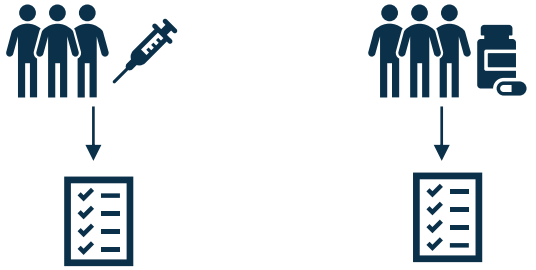
- Several RCTs reported no superiority of LAIs over OAPs; however, RCTs may inadvertently support adherence (eg, appointment reminders)[2]
- RCTs also tend to enroll patients with less severe symptoms[2]

Mirror studies[2]

Compare data from when patients were receiving OAP vs when they were receiving LAI

- A meta-analysis of mirror studies found superiority of LAIs over OAPs
- Expectation bias is a limitation of these studies as patients are unblinded to the treatment they receive

Parallel cohorts[2]



Compare data from patients receiving LAI vs those receiving OAP

- A meta-analysis of parallel-cohort studies found superiority of LAIs over OAPs in reducing hospitalizations and increasing adherence
- Design is limited by patient selection bias (eg, clinicians may administer LAIs to more severely ill patients)

AP, antipsychotic; LAI, long-acting injectable; OAP, oral AP; RCT, randomized controlled trial.

1. Kabisch et al. *Dtsch Arztebl Int.* 2011;108:663-668. 2. Kishimoto et al. *Schizophr Bull*. 2018;44:603-619.

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Oral APs Are Effective But May Face Adherence Challenges

Advantages

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

Disadvantages

- Daily administration[4]
- Potential for misuse[3]
- Influenced by first-pass metabolism[5]
- Adherence rates can be inaccurate unless ingestion of the medication is closely monitored[6]

AP, antipsychotic.

1. Citrome. *Expert Opin Pharmacother*. 2012;13:1545-1573. 2. Albright. https://www.psychcongress.com/article/three-key-antipsychotics-lose-patent-protection. Accessed March 3, 2020. 3. Burton. *Psychiatry*. 2010. 4. Bera. *J Clin Psychiatry*. 2014;75(suppl 2):30-33. 5. Zhornitsky and Stip. *Schizophr Res Treatment*. 2012;2012:407171. 6. Velligan et al. *Schizophr Res*. 2020;215:17-24.

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LAIs Promote Adherence But May Have Negative Perceptions

Advantages

- Promotion of treatment adherence[1-3]
- Transparency of adherence[2]
- Ease of administration[4]
- Reduced peak-trough plasma levels[2]
- Improved patient outcomes[2]
- Improved patient and physician satisfaction[2]
- Lowered relapse rate[2,5]
- Decreased rehospitalizations[6]

Disadvantages

- Patient concerns regarding potential pain of injection[7]
- Slow dose titration and longer time to reach steady state[4]
- May prolong side effects[4]
- Difficult to adjust small doses[7]
- Limited number of available formulations[7]
- Potential for small amount to leak into subcutaneous tissue[4]
- Association with involuntary hospitalization and related trauma[8]
- Perception that treatment is punitive or forced by clinicians without consideration of patient feelings or rights[9]

LAI, long-acting injectable.

1. Patel et al. *Br J Psychiatry Suppl*. 2009;195:S1-S4. 2. Geerts et al. *BMC Psychiatry*. 2013;13:58. 3. Lang et al. *Psychiatr Serv*. 2010;61:1239-1247. 4. Agid et al. *Expert Opin Pharmacother*. 2010;11:2301-2317. 5. Zhornitsky and Stip. *Schizophr Res Treatment*. 2012;2012:407171. 6. Lafeuille et al. *BMC Psychiatry*. 2013;13:221. 7. Jeong and Lee. *Clin Psychopharmacol Neurosci*. 2013;11:1-6. 8. Iyer et al. *Can J Psychiatry*. 2013;58(5 suppl 1):14S-22S. 9. Brissos et al. *Ther Adv Psychopharmacol*. 2014;4:198-219.

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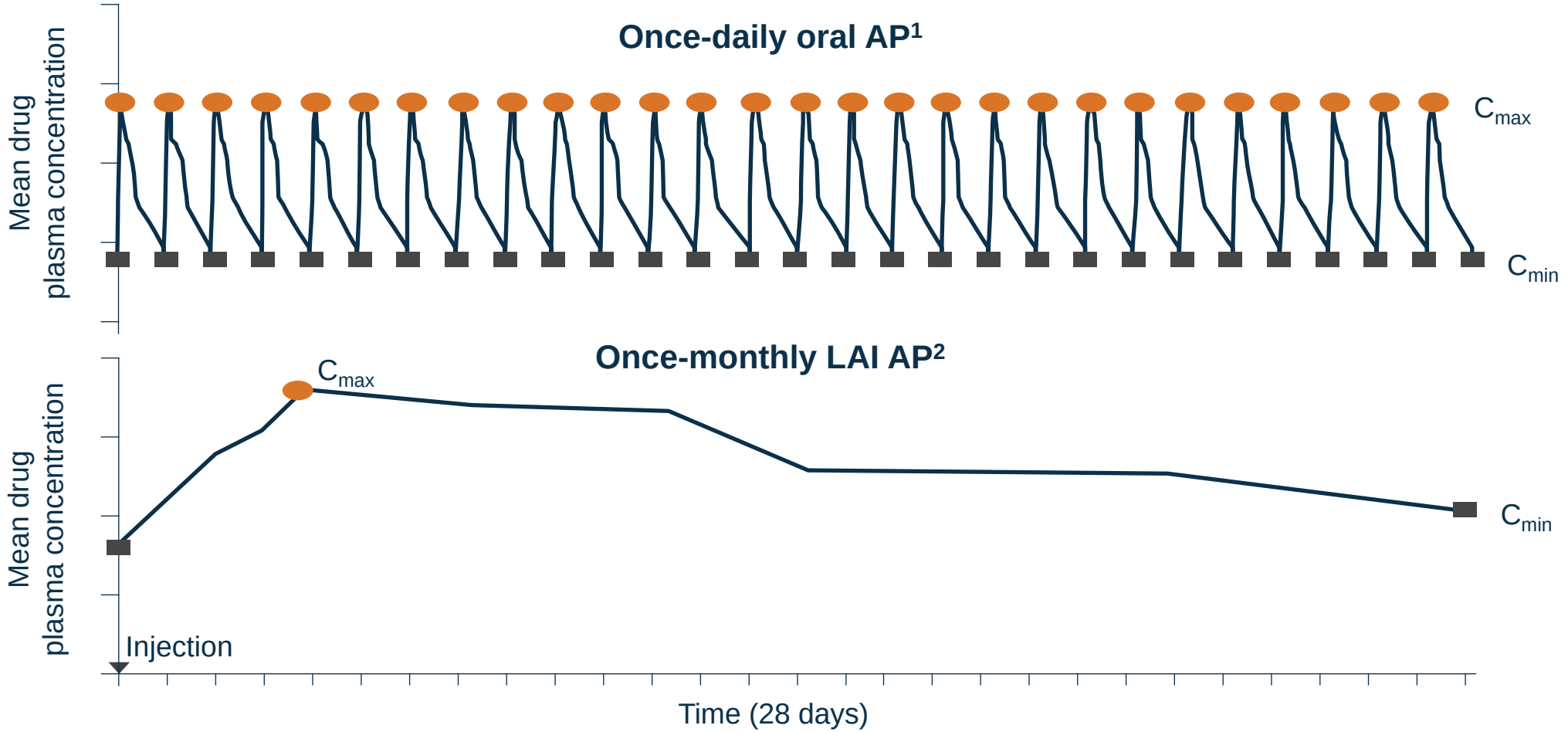
Hypothetical Steady-State Plasma Levels Over 1 Month With Once-Daily Oral and Once-Monthly LAI APs



AP, antipsychotic; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; LAI, long-acting injectable.

Modeled data are based on the recommended starting dose of an actual daily oral AP,[1] with variations expected between the pharmacokinetic parameters of different daily oral APs.[1,3] Some long-acting formulations require overlapping dosing of oral AP treatment at initiation[4]; modeled data are based on the recommended starting dose of a once-monthly LAI AP,[2] with variations between the pharmacokinetic parameters of different once-monthly LAI APs.[2,3]

1. Mallikaarjun et al. *J Clin Pharmacol*. 2004;44:179-187. 2. Mallikaarjun et al. *Schizophr Res*. 2013;150:281-288. 3. Sheehan et al. *Innov Clin Neurosci*. 2012;9(7-8):17-23. 4. Kane et al. *Eur Neuropsychopharmacol*. 1998;8:55-66.

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Potential Reasons for Low LAI Use in Early-Phase Schizophrenia

Challenges in perception

- Overestimate of adherence
- Bias against injections
- Perception of inappropriate in early-phase disease

Challenges in education

- Poor understanding of LAI benefit
- Lack of LAI training
- Inadequate training in shared decision-making
- Communication strategies needed

Challenges in clinical use

- Impact on therapeutic alliance
- Inadequate implementation by inpatient referrals
- Insufficient caregiver involvement
- Mixed results of oral vs LAI trials

LAI, long-acting injectable.

Kane and Correll. *J Clin Psychiatry.* 2019;80:IN18031AH1C.

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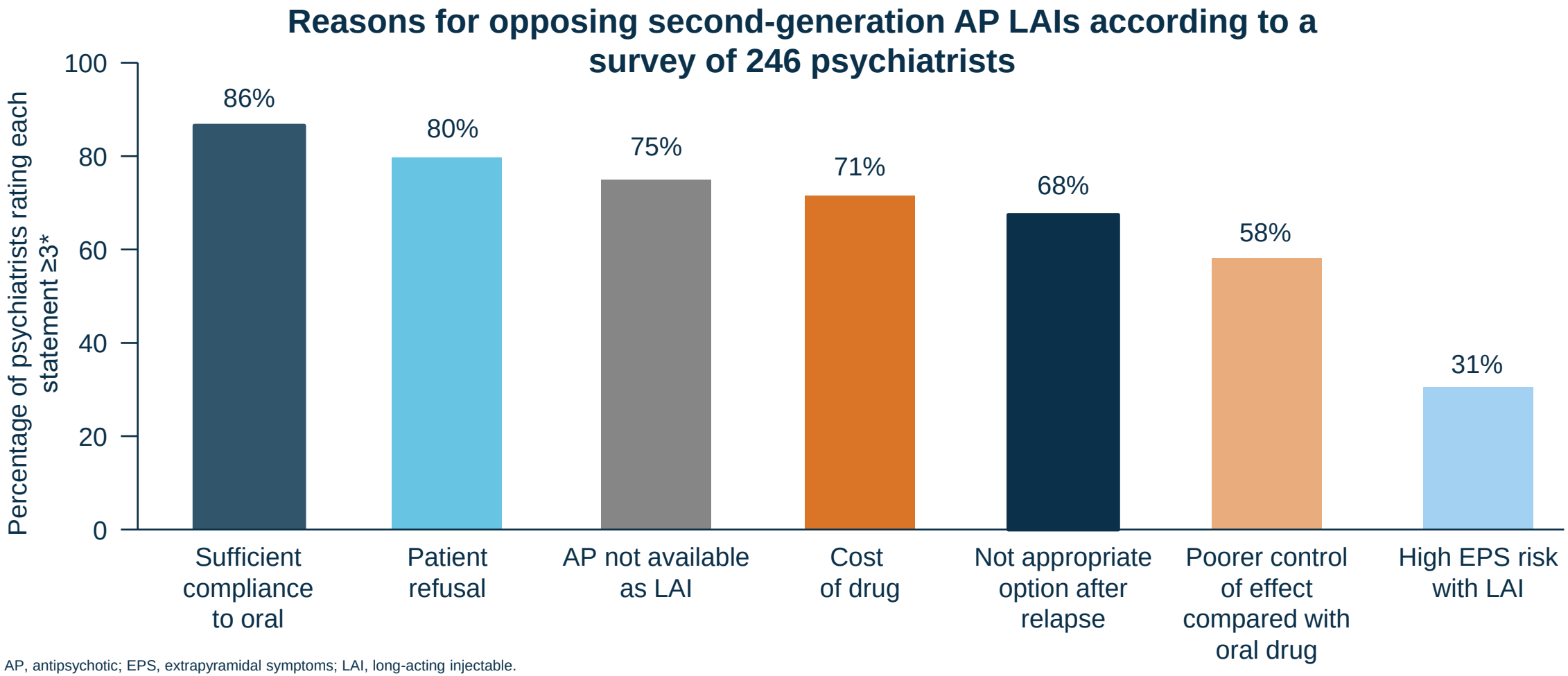
Sufficient Compliance With Oral APs Is the Leading Factor for Psychiatrists Opposing LAIs



AP, antipsychotic; EPS, extrapyramidal symptoms; LAI, long-acting injectable.
*Based on scale of 0-5, with 3 being "sometimes" and 5 being "very frequently."
Heres et al. *J Clin Psychiatry*. 2006;67:1948-1953.

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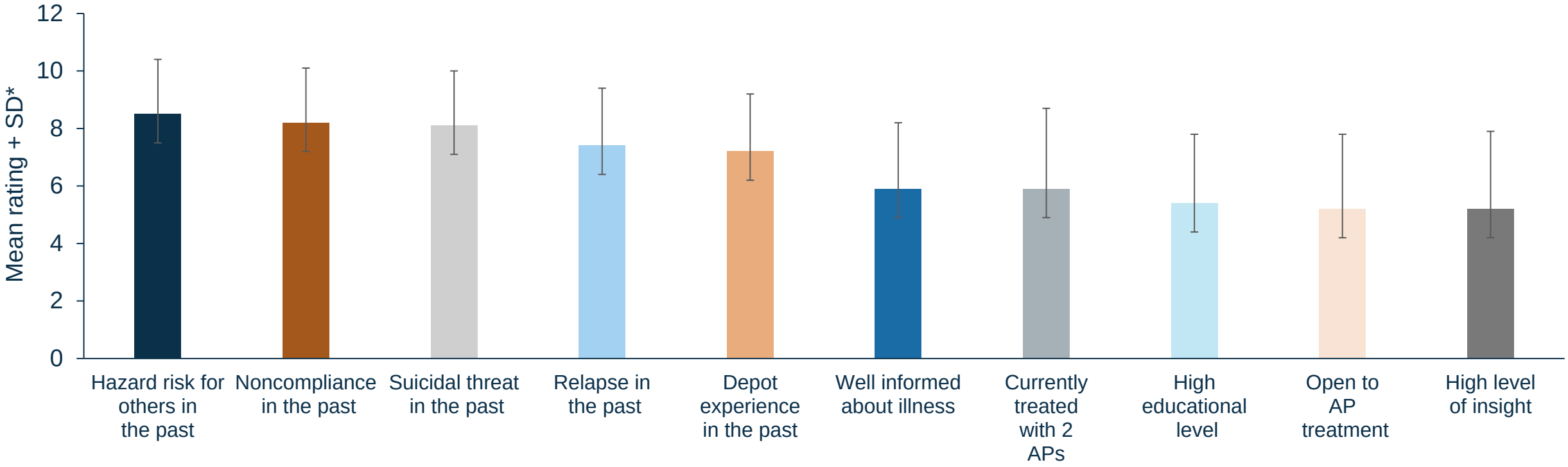
Primary Patient Characteristic Influencing Psychiatrist Decision to Initiate LAI Use Was “Hazard Risk for Others”

Mean rating of the top 10 patient attributes potentially influencing qualification for LAI treatment based on survey of 201 psychiatrists



AP, antipsychotic; LAI, long-acting injectable; SD, standard deviation.

*Scale ranged from 0-10 with 0 indicating not qualified for LAI treatment and 10 indicating highly qualified for LAI treatment.

Heres et al. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008;32:1987-1993.

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Patient-Centric Methods Leading to Treatment Acceptance

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Patients Tend to View LAIs Favorably

As recorded in focus groups, patients reported that LAIs were easier to use and noted the advantage of consistent dosage[2]

A survey of 206 patients with ≥3 months of experience with a LAI formulation found that injectable APs were the preferred formulation, with 70% reporting that the added benefit of regular contact with a doctor or nurse administering treatment made them feel more supported[3]

Many studies have found that patients prefer LAI over oral medication[1]

In a separate study of 83 patients with schizophrenia, only 21% of patients who were naive to LAI treatment reported receiving information about LAIs from their psychiatrist[4]

LAI, long-acting injectable.

1. Walburn et al. *Br J Psychiatry*. 2001;179:300-307. 2. Iyer et al. *Can J Psychiatry*. 2013;58(5 suppl 1):14S-22S. 3. Caroli et al. *Patient Prefer Adherence*. 2011;5:165-171. 4. Jaeger and Rossler. *Psychiatry Res*. 2010;175(1-2):58-62.

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However, Clinicians May Generally Believe Patients Do Not View LAIs Favorably

Clinicians generally viewed LAIs as being less acceptable to patients[1]

Clinicians should self-reflect on their own beliefs as negative assumptions about patient preferences may result in a pessimistic style of delivering information[1]

In a survey of 102 consultant psychiatrists, 33% believed patients always prefer oral medications over LAIs[1]

In a survey of 83 patients with schizophrenia and 81 psychiatrists, 75% of psychiatrists felt that they informed the patient about LAIs, but only 33% of patients felt informed[2]

LAI, long-acting injectable.

1. Patel et al. *J Psychopharmacol*. 2010;24:1473-1482. 2. Jaeger and Rossler. *Psychiatry Res*. 2010;175(1-2):58-62.

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Communication Is Key to Assessing Patient Adherence

Ask	Use open-ended questions that avoid “yes” or “no” answers[1]
Paraphrase	Phrase patient reflections into statements, not questions[1]
Encourage	Help patients verbalize changes in their behavior[1]
Affirm	Support, encourage, and recognize difficulties[1]
Summarize	Reiterate the comments made by patients[1]
Assess	Determine if the patient is ready to change behavior[2]

1. Levensky et al. *Am J Nurs*. 2007;107:50-58. 2. Zimmerman et al. *Am Fam Physician*. 2000;61:1409-1416.

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Examples of How to Assess for Adherence

Questions about patient attitudes

- Do you feel that your medication helps you?
- Have you ever decided not to take your medication on purpose?

Questions about cognitive impairment

- What time do you take your medication?
- How much do you take?

Questions about home life and social support

- Who, if anyone, reminds you to take your medication?
- Does anyone think you shouldn't take your medication?

Questions about healthcare delivery

- Where do you get your refills?
- Do you feel that we understand your concerns about treatment?

Kane and Correll. *J Clin Psychiatry*. 2019;80:IN18031AH1C.

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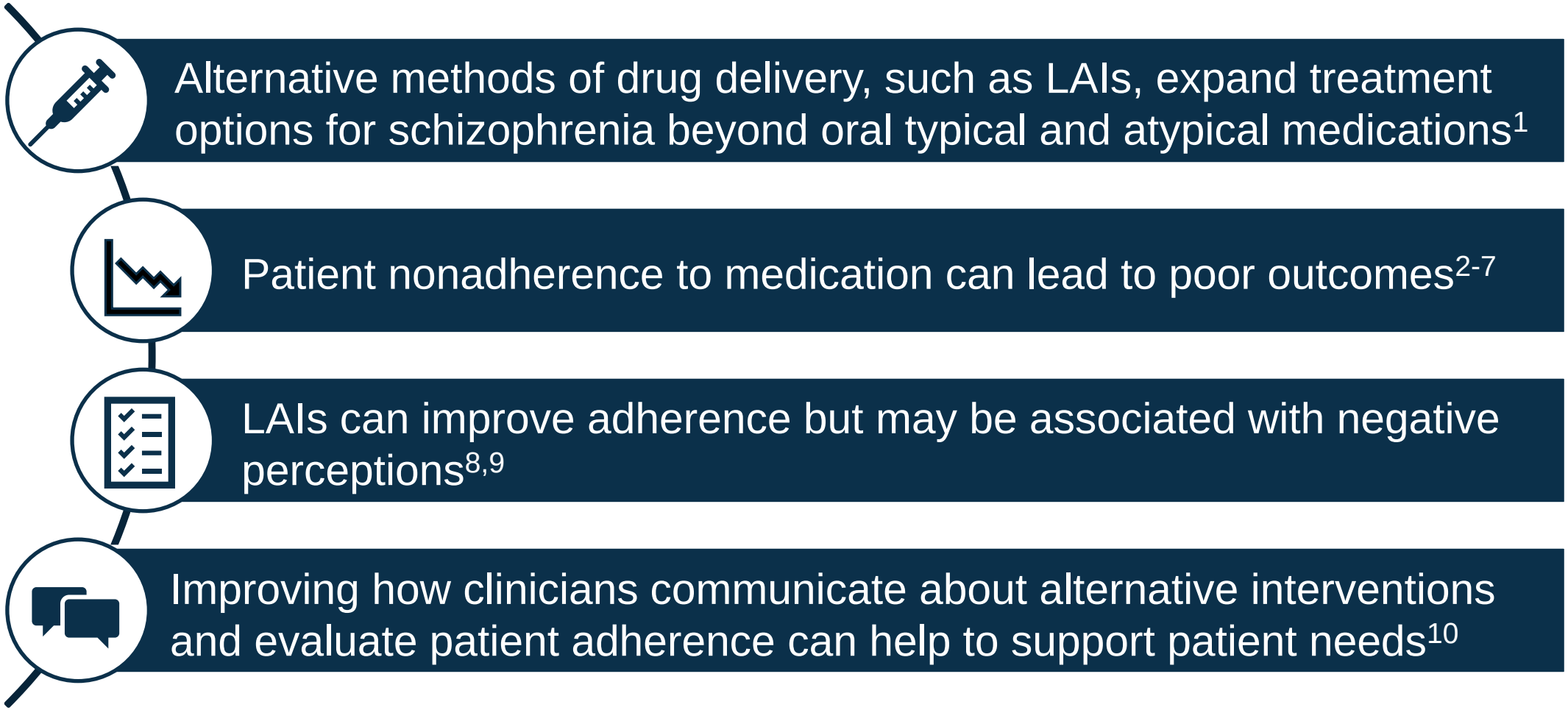
Summary



LAI, long-acting injectable.

1. Karas et al. *P.T.* 2019;44:460-466. 2. Velligan et al. *J Clin Psychiatry*. 2009;70(suppl 4):1-46. 3. Ascher-Svanum et al. *BMC Res Notes*. 2009;2:6. 4. Sun et al. *Curr Med Res Opin*. 2007;23:2305-2312. 5. Morken et al. *BMC Psychiatry*. 2008;8:32. 6. Higashi et al. *Ther Adv Psychopharmacol.* 2013;3:200-218. 7. Novick et al. *Schizophr Res*. 2009;108:223-230. 8. Patel et al. *Br J Psychiatry Suppl*. 2009;52:S1-S4. 9. Brissos et al. *Ther Adv Psychopharmacol*. 2014;4:198-219. 10. Kane and Correll. *J Clin Psychiatry*. 2019;80:IN18031AH1C.

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Questions

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