

Tackling the Great Challenge of Medication Adherence in Schizophrenia

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Faculty Disclosure

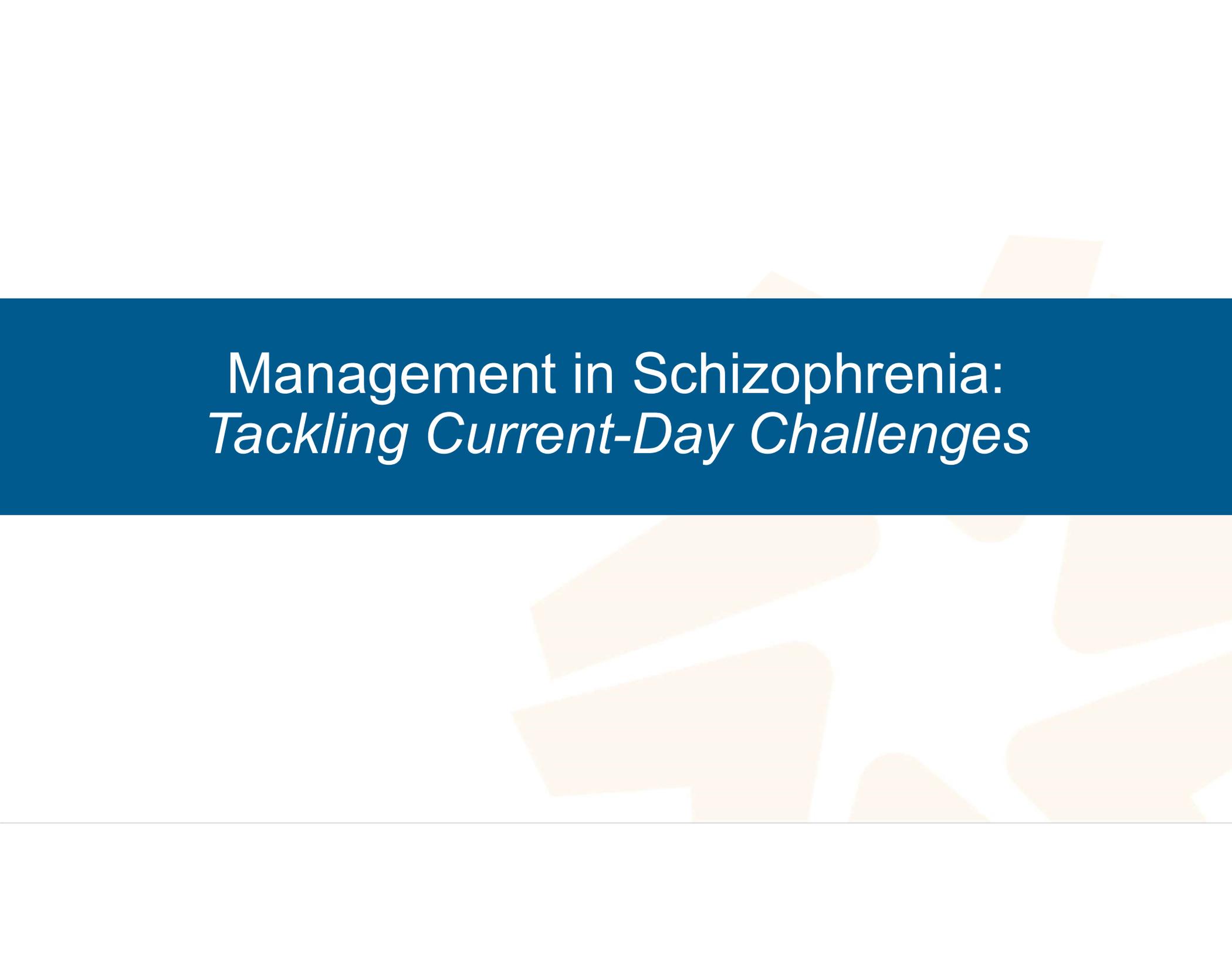
- **Dr. Citrome:** Consultant—Acadia, Alkermes, Allergan, Intra-Cellular Therapeutics, Janssen, Lundbeck, Merck, Neurocrine, Noven, Osmotica, Otsuka, Pfizer, Shire, Sunovion, Takeda, Teva, Vanda; Royalties—Springer Healthcare (book), *UpToDate* (reviewer), Wiley (Editor-in-Chief, *International Journal of Clinical Practice*); Shareholder (and spouse)—Bristol-Myers Squibb, Eli Lilly, J & J, Merck, Pfizer; Speaker—Acadia, Alkermes, Allergan, Janssen, Lundbeck, Merck, Neurocrine, Otsuka, Pfizer, Shire, Sunovion, Takeda, Teva.

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Learning Objectives

- Discuss the consequences associated with medication nonadherence in schizophrenia, its underlying causes, and strategies involving improved patient communication that may be utilized to overcome it
- Evaluate clinical data of current and emerging antipsychotics surrounding their efficacy, safety, tolerability, limitations, and implications on patient adherence
- Develop long-term treatment plans for schizophrenia that are informed by the latest evidence, address patient-centric barriers to medication nonadherence, and are communicated to patients in an effective manner



Management in Schizophrenia: *Tackling Current-Day Challenges*

Preventing Relapse Today: Makes a Difference for a Lifetime

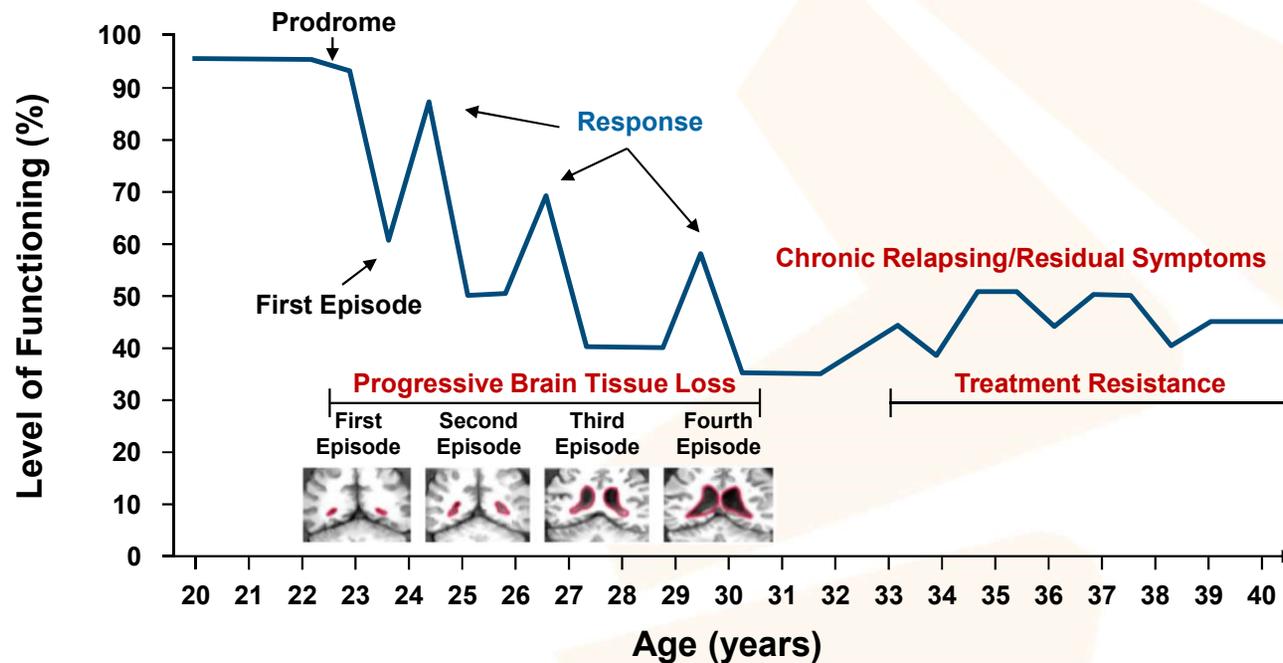
- ***Irreversible functional decline occurs with each relapse***
- Thus, preventing relapse is a key goal in many international clinical guidelines for schizophrenia
- “Minimizing risk of relapse in a remitted patient is a high priority, given the potential clinical, social, and vocational costs of relapse”

APA Work Group on Schizophrenia. Practice Guideline for the Treatment of Patients With Schizophrenia. Second Edition. 2010. https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/schizophrenia.pdf. Accessed February 22, 2019.

NICE. Psychosis and schizophrenia in adults: prevention and management. February 12, 2014. www.nice.org.uk/guidance/cg178. Accessed February 22, 2019.

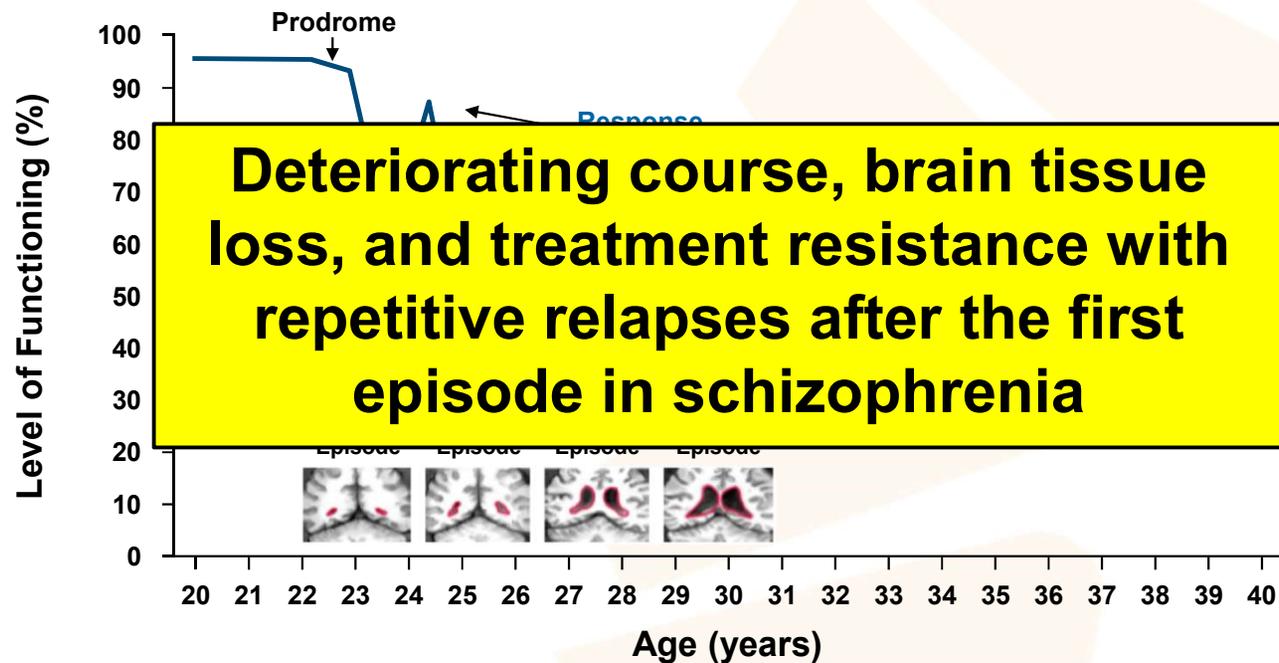
Barnes TR; Schizophrenia Consensus Group of British Association for Psychopharmacology. *J Psychopharmacol*. 2011;25(5):567-620.

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.

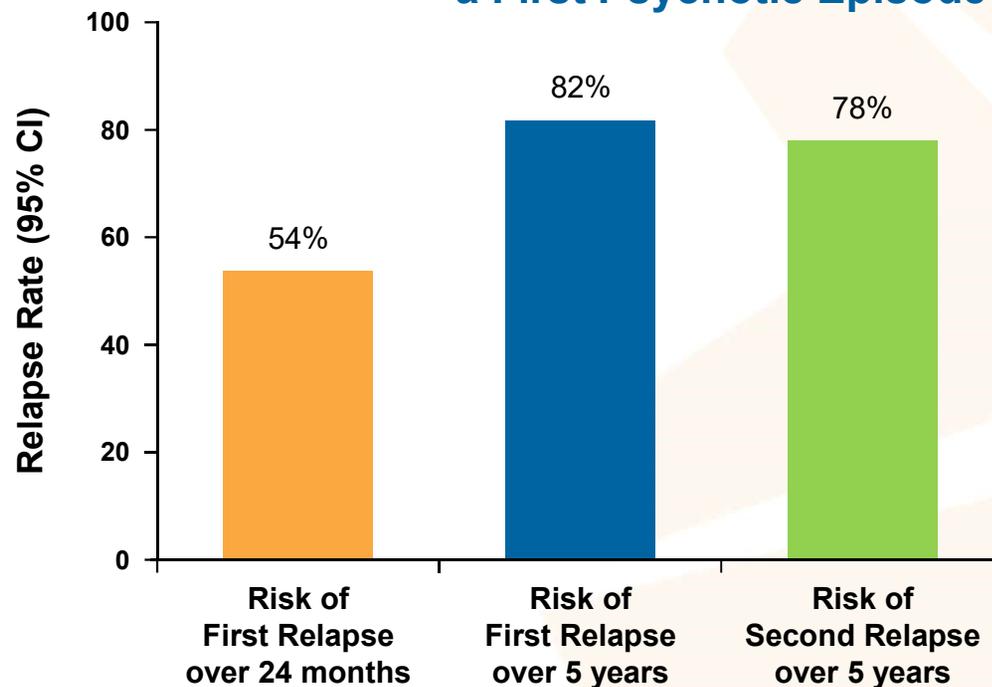
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Gardner KN, et al. *Current Psychiatry*. 2015;14(7):33-45. Lieberman JA. *J Clin Psychiatry*. 1996;57 Suppl 11:68-71. Birchwood M, et al. *Br J Psychiatry Suppl*. 1998;172(33):53-59.

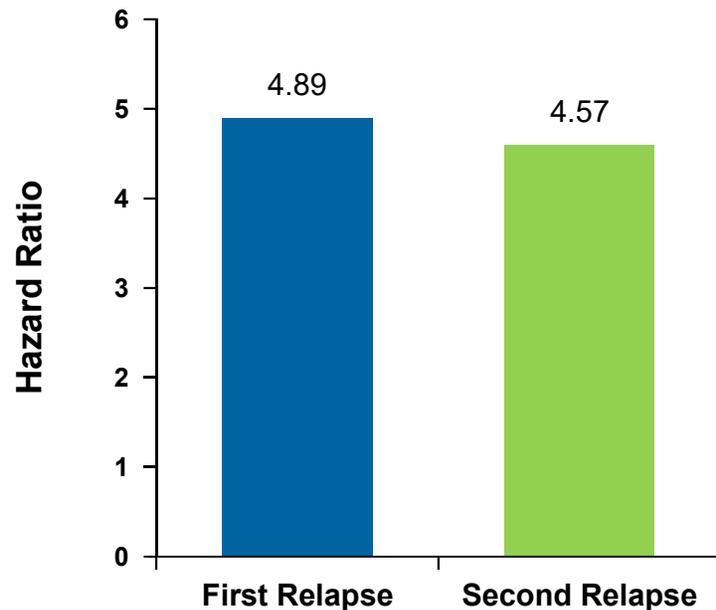
Unfortunately, Majority of Patients with Schizophrenia Will Relapse

Relapse Rates among Patients Experiencing a First Psychotic Episode



About 80% of first-episode patients suffered a relapse within 5 years

Stopping Medication is the Most Powerful Predictor of First-Episode Relapse



Sample of 104 patients with first-episode schizophrenia who responded to treatment of their index episode, but were at risk for relapse.

- Relapse risk is 5 × higher after a first-episode patient stops antipsychotic medication
- Predictors of nonadherence in first year:
 - Early adolescent premorbid adjustment ($P < .01$)
 - Worse premorbid cognitive function ($P = .01$)
 - Parkinsonian side effects ($P = .01$)
 - Worse executive function ($P = .02$)

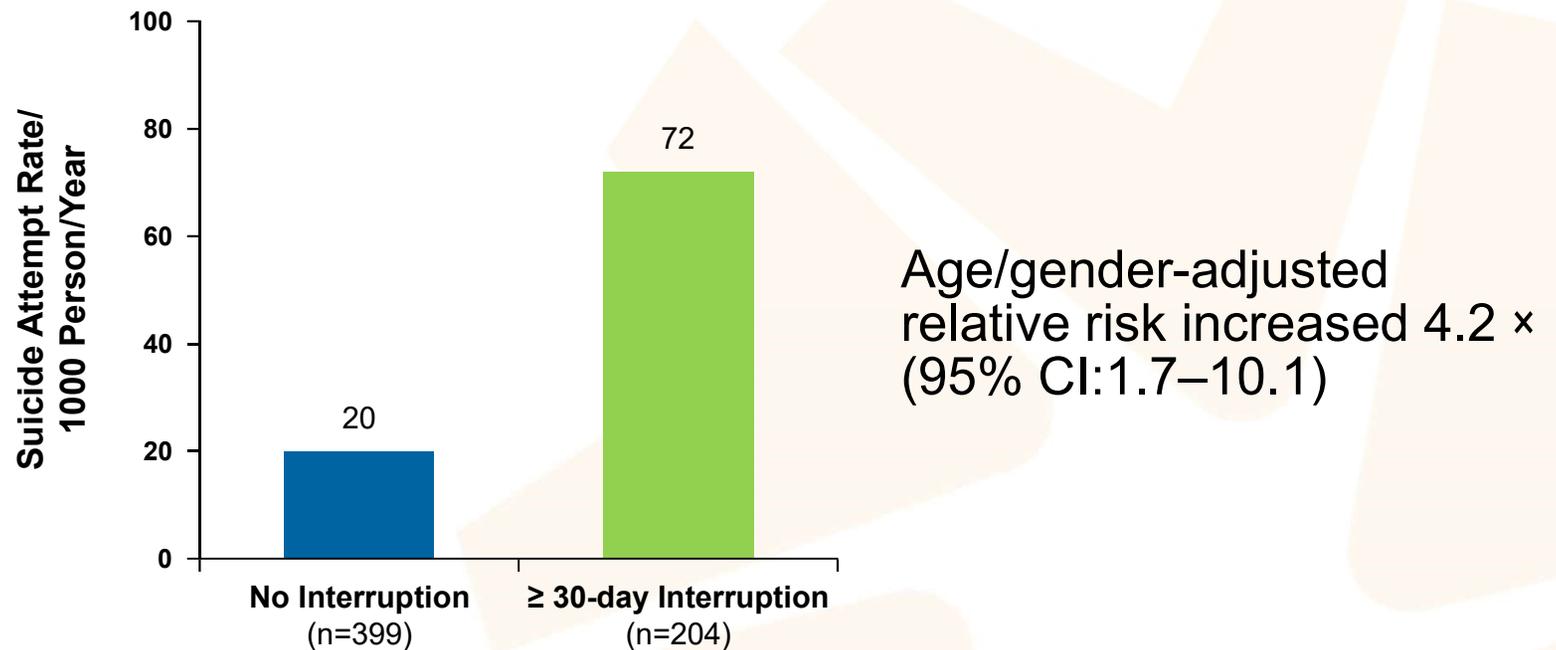
Consistent Medication Treatment is Key in Preventing Relapse

- ~ 50% of patients who discontinue/do not take antipsychotics will relapse within 3 to 10 months
- With drug discontinuation, there is no reliable indicator to differentiate the minority who will not relapse, from the majority who will relapse
- What I tell patients and families: within 2 years about 75% relapse when off medications vs 25% when on medications – medications are not perfect, but much better than not taking them
- Risk of relapse is 3 × as high ($75/25 = 3$) when not taking medication
- Number needed to treat (NNT) is 2 ($1/|.75-.25| = 2$)
- **For every 2 persons taking medication vs not taking medication you avoid 1 relapse event over a 2-year period**

Blackwell B. *Clin Pharmacol Ther.* 1972;13(6):841-848. Hirsch SR, et al (Eds). *Schizophrenia*. Oxford, England: Blackwell Science; 1995:443-468. APA Work Group on Schizophrenia. Practice Guideline for the Treatment of Patients With Schizophrenia. Second Edition. 2010. https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/schizophrenia.pdf. Accessed February 22, 2019. Citrome L. *Acta Psychiatr Scand.* 2010;121(2):94-102.

Urgent!

Suicide Attempts Increase When Therapy is Interrupted



Data obtained from drug-dispensing and hospital discharge records (Netherlands) for patients with schizophrenia (sample size, 603) in database (N=865,000) with drug interruption and ≥ 30 -day gap in treatment. Risk estimates were controlled for differences in age and gender.

When Treatments Fail

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

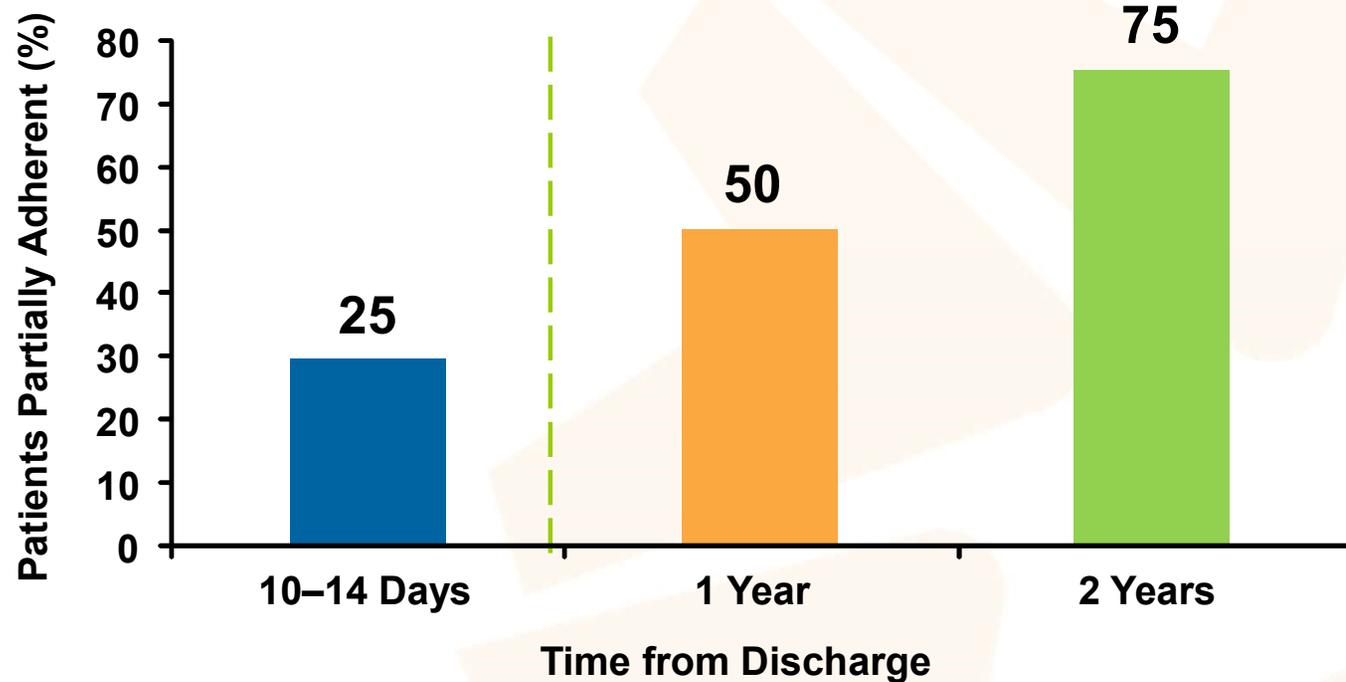
When Treatments Fail

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

Medication adherence is poor across most chronic physical and psychiatric disorders

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

Partial Adherence in Schizophrenia Begins Early and Prevalence Increases 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.

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

Risk Factors for Nonadherence

(but differs for each patient and can change over time)

Patient-related

- Poor insight
- Negative attitude toward medication
- Prior nonadherence
- Substance abuse
- Cognitive impairment

Environment/ Relationship-related

- Lack of family/social support
- Problems with therapeutic alliance
- Practical problems (financial, transportation, etc.)

Treatment-related

- Side effects
- Lack of efficacy/
continued symptoms

Societal-related

- Stigma attached to illness
- Stigma caused by medication side effects

Medication-Related Side Effects and Nonadherence

- Potential drivers
 - Level of distress rather than severity (as perceived by the patient and not by the clinician; eg, what is “mild” or “severe” is in the eye of the beholder)
 - Attribution to the medication (eg, “my teeth itch” can drive poor adherence)
 - Varies from patient to patient
- Most commonly associated with nonadherence
 - Weight gain (patient attitudes vary and may be offset by efficacy after many failures)
 - Sedation
 - Akathisia
 - Sexual dysfunction
 - Parkinsonian symptoms
 - Cognitive problems
- Influencing clinician response to a side effect is objective severity and ultimately safety and risk

Interventions: *First Address 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

What's the next step?

- If the adherence problem is that the patient **will not**, focus intervention on strengthening perceived benefits of medication and minimizing perceived costs/harms – use **Motivational Interviewing**
- If the adherence problem is that the patient **cannot**, then address barriers to adherence
 - Pill boxes in obvious locations
 - Self-monitoring tools
 - Establishment of routines
 - Consider **Long-Acting Injectable Medication**



Clinical Update:
*Available and Emerging Long-Acting Injectable
Antipsychotics for Schizophrenia*

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

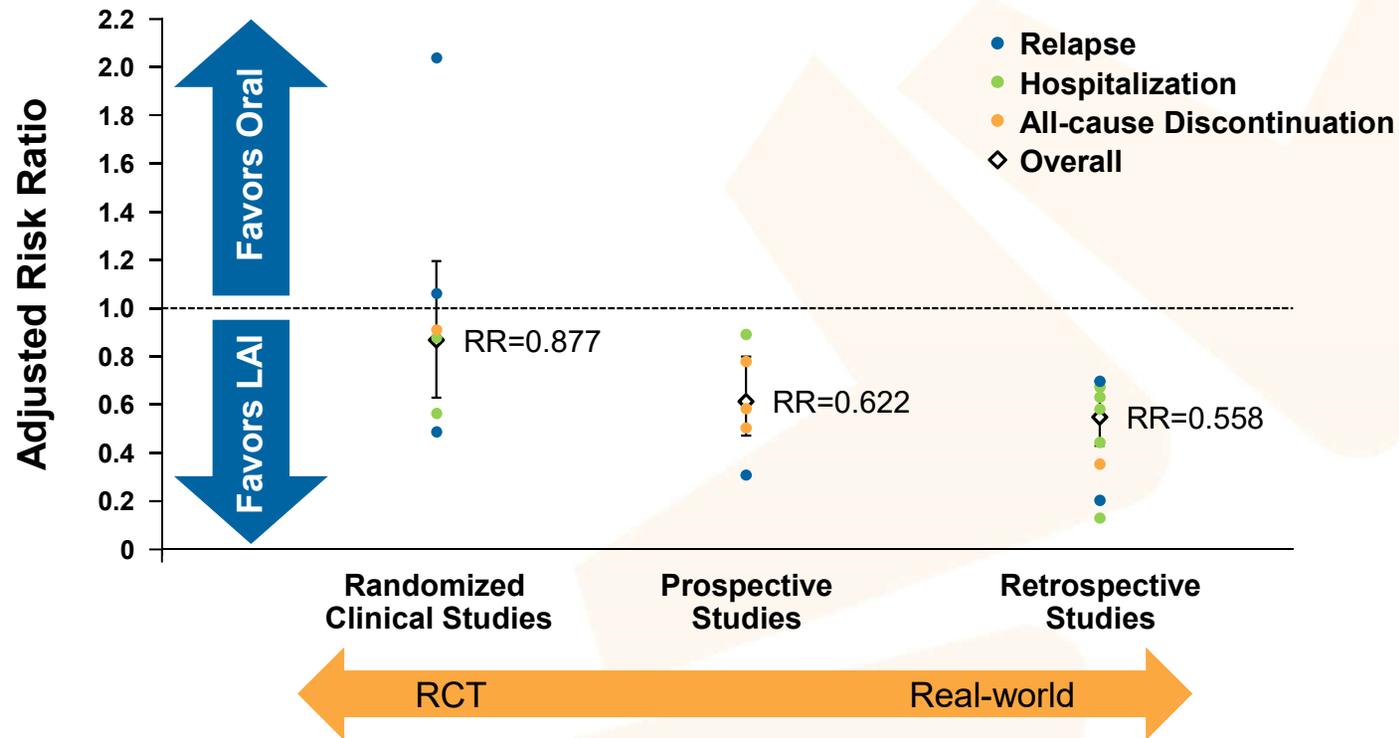
LAI = long-acting injectable. McEvoy JP. *J Clin Psychiatry*. 2006;67 Suppl 5:15-18. Olfson M, et al. *Schizophr Bull*. 2007;33(6):1379-1387. Kane JM, et al. *J Clin Psychiatry*. 2003;64 Suppl 12:5-19. Patel MX, et al. *J Psychiatr Ment Health Nurs*. 2005;12(2):237-244.

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.

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.

Is there a case for *earlier* use of LAI antipsychotics?

- Potentially decrease the percentage of time spent experiencing psychotic symptoms
 - In the first 2 years, experiencing psychotic symptoms is the strongest predictor of long-term symptoms and disability
- Potentially decrease number of psychotic episodes
 - Patients experience a decrease in treatment response with subsequent exacerbations
 - Neuropathological brain changes often progress with subsequent clinical episodes
- LAI antipsychotics allow for swift identification of overt nonadherence and eliminate covert nonadherence

Patients are Willing to Accept LAI Antipsychotic Therapy When Properly Informed

- In a survey of patients with > 3 months of LAI antipsychotic experience:
 - Injectable antipsychotics were the **preferred** formulation
 - 70% of patients felt better **supported** in their illness by virtue of regular contact with the doctor or nurse who administered their injection

LAI Options in the United States

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

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

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)
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 pill 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.

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, 19G 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.

Late Stage of Clinical Development

- BB-0817 – Phase 3
 - 6-month risperidone polyurethane implant
- Paliperidone palmitate 6-month – Phase 3
- Risperidone *in situ* microparticles – Phase 3
 - Risperidone once-monthly intramuscular formulation; does not require oral supplementation
 - Biodegradation of this risperidone formulation occurs slowly, providing a sustained and controlled release of medication for up to 1 month
- TV-46000 – Phase 3
 - Risperidone extended-release injectable suspension for subcutaneous use as maintenance treatment in adult patients with schizophrenia

NDA = new drug application.

Citrome L. *Expert Rev Neurother.* 2017;17(10):1029-1043. Citrome L. *Clin Schizophr Relat Psychoses.* 2018;12(3):130-141.
ClinicalTrials.gov Identifier: NCT03503318. ClinicalTrials.gov Identifier: NCT03345342.

Strategies to Improve Medication Adherence and Patient Outcomes

A Tale of Two Cases

Frank

- Frank is a 20-year-old White sophomore at a prestigious private university who lives at a fraternity house. He comes from a well-educated and wealthy family
- However, mental illness is no stranger to the family—Frank has an aunt and a great uncle who were diagnosed with schizophrenia and a cousin who committed suicide after several psychotic relapses and hospitalizations
- During the winter break, Frank’s mother becomes worried when Frank refuses to leave his room, does not allow any of his friends to visit him, and appears preoccupied with Satan and “the end of days”
- Frank is eventually coaxed into seeing his pediatrician (who is a family friend), and Frank passively allows his admission to a famous and well-respected inpatient psychiatric facility

Roger

- Roger is a 19-year-old African American freshman at the local state college
- He is the first in his family to attend college. Roger has ambitions to become a physician, based in part on the chronic physical ailments that his grandmother suffered with before she passed away in Roger'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 Roger is brought to the local emergency department for an emergency evaluation. He is admitted to the locked inpatient psychiatric unit

Who will have the better outcomes?

- A. Frank, because he was admitted to a famous and well-respected inpatient psychiatric facility, and the family has access to many helpful resources
- B. Roger, because he doesn't have a family history of psychotic disorders
- C. Both have very poor prognoses
- D. Both can do well, provided that they continue in treatment

Use your keypad to answer now!



What is the most likely outcome when either Frank or Roger first receive an antipsychotic?

- A. Because both Frank and Roger are young adult males, they are likely to experience side effects such as dystonia, akathisia, and sexual dysfunction, and will want to stop their medication treatment because of that
- B. Both Frank and Roger will experience a substantial resolution of their acute psychotic symptoms
- C. Because Frank's family can afford it, Frank will be able to get a branded antipsychotic medication that is better tolerated and thus will be more likely to be adherent to his medication regimen
- D. Because Roger's family has no prior experience with anyone else in the family having a mental illness, they will not understand the importance of Roger continuing on medication beyond his hospital stay

Use your keypad to answer now!



Frank's Initial Course

- During his stay at the inpatient psychiatric facility, Frank is diagnosed with schizophrenia based on a careful diagnostic interview and is prescribed lurasidone 80 mg hs
- Frank seems to “snap out of it” relatively quickly, expresses surprise that he is in a hospital, and is eager to return to school. He is given a prescription for lurasidone with instructions to return home in 1 month for a follow-up visit
- Upon return to the fraternity house, Frank becomes worried about what his fraternity brothers will say about his “crazy pills” and, thus, he throws them out, telling himself that he feels fine
- About 3 weeks later, Frank barricades himself in a bathroom and shouts repeatedly that he is in mortal danger. The campus police are called, and Frank is brought to the local emergency department for an emergency evaluation. He is admitted to the locked inpatient psychiatric unit under the emergency commitment statutes

Roger's Initial Course

- While he is under care at the locked inpatient psychiatric unit, Roger is initially treated with risperidone 3 mg hs and appears to respond well. His delusions are no longer intrusive, and he feels that he is able to “think more clearly”
- Roger'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.” Roger is very interested in this opportunity, and although he is surprised to hear that the medication would be administered by injection, it sounds very convenient to him. Additionally, he would be able to avoid having to explain to his roommate why he has to take pills
- Roger is able to return to college for a summer session and eventually catches up to the rest of his class. He goes on to graduate

Roger develops sexual dysfunction. What can be tried next?

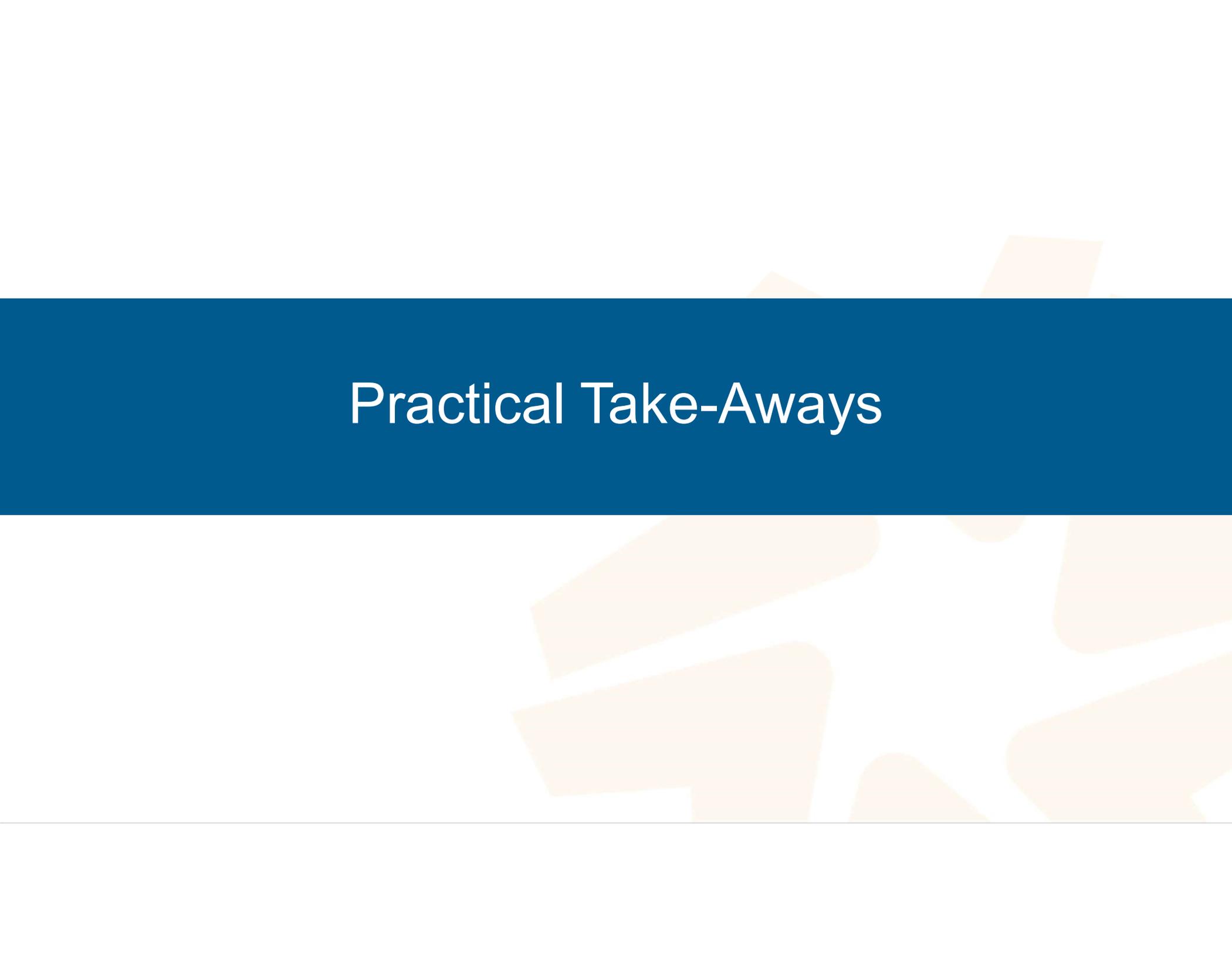
- A. Switch Roger to a subcutaneous LAI antipsychotic
- B. Switch Roger to another LAI antipsychotic that has a lesser effect on prolactin levels
- C. Prescribe a medication for erectile dysfunction
- D. Prescribe benztropine

Use your keypad to answer now!



Frank and Roger: *Worlds Apart!*

- Frank suffers repeated relapses and rehospitalizations
- He is never offered LAI antipsychotics because they are deemed stigmatizing by his physicians as well as his family
- Frank's insight into his illness and subsequent adherence behavior remain erratic—some days he takes his medication and other days he does not
- Frank's family accepts this as a normal course of events because it is what they had previously experienced with other family members
- Roger graduates from college, and, although he does not become a physician, he becomes interested in computers
- He begins a promising career in computer and networking hardware installation under the supportive tutelage of a local tech-savvy businessman
- Roger remains adherent to his LAI antipsychotic medication, and, although he experiences symptom exacerbation from time to time, it is managed on an outpatient basis

The background features several large, semi-transparent orange geometric shapes, including rectangles and trapezoids, scattered across the white space. A solid dark blue horizontal band is positioned in the upper middle section of the slide.

Practical Take-Aways



Poor adherence to antipsychotic medication is common and likely exists in your practice



Poor adherence will drive poor outcomes



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