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Long-Acting Injectable Antipsychotics: *Practical Considerations and Impact on Adherence in Schizophrenia*

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Faculty Disclosure

- **Dr. Citrome**: Consultant—AbbVie, Acadia, Alkermes, Allergan, Angelini, Astellas, Avanir, Axsome, BioXcel, Cadent Therapeutics, Eisai, Impel, Intra-Cellular Therapies, Janssen, Karuna, Lundbeck, Luye, Lyndra, Medavante-ProPhase, Merck, Neurocrine, Noven, Osmotica, Otsuka, Relmada, Sage, Shire, Sunovion, Takeda, Teva, University of Arizona, and one-off ad hoc consulting for individuals/entities conducting marketing, commercial, or scientific scoping research; Speaker—AbbVie, Acadia, Alkermes, Allergan, Angelini, Eisai, Intra-Cellular Therapies, Janssen, Lundbeck, Merck, Neurocrine, Noven, Otsuka, Sage, Shire, Sunovion, Takeda, Teva, and CME activities organized by medical education companies such as Medscape, NACCME, NEI, Vindico, and Universities and Professional Organizations/Societies; Stocks (small number of shares of common stock)—Bristol-Myers Squibb, Eli Lilly, J & J, Merck, Pfizer purchased > 10 years ago; Royalties—Wiley (Editor-in-Chief, *International Journal of Clinical Practice*, through end 2019), *UpToDate* (reviewer), Springer Healthcare (book), Elsevier (Topic Editor, Psychiatry, Clinical Therapeutics); In the past 5 years Dr. Citrome has engaged in collaborative research with, or received consulting or speaking fees, from: AbbVie, Acadia, Alexza, Alkermes, Allergan, Angelini, Astellas, AstraZeneca, Avanir, Axsome, BioXcel, Boehringer Ingelheim, Bristol-Myers Squibb, Cadent Therapeutics, Eisai, Eli Lilly, Forum, Genentech, Impel, Indivior, Intra-Cellular Therapies, Janssen, Jazz, Karuna, Lundbeck, Luye, Lyndra, Medavante-Prophase, Meiji, Merck, Medivation, Mylan, Neurocrine, NeuroRx, Novartis, Noven, Osmotica, Otsuka, Pfizer, Reckitt Benckiser, Relmada, Reviva, Sage, Shire, Sunovion, Takeda, Teva, University of Arizona, Valeant, Vanda, and one-off ad hoc consulting for individuals/entities conducting marketing, commercial, or scientific scoping research.
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Learning Objectives

- Outline the role that long-acting injectable antipsychotics (LAIs) can play in patient preferences and overcoming medication adherence challenges for patients with schizophrenia
- Summarize LAI pharmacology and factors informing patient selection
- Implement strategies for patient-centric communication to facilitate patient acceptance of LAIs

Peter

19-year-old freshman at the local state college

He is the first in his family to attend college.

Peter has ambitions to become a physician, based in part on the chronic physical ailments that his grandmother suffered with before she passed away in Peter's senior year of high school.

There is no family history of mental illness.

In the fall semester of his first year of college, he finds himself already falling behind in his schoolwork and experiences difficulties concentrating.

He becomes preoccupied with thoughts that satellites are beaming instructions to the "chosen few" in the capital cities of Europe.

By winter, he has failed a course and received a "D" in another; he is put on probation.

In March, he is arrested at a local supermarket after destroying part of the dairy section, claiming that the food is tainted by "aliens."

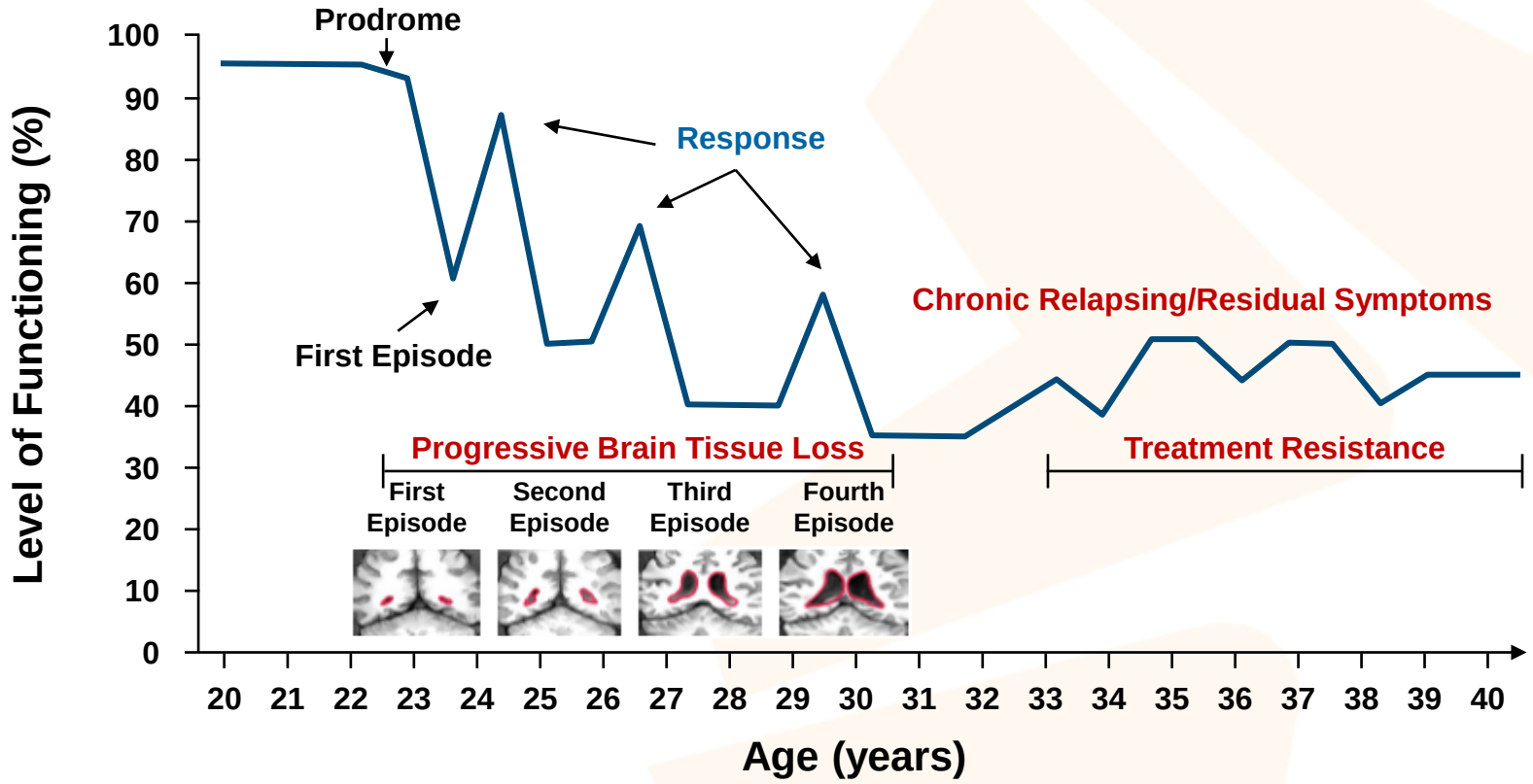
The police are called, and Peter is brought to the local emergency department for an emergency evaluation.

He is admitted to the locked inpatient psychiatric unit.

While he is under care at the locked inpatient psychiatric unit, Peter is initially treated with risperidone 3 mg hs and appears to respond well.

He is offered the option of an LAI but is reluctant to start an injectable.

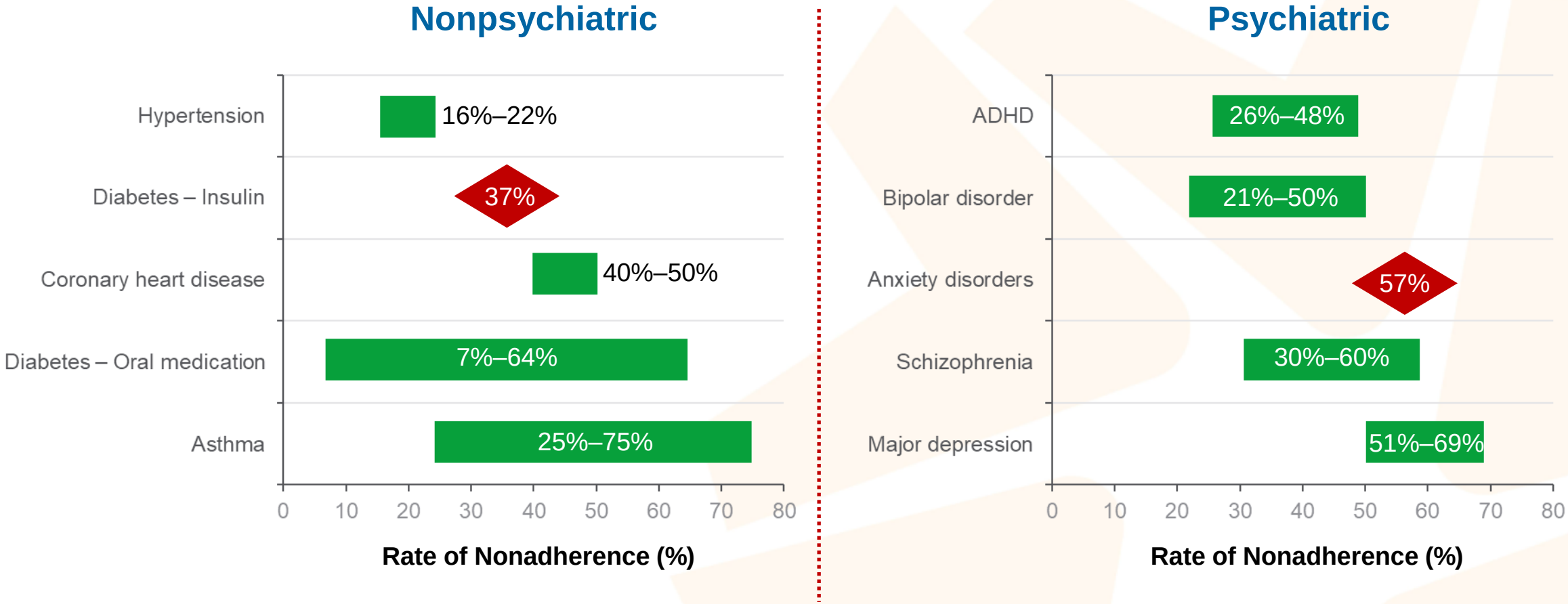
With Every Relapse, Patients are at Risk of Irreversible Lifetime Functional Impairment



Gardner KN, et al. *Current Psychiatry*. 2015;14(7):33-45. Lieberman JA. *J Clin Psychiatry*. 1996;57 Suppl 11:68-71. Birchwood M, et al. *Br J Psychiatry Suppl*. 1998;172(33):53-59.

Adherence Challenges

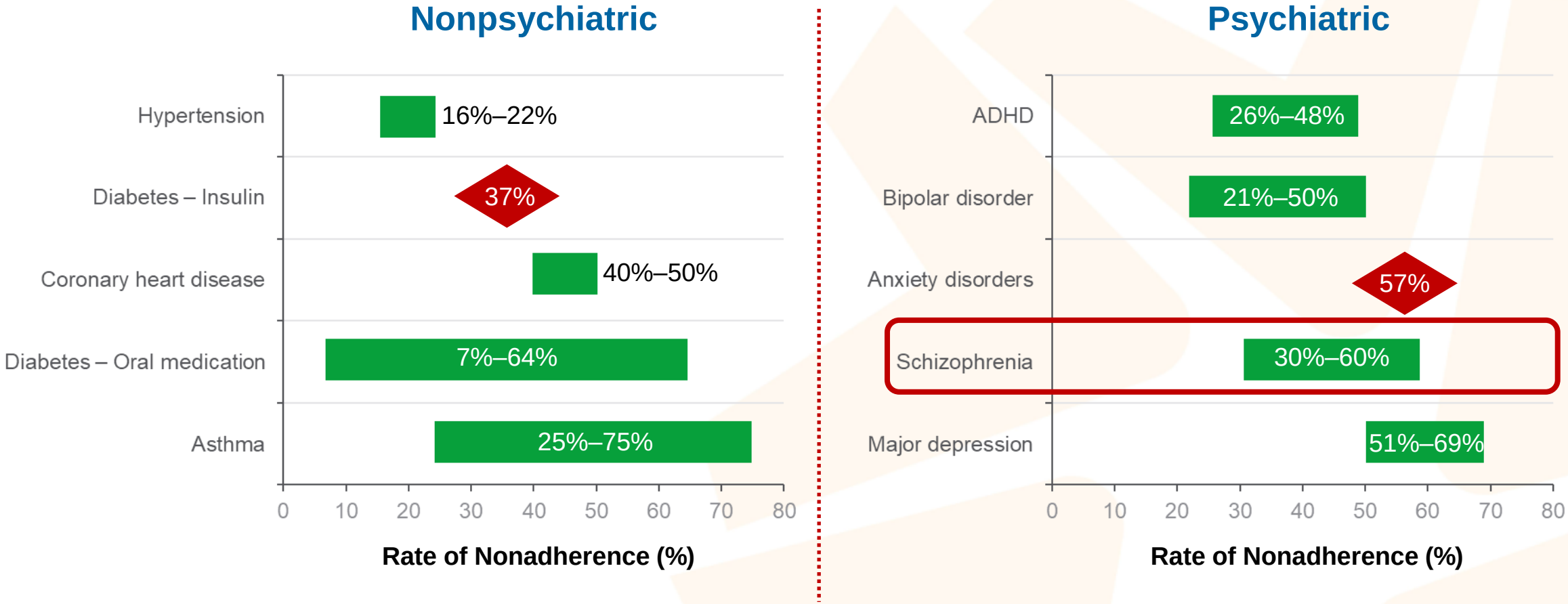
Many Chronic Conditions Have High Rates of Medication Nonadherence



ADHD = attention-deficit/hyperactivity disorder.

Parks J. Clinical Strategies to Promote Medication Adherence. Accessed February 3, 2021. www.thenationalcouncil.org/wp-content/uploads/2020/04/Clinical-Strategies-to-Promote-Medication-Adherence-6.20.18.pdf?daf=375ateTbd56

Many Chronic Conditions Have High Rates of Medication Nonadherence



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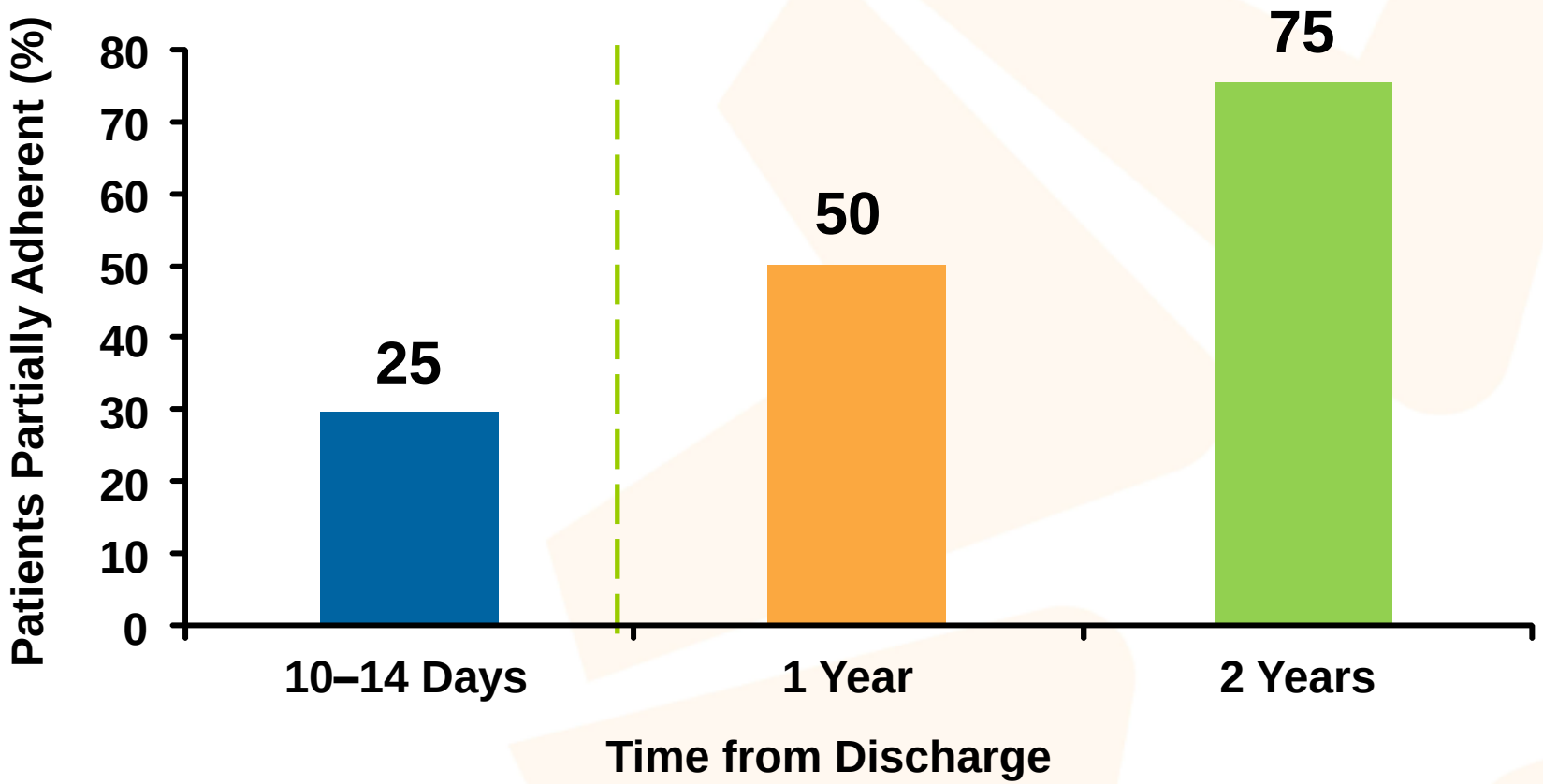
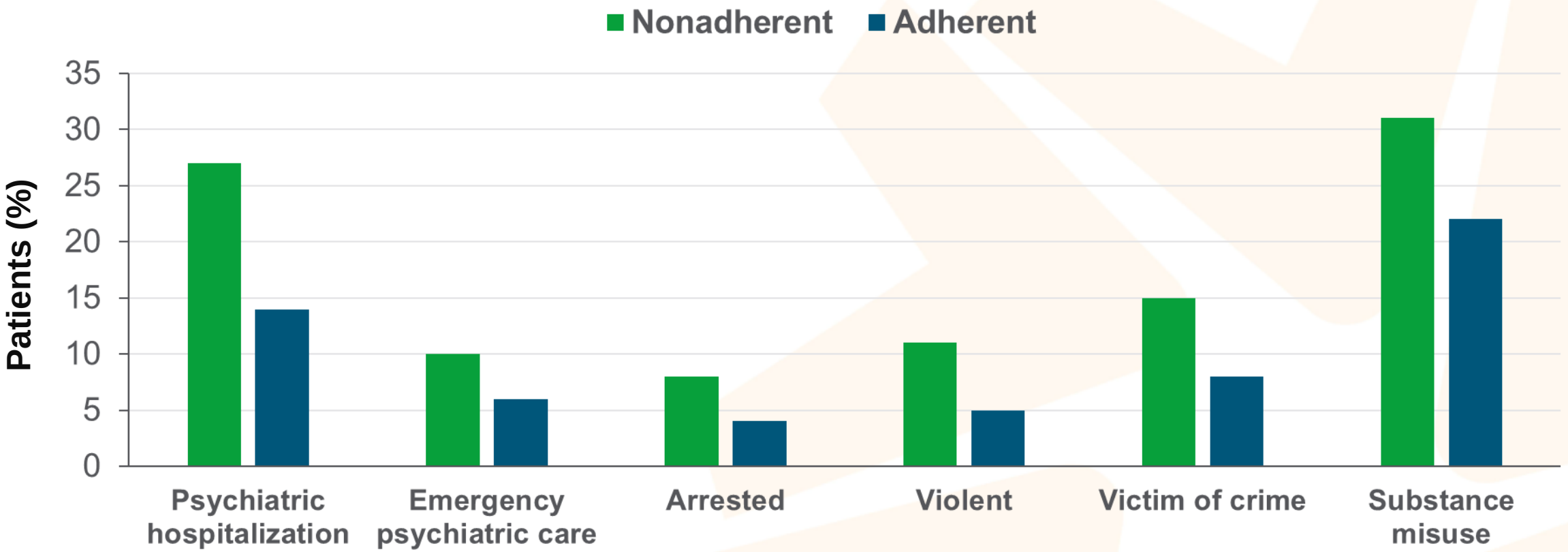
Partial Adherence in Schizophrenia Begins Early after Hospital Discharge and Worsens over Time



Velligan DI, et al. *Psychiatr Serv*. 2003;54(5):665-667. Weiden PJ, et al. Medication noncompliance in schizophrenia: I. assessment. *Journal of Practical Psychiatry and Behavioral Health*. 1997;3:106-110.

Nonadherence to Antipsychotics Impacts Physical, Emotional, and Social Well-being



Haddad PM, et al. *Patient Relat Outcome Meas*. 2014;5:43-62.

Consistent Medication Treatment is Key in Preventing Relapse

- ~ 50% of patients who discontinue/do not take antipsychotics will relapse within 3 to 10 months
- Relapse rates are much higher in nonadherent patients
  - 69% of patients with poor adherence relapsed compared to 18% of patients with good adherence (NNT=2)
  - This is a HUGE effect size!

NNT = number needed to treat.

Blackwell B. *Clin Pharmacol Ther*. 1972;13(6):841-848. Hirsch SR, et al., eds. *Schizophrenia*. Blackwell Science; 1995:443-468. Morken G, et al. *BMC Psychiatry*. 2008;8:32.

There are Multiple Risk Factors for Poor Adherence to Antipsychotics

Patient	Treatment	Environmental / Relationship	Societal
• Poor insight into need for medications • Negative attitude • Prior nonadherence • Substance abuse • Cognitive impairment	• Side effects • Lack of efficacy/ continued symptoms	• Lack of family/ social support • Problems with therapeutic alliance • Practical problems with getting/taking medications	• Stigma attached to illness • Stigma caused by medication side effect

Ascher-Svanum H, et al. *J Clin Psychiatry*. 2006;67(7):1114-1123. Lacro JP, et al. *J Clin Psychiatry*. 2002;63(10):892-909. Lee S, et al. *Soc Sci Med*. 2006;62(7):1685-1696. Velligan DI, et al. *J Clin Psychiatry*. 2009;70 Suppl 4:1-46.

When Treatments Fail

- Wrong diagnosis and thus incorrect treatment
- Wrong dose of the right medication
- Inadequate duration of treatment
- “Treatment resistance”
- Think about ***nonadherence***

Nosé M, et al. *Psychol Med*. 2003;33(7):1149-1160. Weiden P, et al. *Psychiatr Serv*. 1995;46(10):1049-1054.

When Treatments Fail

- Wrong diagnosis and thus incorrect treatment
- Wrong dose of the right medication
- Inadequate duration of treatment
- “Treatment resistance”
- Think about ***nonadherence***

Remember: Medication adherence is poor across most chronic physical and psychiatric disorders

Remember: ~ 75% of patients with schizophrenia become nonadherent within 2 years of hospital discharge

Nosé M, et al. *Psychol Med*. 2003;33(7):1149-1160. Weiden P, et al. *Psychiatr Serv*. 1995;46(10):1049-1054.

Unfortunately, We Overestimate Adherence

- Nonadherence viewed as failure → consistent ***bias*** to overestimate adherence/underestimate nonadherence
- We assume lack of adequate response as “treatment-resistance” and lack of efficacy for the antipsychotic for that patient
  - This is a possible explanation for high dosing of antipsychotics, polypharmacy with other antipsychotics, and combination treatment with anticonvulsants
- This is a no-win cycle: adherence is even more of a challenge with complex regimens

- ➢ Poor adherence to antipsychotic medication is common and likely exists in your practice
- ➢ Poor adherence will drive poor outcomes

Velligan DI, et al. *Psychiatr Serv*. 2007;58(9):1187-1192.

New Guidance

- 2020 American Psychiatric Association *Practice Guideline for the Treatment of Patients with Schizophrenia*
  - LAI antipsychotic medication is advocated *if they **prefer** such treatment* **or** *if they have a history of poor or uncertain **adherence***

LAI = long-acting injectable.

Keepers GA, et al. *Am J Psychiatry*. 2020;177(9):868-872.

Peter

Peter returns to school but does not take his medication regularly.

He is embarrassed to take his pills since he does not want to explain to his roommate why he has to take pills.

Peter is also concerned that he might have to go back to the locked inpatient psychiatric unit and falling further behind in school.

Caregiver Attitudes about Long-Acting Injectable Antipsychotics

- Survey of caregivers in the United States: Symptoms that are most worrisome include **positive symptoms** such as delusions, hallucinations, disorganized behavior, thought disorder, verbal aggression, and physical aggression, and when the patient is out of the hospital, **negative symptoms** also become worrisome, including social withdrawal, lack of pleasure/interest in everyday life, and loss of motivation
  - Most caregivers feel that they act as a mediator between the medical team and the patient, and that they are responsible for the patient's therapeutic adherence
  - Caregivers generally have fewer barriers caring for patients on LAI antipsychotics than for those not on LAI antipsychotics
  - Caregivers were interested in learning more about schizophrenia and its treatment, including information on new medications, coping as a caregiver, understanding specific symptoms, housing and helping patients become independent, and establishing support groups in their areas

Citrome L, et al. Educational needs of caregivers of patients with schizophrenia: results of a national survey study. Poster presented at: 2020 Psych Congress Virtual Experience; September 10–13, 2020.

Patient Attitudes about Long-Acting Injectable Antipsychotics

- Survey in France: Patients with schizophrenia with ≥ 3 months treatment with an LAI antipsychotic, injections were the favored dosage form
  - 67% said they felt better having received an injectable treatment than they felt before
  - 51% considered injectable therapy to be more effective than other medication
  - 70% felt better supported in their illness by virtue of regular contact with the doctor or nurse who administered their injection

Caroli F, et al. *Patient Prefer Adherence*. 2011;5:165-171.

Clinician Attitudes about Long-Acting Injectable Antipsychotics

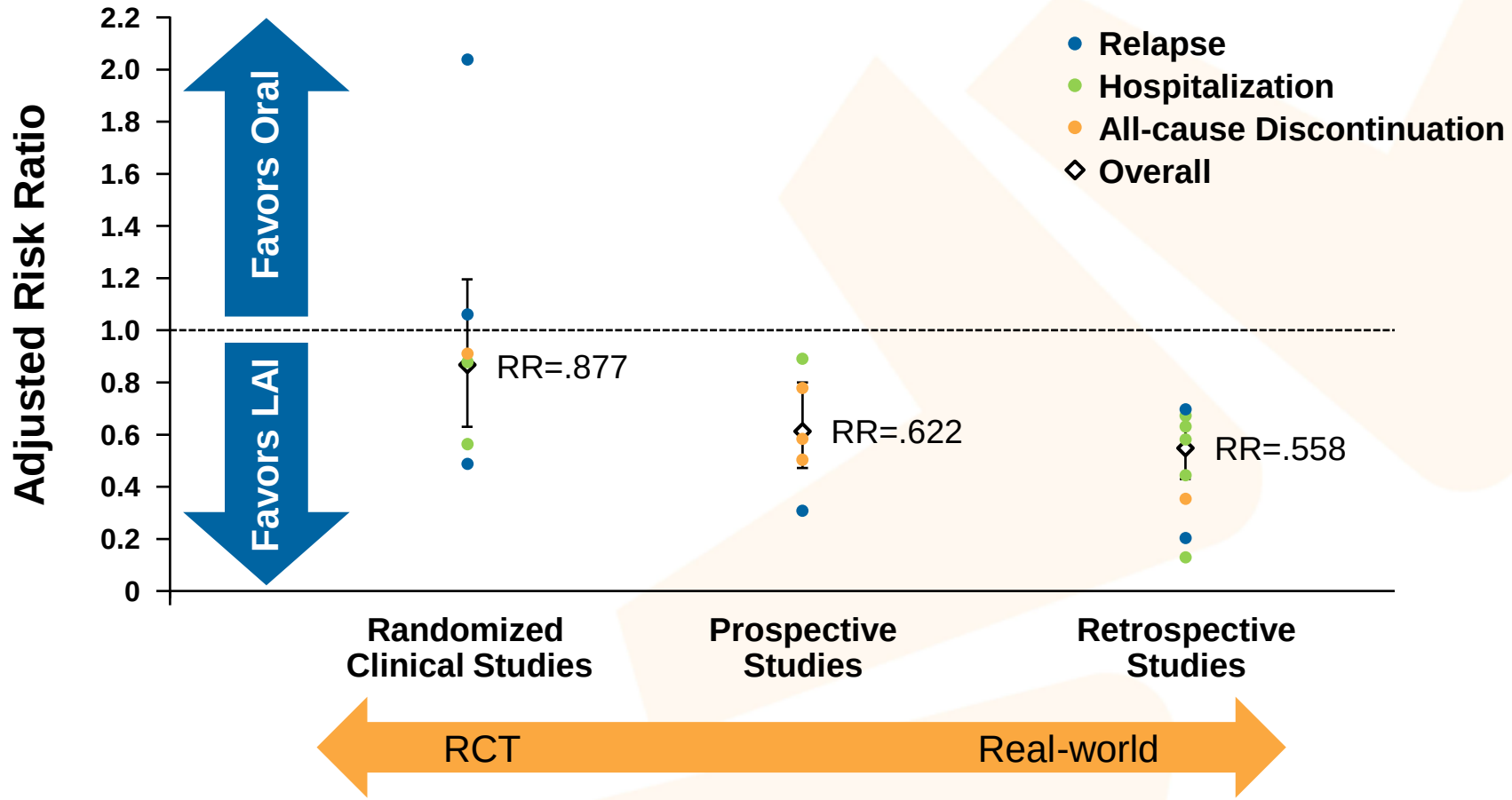
- Survey at an international conference: The most important factor against Rx LAI is presumed sufficient adherence with oral antipsychotic treatment
  - FGA LAIs are avoided due to the threat of EPS, and SGA LAIs are associated with high treatment costs
  - < 36% of participants' patients have ever been offered antipsychotic depot treatment
- Survey in Switzerland: 67% of the patients did not receive information about depot antipsychotics from their psychiatrist
- Survey of psychiatrists and psychiatric NPs/PAs in the United States: Perceived barriers to LAI use were needle aversion, logistical issues, increased cost and short dosing intervals, as well as insurance, patient perception of LAI antipsychotics as signifying disease severity, lack of staff to administer injections, and treatment availability

EPS = extrapyramidal symptoms; FGA = first-generation antipsychotic; SGA = second-generation antipsychotic.

Heres S, et al. *J Clin Psychiatry*. 2006;67(12):1948-1953. Jaeger M, et al. *Psychiatry Res*. 2010;175(1-2):58-62. Citrome L, et al. Barriers to the use of long-acting injectable antipsychotics in patients with schizophrenia: a survey to understand clinician educational needs. *Eur Neuropsychpharmacol*. 2020;40(Suppl 1):S318-S319.

Long-Acting Injectable Antipsychotics: *Impact on Treatment Outcomes*

Real-World Studies Favor Use of LAI Antipsychotics

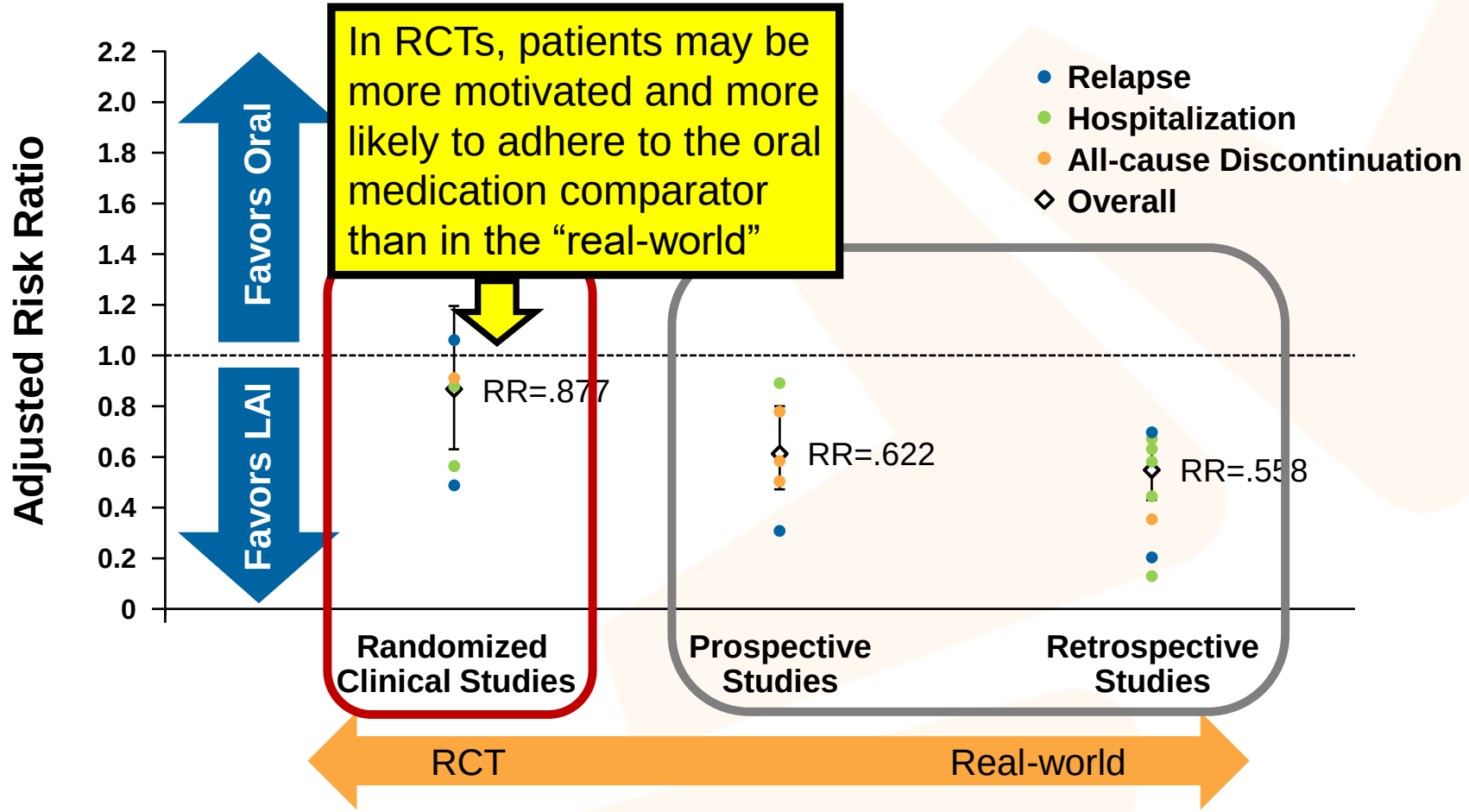


As study design shifts toward real-world populations, LAI formulations display significant advantages

RCT = randomized controlled trial.

Kirson NY, et al. *J Clin Psychiatry*. 2013;74(6):568-575.

Real-World Studies Favor Use of LAI Antipsychotics



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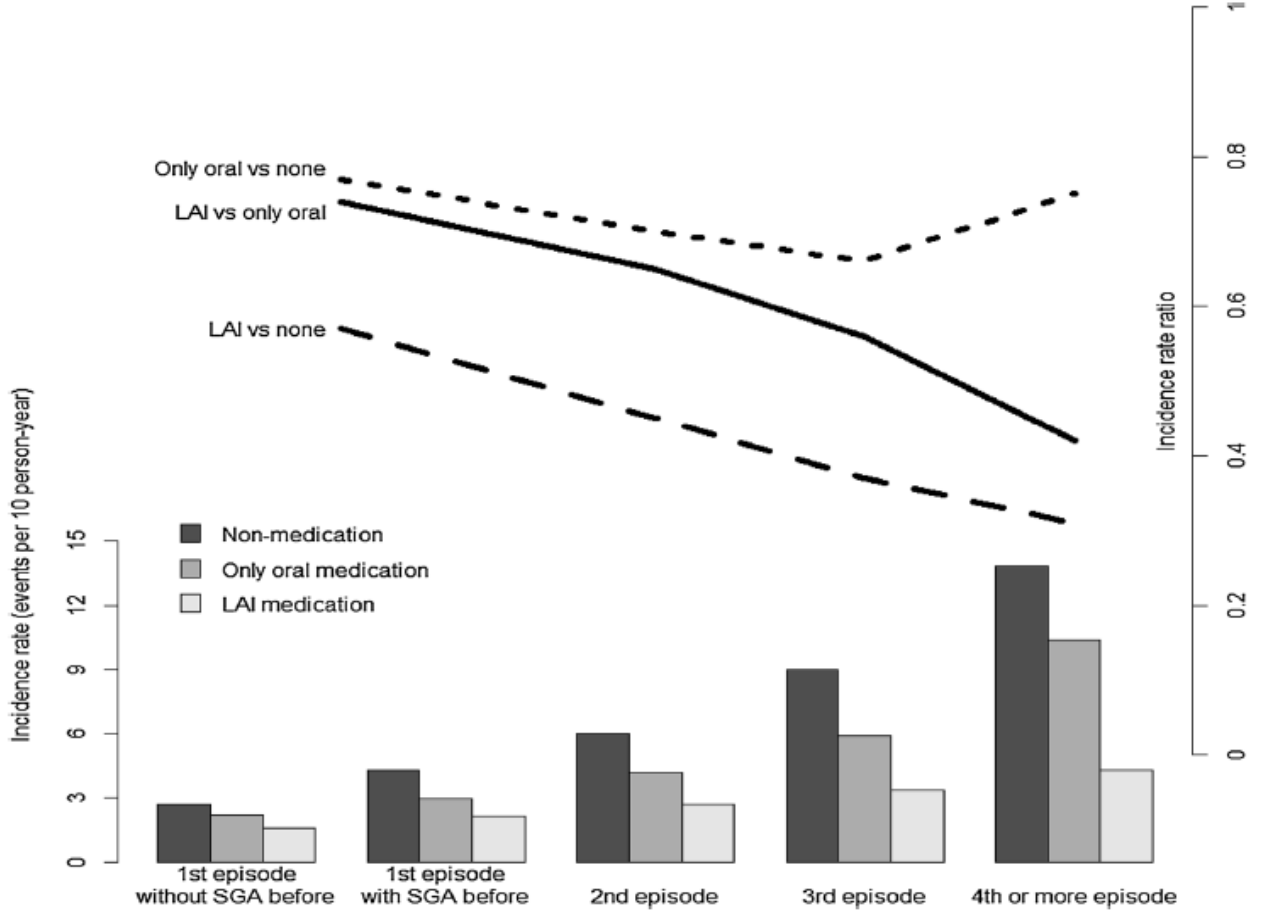
RCT = randomized controlled trial.

Kirson NY, et al. *J Clin Psychiatry*. 2013;74(6):568-575.

LAI Antipsychotics Reduce Readmission Rates

In a recent study comparing the effectiveness of LAIs and oral antipsychotics in preventing readmission in patients with schizophrenia, data collected from 75,274 patients hospitalized with schizophrenia over a 10-year period (2008–2017) showed that LAI treatment reduced the readmission rate by 29% compared with oral medication in real-world settings. Moreover, LAIs reduced the readmission rate by 58% in patients with repeated admissions



Kim HO, et al. *Ann Gen Psychiatry*. 2020;19:1.

Key Learning Point

LAI antipsychotics may be more useful to patients with repeated admissions in real-world settings compared with only oral medication.

Potential Advantages of LAI Antipsychotics

- Reduces dosage deviations
- Eliminates guessing about adherence status
- **Helps disentangle reasons for poor response to medication: can focus on psychosocial issues/stressors, or possibility of substance use, etc., as a cause for exacerbation of illness or relapse**
- Eliminates need for the patient to remember to take a daily pill
- Enables prescribers to avoid first-pass metabolism; therefore, a better relationship between dose and blood level exists
- Results in predictable and stable plasma levels
- Eliminates abrupt loss of efficacy if dose missed
- Many patients prefer them, especially if already receiving them

➢ LAI antipsychotics can address the guess-work about adherence status and patients often prefer them, provided that they are offered this as a choice

McEvoy JP. *J Clin Psychiatry*. 2006;67 Suppl 5:15-18. Olfson M, et al. *Schizophr Bull*. 2007;33(6):1379-1387. Kane JM, et al. *J Clin Psychiatry*. 2003;64 Suppl 12:5-19. Patel MX, et al. *J Psychiatr Ment Health Nurs*. 2005;12(2):237-244.

Potential Obstacles of LAI Antipsychotics

- ***Anti-shot sentiment/stigma***
  - Most clinicians report using LAI atypical antipsychotics in **< 10% of patients**
  - Psychiatrists have **not offered** an LAI antipsychotic to nearly two-thirds of their patients
- Lack of infrastructure in outpatient settings
- Need to refrigerate, store, reconstitute, etc.
- Overburdened public agencies
- Frequency of injections and consequent inconvenience for staff and patients
- Need to take concomitant medications orally
- Acquisition cost

Velligan DI, et al. *J Clin Psychiatry*. 2009;70 Suppl 4:1-46. Heres S, et al. *J Clin Psychiatry*. 2006;67(12):1948-1953. McEvoy JP. *J Clin Psychiatry*. 2006;67 Suppl 5:15-18. Kane JM, et al. *J Clin Psychiatry*. 2003;64 Suppl 12:5-19. Citrome L. *Expert Rev Neurother*. 2013;13(7):767-783.

LAI Options in the United States

- **First-generation antipsychotics** (all are in sesame seed oil)
  - Haloperidol decanoate, usually once monthly
  - Fluphenazine decanoate, usually every 2 weeks
- **Second-generation antipsychotics** (all IM formulations are water-based)
  - Risperidone- or paliperidone-containing formulations
    - Risperidone microspheres every 2 weeks
    - Risperidone subcutaneous LAI once monthly
    - Paliperidone palmitate monthly
    - Paliperidone palmitate every 3 months
  - Aripiprazole-containing formulations
    - Aripiprazole monohydrate once monthly
    - Aripiprazole lauroxil once monthly, every 6 weeks, or every 2 months
  - Olanzapine pamoate every 2 weeks or once monthly

Citrome L. *Expert Rev Neurother*. 2017;17(10):1029-1043. Citrome L. *Clin Schizophr Relat Psychoses*. 2018;12(3):130-141.

In the Pipeline: Additional Choices

- **Risperidone- or paliperidone-containing formulations**
  - Risperidone subcutaneous LAI, every 1 or 2 months (Teva)
  - Risperidone intramuscular LAI that does not require oral supplementation or a loading dose, once monthly (Rovi)
  - Paliperidone palmitate every 6 months (Janssen)
  - Risperidone extended-release oral capsules, once weekly (Lyndra)
- **Aripiprazole-containing formulations**
  - Aripiprazole monohydrate every 2 months (Otsuka/Lundbeck)

ClinicalTrials.gov Identifier: NCT03503318. Correll CU, et al. *NPJ Schizophr*. 2020;6(1):37. ClinicalTrials.gov Identifier: NCT03345342. ClinicalTrials.gov Identifier: NCT04567524. ClinicalTrials.gov Identifier: NCT04030143.

Key Learning Point

There are several risperidone-, paliperidone-, and aripiprazole-containing formulations in different stages of clinical development.

First-Generation Antipsychotic LAIs in More Detail

- Haloperidol decanoate
  - Approved for use in the United States in 1986; among inpatients in New York state, the average dose is 135 mg administered monthly (maximum approved dose is 450 mg/4 weeks)
  - Available as 50 and 100 mg/mL in 1- and 5-mL ampules/vials, 21 G needles used; do not exceed 3 mL injection volume
  - No oral supplementation; no refrigeration needed
- Fluphenazine decanoate (IM or sc)
  - Fluphenazine enanthate was approved for marketing in 1967 and in 1972, fluphenazine decanoate replaced it as it has a longer half-life; among inpatients in New York state, the average dose is ~ 38 mg administered every 2 weeks (maximum approved dose is 100 mg/2 weeks)
  - Available as 25 mg/mL 5-mL vials, 21 G needles used
  - No oral supplementation; no refrigeration needed

Citrome L. *Expert Rev Neurother*. 2013;13(7):767-783.

What's different among the risperidone- or paliperidone-containing LAIs?

	Risperidone Subcutaneous	Risperidone Microspheres	Paliperidone Palmitate Monthly	Paliperidone Palmitate Every 3 Months
Brand Name (US)	Perseris®	Risperdal Consta®	Invega® Sustenna®	Invega Trinza®
Year Approved	2018	2003	2009	2015
Active Moiety	Risperidone and paliperidone	Risperidone and paliperidone	Paliperidone	Paliperidone
Approved Indications (all adult)	Schizophrenia	Schizophrenia; bipolar I disorder maintenance treatment (monotherapy or adjunctive to lithium or valproate)	Schizophrenia; schizoaffective disorder (monotherapy or adjunctive to mood stabilizers or antidepressants)	Schizophrenia
Dosage Forms/Strengths	Syringe kits: 90 mg, 120 mg	Vial kits: 12.5 mg, 25 mg, 37.5 mg, 50 mg	Injectable suspension: 39 mg, 78 mg, 117 mg, 156 mg, 234 mg	Injectable suspension: 273 mg, 410 mg, 546 mg, 819 mg
Requires Adding Diluent/Liquid	Yes	Yes	No	No
Injection Type	Subcutaneous	Intramuscular	Intramuscular	Intramuscular
Injection Sites	Abdomen	Deltoid or gluteal muscle	Deltoid or gluteal muscle	Deltoid or gluteal muscle
Needle Gauge and Length	18 G and 5/8-inch	20 G and 2-inch, 21 G and 1-inch	22 G and 1.5-inch, 23 G and 1-inch	22 G and 1 or 1.5-inch
Injection Volume	0.6 mL (90 mg), 0.8 mL (120 mg)	Approximately 2 mL	156 mg/mL; range 0.25 mL (39 mg) to 1.5 mL (234 mg)	312 mg/mL; range 0.9 mL (273 mg) to 2.6 mL (819 mg)
Injection Interval	4 weeks	2 weeks	4 weeks	12 weeks

Citrome L. *Clin Schizophr Relat Psychoses*. 2018;12(3):130-141.

What's different among the risperidone- or paliperidone-containing LAIs? (cont'd)

	Risperidone Subcutaneous	Risperidone Microspheres	Paliperidone Palmitate Monthly	Paliperidone Palmitate Every 3 Months
Brand Name (US)	Perseris®	Risperdal Consta®	Invega® Sustenna®	Invega Trinza®
Starting Dose	90 or 120 mg	25 mg	234 mg day 1 and 156 mg day 8 (deltoid)	After treatment with 1-month paliperidone palmitate for at least 4 months: 273 mg, 410 mg, 546 mg, 819 mg (3.5 × the last dose of the once monthly formulation)
Maintenance Dose	90 or 120 mg	25 mg, maximum 50 mg/2 weeks	117 mg, range 39–234 mg/4 weeks	Same as above
Half-life	9–11 days	3–6 days	25–49 days	84–95 days (deltoid), 118–139 days (gluteal)
Oral Supplementation?	No	21 days after the initial injection and after any change in dose	No	No
Stored Refrigerated?	Yes	Yes	No	No

Citrome L. *Clin Schizophr Relat Psychoses*. 2018;12(3):130-141.

What's different among the long-acting IM aripiprazole-containing formulations?

	Aripiprazole Monohydrate	Aripiprazole Lauroxil
Brand name (US)	Abilify Maintena®	Aristada® (and Aristada Initio®)
Year Approved	2013	2015 (2018)
Other Indications	Bipolar disorder	No
Injection Sites	Deltoid or gluteal	Deltoid (441 mg dose and NCD 675 mg dose*) or gluteal (all doses) – INJECT RAPIDLY!
Needle Gauge	21 G, 22 G, or 23 G	20 G or 21 G
Injection Volume	2 mL (400 mg)	1.6 to 3.9 mL
Injection Interval	Every 4 weeks	Every 4 weeks (all doses), every 6 weeks (882 mg), or every 2 months (1064 mg)
Starting Dose	400 mg	441, 662, 882, or 1064 mg
Maintenance Dose	300 or 400 mg (adjust for CYP2D6 or CYP3A4 inhibitors; can't give with CYP3A4 inducers)	441, 662, 882, or 1064 mg (adjust for CYP2D6 or CYP3A4 modulators)
Half-life	29.9 days (300 mg), 46.5 days (400 mg)	53.9–57.2 days; 15–18 days (NCD formulation)
Oral Supplementation	Yes (14 days)	1 day with NCD 675 mg*, otherwise 21 days
Reconstitution	Yes, but dual-chamber syringe available	No
Refrigeration	No	No

***NCD = a single 30 mg dose and initial injection of nano-crystal formulation (Aristada Initio®) can substitute for 21-day oral aripiprazole supplementation. Updated from: Citrome L. *Expert Rev Clin Pharmacol*. 2016;9(2):169-186. Citrome L. *Expert Rev Neurother*. 2017;17(10):1029-1043. Farwick S, et al. *J Psychiatr Pract*. 2019;25(2):82-90.**

Key Learning Point

Injection techniques differ from formulation to formulation.

What about olanzapine pamoate?

- OLAI is a crystalline salt of olanzapine and pamoic acid in water, approved in 2009 for schizophrenia; no other approved indications
- Efficacy was established in 2 double-blind, randomized clinical trials of OLAI for the treatment of ***acute*** schizophrenia and for the ***maintenance*** of response
- Therapeutic OLAI dosages are 150 mg every 2 weeks, 210 mg every 2 weeks, 300 mg every 2 weeks or every 4 weeks, and 405 mg every 4 weeks
- Gluteal injection only, 19 G needle, 1–2.7 mL volume, reconstitution required, stored at room temperature, no oral supplementation but higher dose at start
- OLAI has essentially the same general tolerability as that of oral olanzapine; however, with the depot there is the additional risk of a **post-injection delirium sedation syndrome** occurring at a rate of 0.07% of injections, requiring a risk-management plan that includes **observing the patient for 3 hours after each injection**

OLAI = olanzapine pamoate.

Citrome L. *Patient Prefer Adherence*. 2009;3:345-355.

How to Choose a Long-Acting Injectable Antipsychotic from *A* to *G*

A: Is the patient demonstrating adequate efficacy and tolerability on oral fluphenazine, haloperidol, risperidone, paliperidone, olanzapine, or aripiprazole?

- Offer and switch to the corresponding LAI formulation
- For patients receiving oral risperidone, ***consider paliperidone palmitate instead of risperidone microspheres*** because of convenience
  - *No requirement for oral Rx upon initiation*
  - *Less frequent injections, eventually q3 months*
  - *Supplied in prefilled syringes*
  - *Smaller needle bore, lower injection volume*
  - *No requirement for refrigeration*

Updated from: Citrome L. *Expert Rev Neurother*. 2017;17(10):1029-1043.

B: What is the downside to fluphenazine or haloperidol? What is the downside to olanzapine LAI?

- For patients receiving oral fluphenazine or haloperidol, concomitant oral anticholinergics for the management of motoric adverse effects are problematic – especially because anticholinergic agents ***can interfere with memory*** and other cognitive functions
  - Exposure to benztropine or other anticholinergics can also increase the risk to develop tardive dyskinesia, and can make existing tardive dyskinesia worse

- For patients receiving oral olanzapine, olanzapine pamoate will require close *monitoring*

Updated from: Citrome L. *Expert Rev Neurother*. 2017;17(10):1029-1043.

C: What do we need to know about aripiprazole?

- For patients receiving oral aripiprazole there are 2 competing formulations of LAI aripiprazole in the United States—aripiprazole monohydrate and aripiprazole lauroxil—they have differing doses and injection intervals, as well as initiation strategies

Updated from: Citrome L. *Expert Rev Neurother*. 2017;17(10):1029-1043.

D: Is the patient being treated acutely and avoiding/minimizing oral Rx is desired?

- Consider LAI antipsychotics that do not require oral supplementation and where the clinical trials have demonstrated acute efficacy—paliperidone palmitate or olanzapine pamoate, and possibly aripiprazole lauroxil/NCD

- A new subcutaneous long-acting injectable formulation of risperidone is also now available—administered monthly with no oral supplementation required—and efficacy established with acute use
  - Dosage equivalents are 3 mg/day oral = 90 mg sc, 4 mg/day oral = 120 mg sc

Updated from: Citrome L. *Expert Rev Neurother*. 2017;17(10):1029-1043.

E: Are weight gain and metabolic adverse effects a concern for this individual patient?

- Consider an aripiprazole LAI, paliperidone palmitate, risperidone subcutaneous LAI, and risperidone microspheres among the SGA LAIs; avoid olanzapine pamoate
- Can possibly consider the FGA LAIs as well

Updated from: Citrome L. *Expert Rev Neurother*. 2017;17(10):1029-1043.

F: Are prolactin-related adverse effects a clinical concern for this individual patient?

- Consider an aripiprazole LAI
- Avoid paliperidone palmitate, risperidone microspheres, risperidone subcutaneous LAI, or FGA LAIs

Updated from: Citrome L. *Expert Rev Neurother*. 2017;17(10):1029-1043.

G: Is acquisition cost the primary concern?

- FGA LAIs may be the only option available but using concomitant oral anticholinergics for the management of motoric adverse effects add complexity and can interfere with memory; overall health care costs are not always lower!
- There are sometimes shortages of FGA LAIs
- *Patient-assistance programs* should be considered for outpatients who are not covered to receive SGA LAI options

Updated from: Citrome L. *Expert Rev Neurother*. 2017;17(10):1029-1043.

Manufacturers Have Been Conducting Studies to Help Characterize Their Agents

- Double-blind, randomized, 6-month, aripiprazole lauroxil and paliperidone palmitate (Alkermes)
  - Both were efficacious and well-tolerated for initiating treatment of schizophrenia in the hospital and continuing outpatient treatment
- Open-label, randomized, 15-month, paliperidone palmitate and oral antipsychotics in patients with schizophrenia and a history of incarceration (Janssen)
  - Paliperidone palmitate demonstrated superiority compared to oral antipsychotics in delaying time to treatment failure, including arrest/incarceration and psychiatric hospitalization
- Open-label, randomized, 1-year aripiprazole monohydrate and paliperidone palmitate in a psychosis/substance use disorder population (Otsuka/Lundbeck)
  - Aripiprazole monohydrate compared to paliperidone palmitate improved substance craving and quality of life
- Open-label, randomized, 6-month, aripiprazole monohydrate and paliperidone palmitate (Otsuka/Lundbeck)
  - Superior improvements on clinician-rated health-related quality of life and a favorable tolerability profile with aripiprazole monohydrate

Weiden PJ, et al. *J Clin Psychiatry*. 2020;81(3):19m13207. Alphs L, et al. *J Clin Psychiatry*. 2015;76(5):554-561. Cuomo I, et al. *Neuropsychiatr Dis Treat*. 2018;14:1645-1656. Naber D, et al. *Schizophr Res*. 2015;168(1-2):498-504.

Key Learning Point

Consider reviewing studies on different LAI formulations to better select LAIs for each individual patient, including initiating treatment in the hospital, continuing outpatient treatment, delaying time to treatment failure, substance craving, quality of life, and tolerability.

Bottom Line: Effect Sizes in Maintenance Treatment Similar across the Medications and Indications

Disorder	Antipsychotic	Relapse or Recurrence		
		Rate (%)		NNT
		Placebo	Drug	(95% CI)
Schizophrenia	Paliperidone palmitate monthly, flexibly dosed, 39–156 mg/4-weeks	34.0	9.6	5 (4–7)
	Paliperidone palmitate 3-month, flexibly dosed, 273–819 mg/12-weeks	29.0	8.8	5 (4–9)
	Aripiprazole monohydrate, 400 mg/4-weeks	39.6	10.0	4 (3–5)
	Olanzapine pamoate 150 mg/2-weeks	29.2	15.7	8 (5–26)
	Olanzapine pamoate 300 mg/2-weeks	29.2	5.0	5 (4–7)
	Olanzapine pamoate 405/4-weeks	29.2	12.3	6 (4–12)
Schizoaffective Disorder	Paliperidone palmitate monthly, flexibly dosed, 78–156 mg/4-weeks	33.5	15.2	6 (4–11)
Bipolar Disorder	Risperidone microspheres, adjunctive therapy, flexibly dosed, 25–50 mg/2-weeks	45.8	23.1	5 (3–16)
	Risperidone microspheres, monotherapy, flexibly dosed, 25–50 mg/2-weeks	56.3	30.0	4 (3–7)
	Aripiprazole monohydrate, 400 mg/4-weeks	51.1	26.5	5 (3–8)

Prevention of relapse or recurrence as quantified using NNT vs placebo
(vs 45 mg/4 weeks for olanzapine pamoate), data from US registration trials

Citrome L. *Expert Rev Neurother*. 2017;17(10):1029-1043.

What has Not Changed with COVID-19 Public Health Emergency?

- LAIs remain superior to their oral equivalent in helping patients remain relapse-free and out of the hospital
- People are on LAIs for a reason:
  - More convenient
  - Recommended due to partial adherence
  - They wanted to stop the daily reminder of being ill (taking a pill, having a parent or caregiver asking every day, “Did you take your medicine?”)
  - Too cognitively impaired to be sufficiently adherent, despite wanting to be
- Insight into illness fluctuates and, on some days, adherence is in jeopardy, even for some of our most adherent patients
- Those who have only been able to remain in the community because of their LAI regimen, and all other attempts at treatment had failed

Successful Patient-Provider Communication

Patient and Physician Barriers Can Interfere with Adherence and the Therapeutic Alliance in Schizophrenia

- **Patient barriers**
  - Communication difficulties
  - Negative symptoms
  - Cognitive symptoms
  - Stigma associated with schizophrenia
- **Clinician barriers**
  - Underestimation of the importance of the relationship
  - Hopelessness conveyed to the patient
  - Lack of interest in the patient's life goals and other issues important to him/her

Jung E, et al. *Psychother Res*. 2014;24(2):171-183. Personal communication (Dr. Citrome). Velligan DI, et al. *J Clin Psychiatry*. 2009;70 Suppl 4:1-46. Walsh J. *Clin Soc Work*. 2011;39(1):1-8. Weiden PJ. *J Psychiatr Pract*. 2002;8(6):386-392.

Optimizing Medication Adherence: *Practical Tips*

- If the patient is unwilling to adhere:
  - Intervention should focus on strengthening perceived benefits of medication and minimizing perceived negatives
  - Motivational interviewing will help

- If the patient cannot adhere:
  - Intervention should include compensatory behavioral measures (eg, moving pills to obvious locations, establishment of routines, use of self-monitoring tools), and consider LAI antipsychotics

Interventions: *Communication Style*

- Basic premise of **MOTIVATIONAL INTERVIEWING**: a patient's ambivalence to change is normal and that all patients vary in their readiness to change
- Use open-ended questions and reflective listening
- Remember **RULE**
  - ***Resist*** making too many suggestions
  - ***Understand*** the patient's motivation
  - ***Listen*** with a patient-centered empathic approach
  - ***Empower*** the patient

Haque SF, et al. Motivational interviewing: The RULES, PACE, and OARS. *Current Psychiatry*. 2019;18(1):27-28. Lewis-Fernández R, et al. *J Clin Psychiatry*. 2018;79(3).

A Nonjudgmental Interview Approach Can Facilitate an Open Discussion of Medication Adherence

- ✓ Ask for the patient's view about medications
- ✓ Obtain sufficient information before responding
- ✓ Do not jump to conclusions; take comments at face value
- ✓ Explain that you want to hear what the patient really thinks, not what he/she thinks you want to hear
- ✓ If you want to respond, do not try to do too much and make sure you do not go beyond what the patient can accept for now
- ✓ As much as you can, try to keep the discussion about medication adherence positive—even enjoyable
- ✓ Above all, try to maintain and even strengthen the alliance, even if there is disagreement about the need for medication

Weiden PJ. *J Psychiatr Pract*. 2002;8(6):386-392. Weiden PJ. *J Clin Psychiatry*. 2007;68 Suppl 14:14-19.

A Nonjudgmental Interview Approach Can Facilitate an Open Discussion of Medication Adherence (cont'd)

Instead of:

Have you been taking your medications?

OR

You have been taking your medicines, right?

Start with:

Everyone misses doses of their medicines. Can you give me some idea of how many doses you usually miss in any given week? I just need a ballpark figure; you don't have to be exact.

Followed by:

Which doses do you miss the most – morning? evening? with meals? in between meals? This way we can figure out the best time of day to use these medications so we can minimize the number of times you may miss them.

Opening Gambits

Instead of:

“Let’s give you a shot!”

Start with:

“How would you like taking your medicines once a month instead of every day?”

Followed by:

“Yes, it is an injection, kind of like a flu shot. I wish there was one I can take instead of remembering to take my blood pressure medications every day!”

“No, it’s not like that shot you got in the Emergency Department. This is completely voluntary. If you don’t want the second shot, we can go back to pills.”

Peter

Peter's doctor offers him the option to "take a medication only once a month, and then maybe only once every 3 months instead of every day."

He is reluctant to take a medication that would be administered by injection.

Peer and Family Supports, Other Hints to Getting to Yes!

- NAMI educational groups will help demystify treatment
- A peer advocate receiving LAI antipsychotics can be very helpful
- Show what the syringe needle looks like; explain that there are choices that differ in needle gauge, how much is injected, and where, as well as differences in frequency of injections and flexibility in terms of timing (being early or late for an injection)

Bottom Line:
Communication Matters

- A study of communication patterns in the offer of LAI antipsychotics made by psychiatrists to patients with schizophrenia at 10 community mental health clinics found that
  - Only 9% of the communication of psychiatrists presenting LAI antipsychotics to patients focused on positive aspects
  - Consequently, only 11 of 33 LAI treatment recommendations (33%) were accepted by patients
  - During a post-visit interview, in which LAI antipsychotics were presented in a more positive light and with more information, 27 of 28 patients (96%) who seemed to decline the initial recommendation changed their mind, stating that they would be willing to try LAI treatment

Weiden PJ, et al. *J Clin Psychiatry*. 2015;76(6):684-690.

Conclusions

- Schizophrenia relapses result in poorer functioning over time, and potentially treatment resistance
- Adherence remains a challenge for many people
- LAIs positively impact treatment outcomes and patients often prefer them, provided that they are offered this as a choice
- Choosing the right LAI requires a collaborative medication partnership
- Engaging patients in their treatment and recovery requires care in how we communicate