

Breaking Down the Barriers to Utilizing Long-Acting Injectable Antipsychotics for Schizophrenia Management

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- **Dr. Citrome:** Consultant—AbbVie/Allergan, Acadia, Adamas, Alkermes, Angelini, Astellas, Avanir, Axsome, BioXcel, Boehringer Ingelheim, Cadent Therapeutics, Eisai, Enteris BioPharma, HLS Therapeutics, Impel, Intra-Cellular Therapies, Janssen, Karuna, Lundbeck, Lyndra, Medavante-ProPhase, Merck, Neurocrine, Novartis, Noven, Otsuka, Ovid, Relmada, Reviva, Sage, Sunovion, Supernus, Teva, University of Arizona, and one-off ad hoc consulting for individuals/entities conducting marketing, commercial, or scientific scoping research; Speaker's Bureau—AbbVie/Allergan, Acadia, Alkermes, Angelini, Eisai, Intra-Cellular Therapies, Janssen, Lundbeck, Neurocrine, Noven, Otsuka, Sage, Sunovion, Takeda, Teva, and CME activities organized by medical education companies such as Medscape, NACCME, NEI, Vindico, and Universities and Professional Organizations/Societies; Stocks—Bristol-Myers Squibb, Eli Lilly, J & J, Merck, Pfizer, Reviva [options]; Royalties—Wiley, UpToDate, Springer Healthcare, Elsevier
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- **Lesley McCuaig** has no financial relationships to disclose related to the subject matter of this presentation

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- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration)
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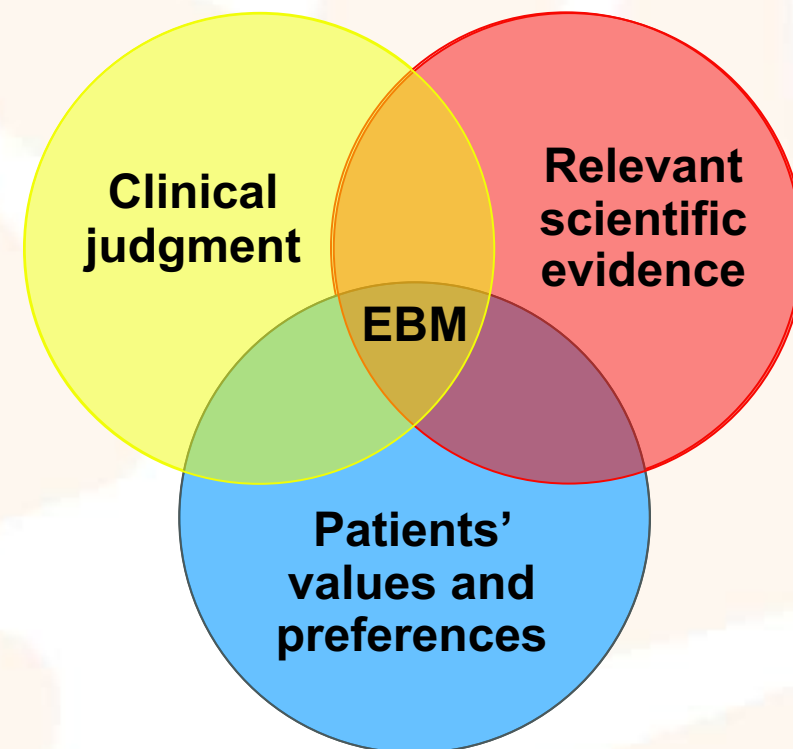
Learning Objectives

- Assess clinician- and patient-related barriers to optimal schizophrenia treatment, and outline strategies to overcome these barriers
- Evaluate the pharmacology, mechanisms of action, safety and efficacy, and administration considerations associated with LAIs
- Implement strategies for proper patient selection and personalized treatment with LAIs

What Is the Evidence for LAIs?

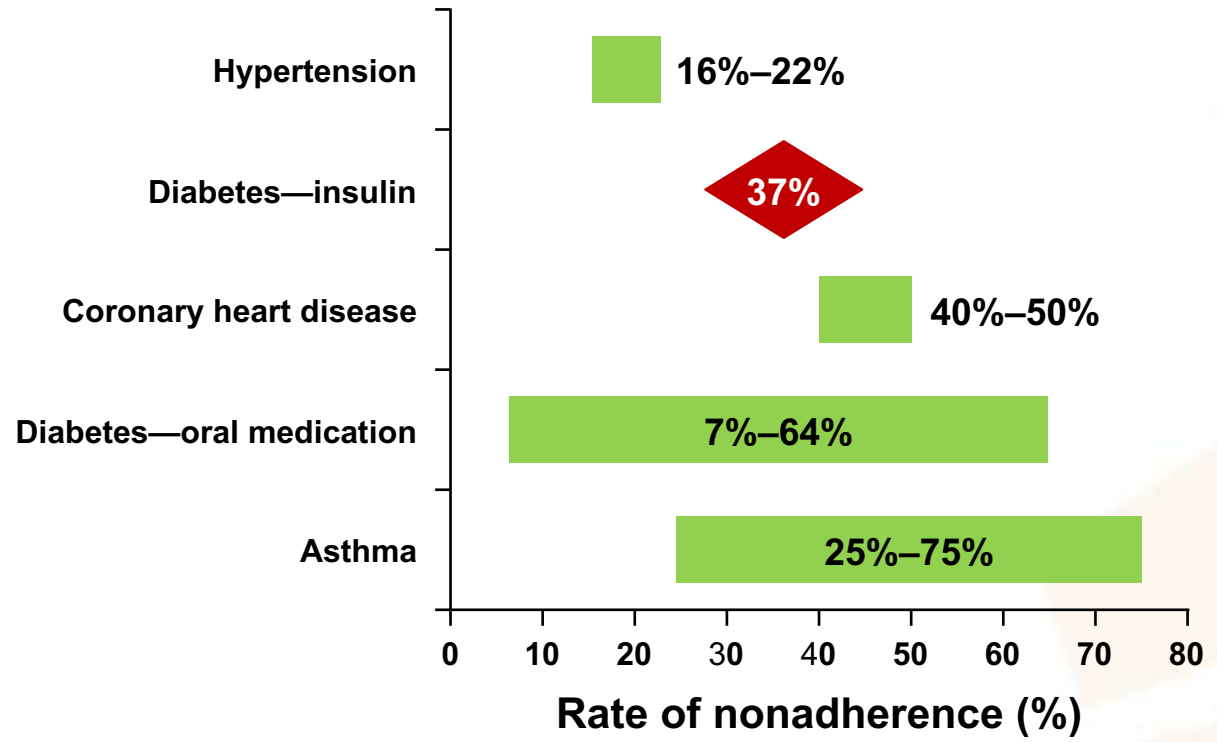
Studies have consistently demonstrated

- The importance of continuous medication treatment of schizophrenia to *minimize the risk of relapse*
- There are substantial *adherence challenges* for patients with chronic disorders
- *Superior overall effectiveness of LAIs vs oral antipsychotics*
- Caregivers may *prefer* LAIs
- Patients may *prefer* LAIs

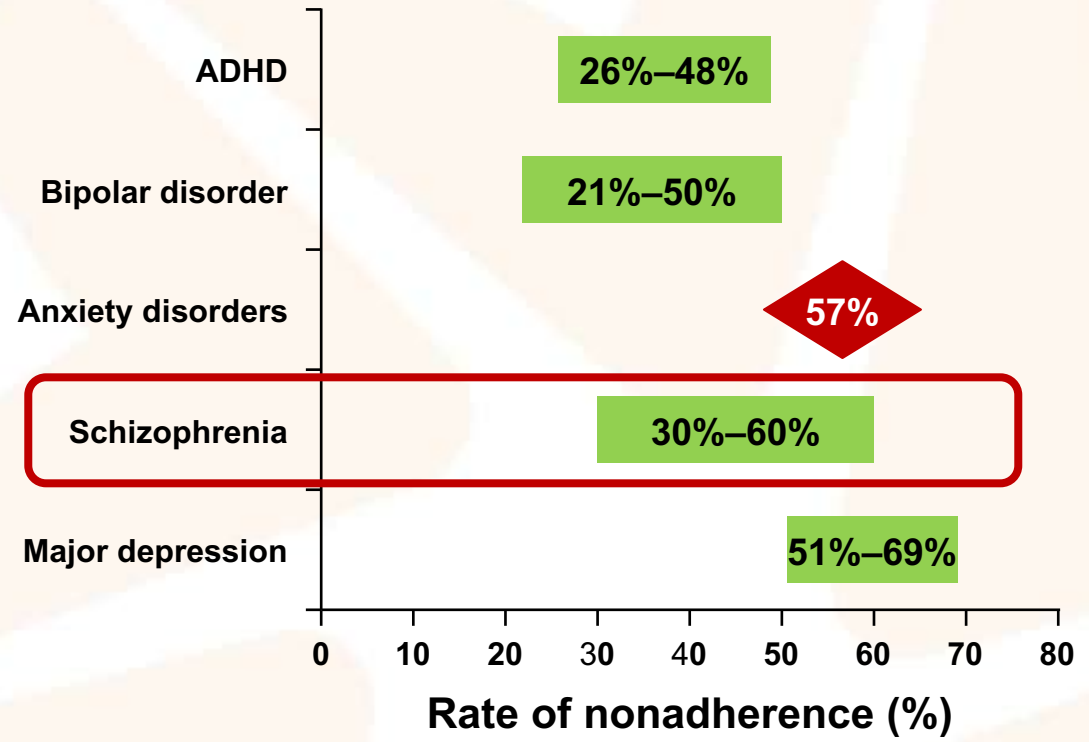


Many Chronic Conditions Have High Rates of Medication Nonadherence

Nonpsychiatric

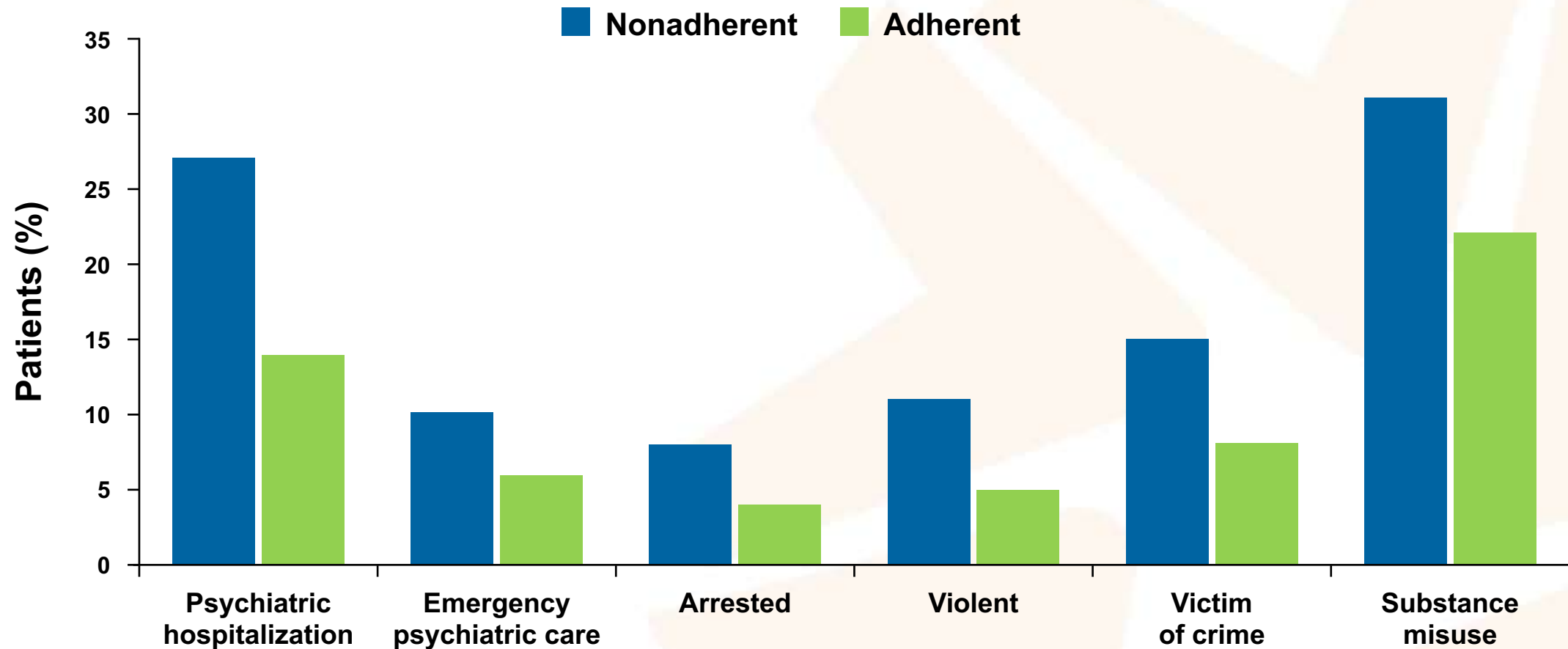


Psychiatric

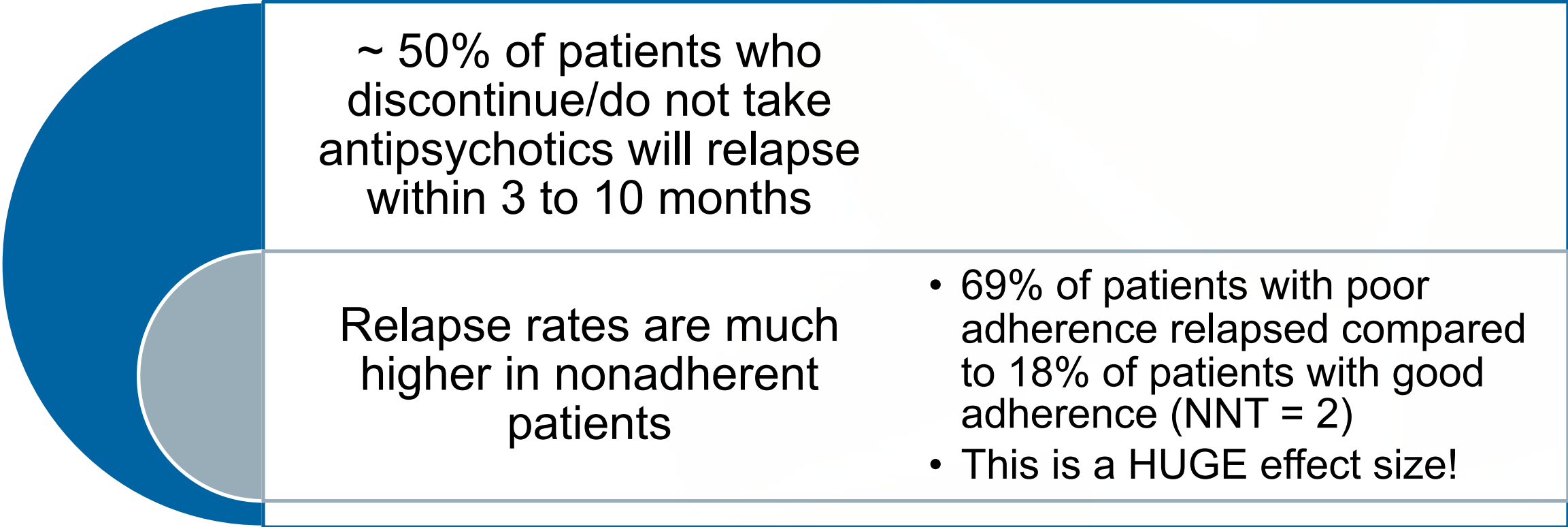


ADHD = attention-deficit/hyperactivity disorder.
 Parks J [www.thenationalcouncil.org]. "Clinical Strategies to Promote Medication Adherence." Accessed August 2021.
www.thenationalcouncil.org/wp-content/uploads/2020/04/Clinical-Strategies-to-Promote-Medication-Adherence-6.20.18.pdf?daf=375ateTbd56.

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



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. Morken G, et al. *BMC Psychiatry.* 2008;8:32.

When Treatments Fail

Wrong diagnosis and thus incorrect treatment?

Wrong dose of the right medication?

Inadequate duration of treatment?

“Treatment resistance”

Think about *nonadherence*

- *To rule out “pseudo-resistance” due to inadequate treatment adherence, the optimal definition of treatment resistance would **include at least 1 failed trial with an LAI antipsychotic**, given for at least 6 weeks after it has achieved steady state (Treatment Response and Resistance in Psychosis [TRRIP] Working Group Consensus Guidelines)*

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**

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.

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

Caregiver Attitudes about Long-Acting Injectable Antipsychotics

A survey was given to caregivers (N=96) in the United States in September/October 2019 via online communities and caregiver newsletters

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**

Patient Attitudes about Long-Acting Injectable Antipsychotics

Survey in France: Patients (N=206) 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

Big Barrier: Clinician Attitudes about Long-Acting Injectable Antipsychotics

Survey at an international conference (N=350): The most important factor against Rx LAI is presumed sufficient adherence with oral antipsychotic treatment

- < 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 (N=302) and psychiatric NPs/PAs (N=77) 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

Rx = prescription; NP = nurse practitioner; PA = physician assistant.

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. *Neuropsychiatr Dis Treat*. 2022;18:111-123.

LAI Options in the United States

Although the number of different molecules are limited, there are many variations among formulations, and more to come!

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
 - Paliperidone palmitate every 6 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**

IM = intramuscular.

Citrome L. *Expert Rev Neurother.* 2017;17(10):1029-1043. Citrome L. *Clin Schizophr Relat Psychoses.* 2018;12(3):130-141. Najarian D, et al. *Int J Neuropsychopharmacol.* 2021:pyab071 [Epub ahead of print].

We Always Want Better Amenities of Care

How often are the injections administered?

What is the needle gauge?

What is the injection volume?

Is there a choice of injection site?

Does this product require reconstitution?

Is oral supplementation required?

Does storage of this product require refrigeration?

Are there any special requirements for post-injection observation?

Are there any important drug-drug interactions, and can they be remedied?

Missed doses: What is the “grace period?”

Is reimbursement an issue if used “off-label”?

In case of reimbursement obstacles, can I easily access a patient-assistance program?

In the Pipeline: Additional Choices

Improving Upon the Amenities of Care

Risperidone- or paliperidone-containing formulations

- Risperidone subcutaneous LAI, every 1 or 2 months
- Risperidone intramuscular LAI that does not require oral supplementation or a loading dose, once monthly
- Risperidone extended-release oral capsules, once weekly

Aripiprazole-containing formulations

- Aripiprazole monohydrate every 2 months

A Tale of Two Cases

“It was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness, it was the epoch of belief, it was the epoch of incredulity, it was the season of light, it was the season of darkness, it was the spring of hope, it was the winter of despair.”

— Charles Dickens, A Tale of Two Cities

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
- 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 and aspires to become a physician; 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 him
- 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 and is involuntarily admitted to the locked inpatient psychiatric unit

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

Roger's Initial Course

- While hospitalized, 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

Who has the better prognosis?

What Happened to Frank?

- 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

What Happened to Roger?

- Roger is able to return to college for a summer session and eventually catches up to the rest of his class
- He continues to receive antipsychotic medication without interruptions
- He goes on to graduate

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

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Practical Considerations for LAI Administration

APA COVID-19 Pandemic Guidance

The role of LAI is a clinically necessary treatment and should be continued for patients with chronic mental illness

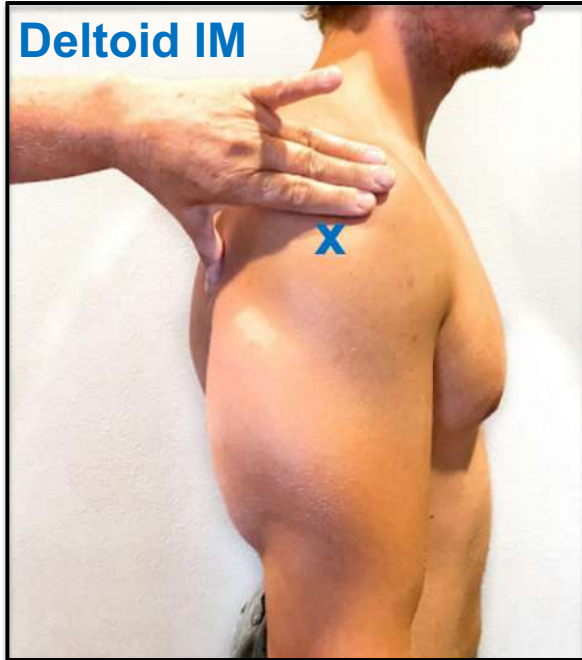
The use of these long-acting formulations can reduce personal suffering and distress, especially in a pandemic

LAI can also help ensure adequate level of functioning and cognitive processing which would enable these patients to practice social distancing in a pandemic



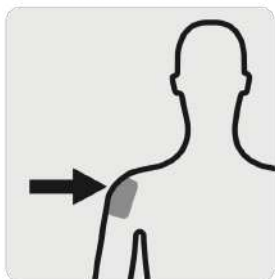
If we're creative and flexible, we can overcome any challenge to meeting our patients' needs!

Administration Techniques



Deltoid IM

If administering a **Deltoid** injection



If patient weighs: **Less than 90 kg**
pink hub

22G x 1"

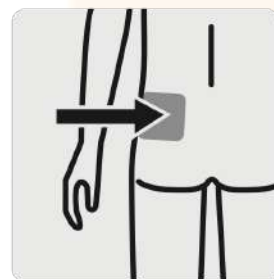
90 kg or more
yellow hub

22G x 1½"



Ventrogluteal IM

If administering a **Gluteal** injection



If patient weighs: **Less than 90 kg**
yellow hub

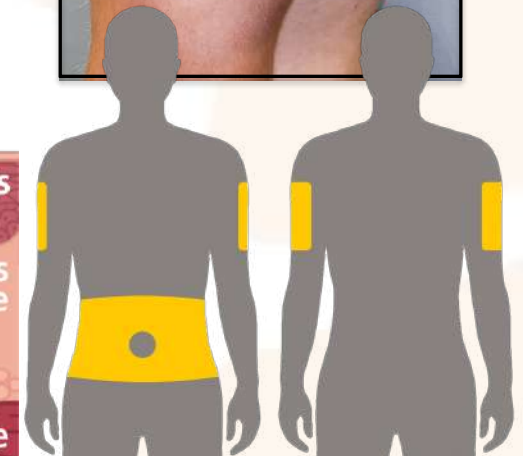
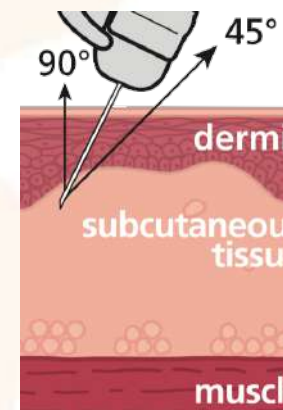
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90 kg or more
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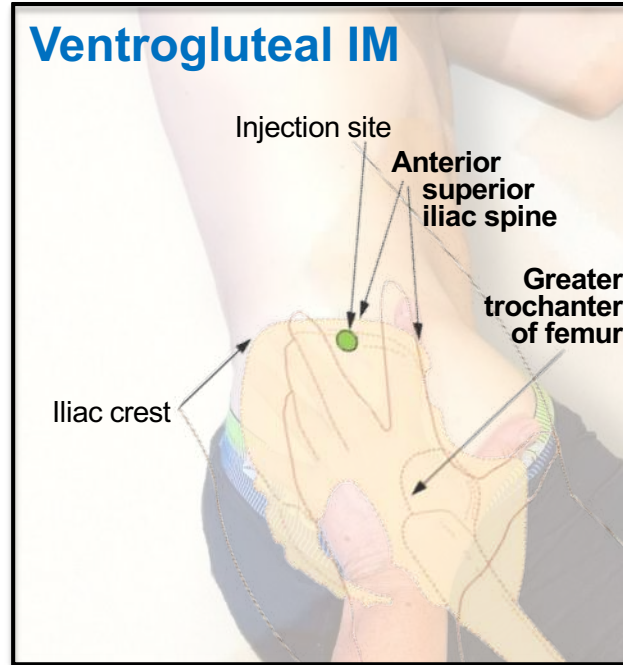
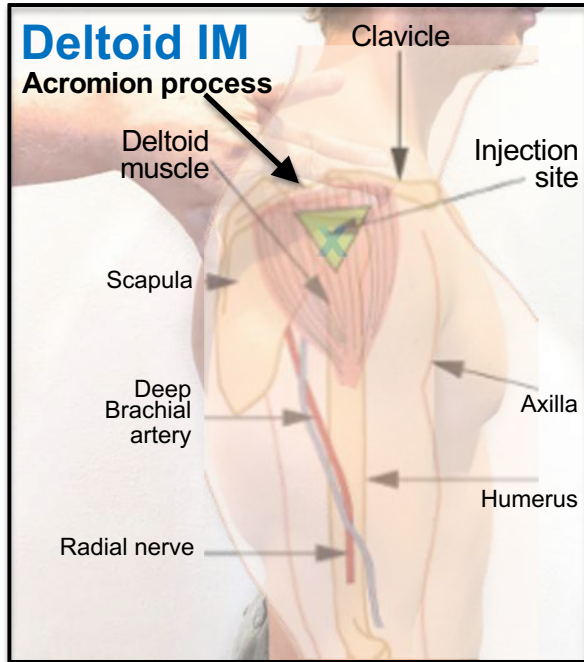
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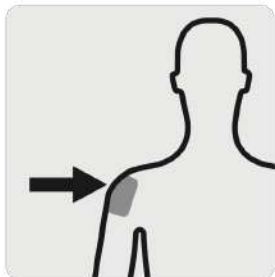
Back of Arm SC



Administration Techniques



If administering a **Deltoid** injection



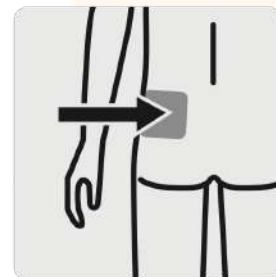
If patient weighs: **Less than 90 kg**
pink hub

22G x 1"

90 kg or more
yellow hub

22G x 1½"

If administering a **Gluteal** injection

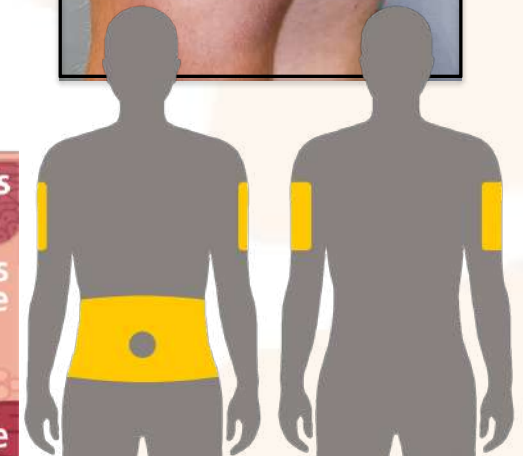
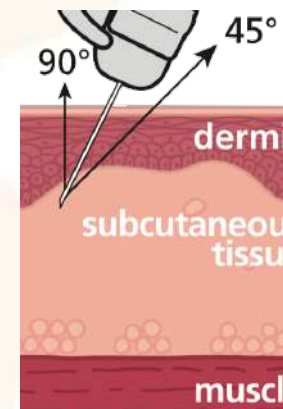


If patient weighs: **Less than 90 kg**
yellow hub

22G x 1½"

90 kg or more
yellow hub

22G x 1½"



The Art of the Jab: Countering Needle Pain/Anxiety

Encourage breathing exercises

Distract the patient by engaging in conversation



Insert needle quickly, in a dart-like fashion

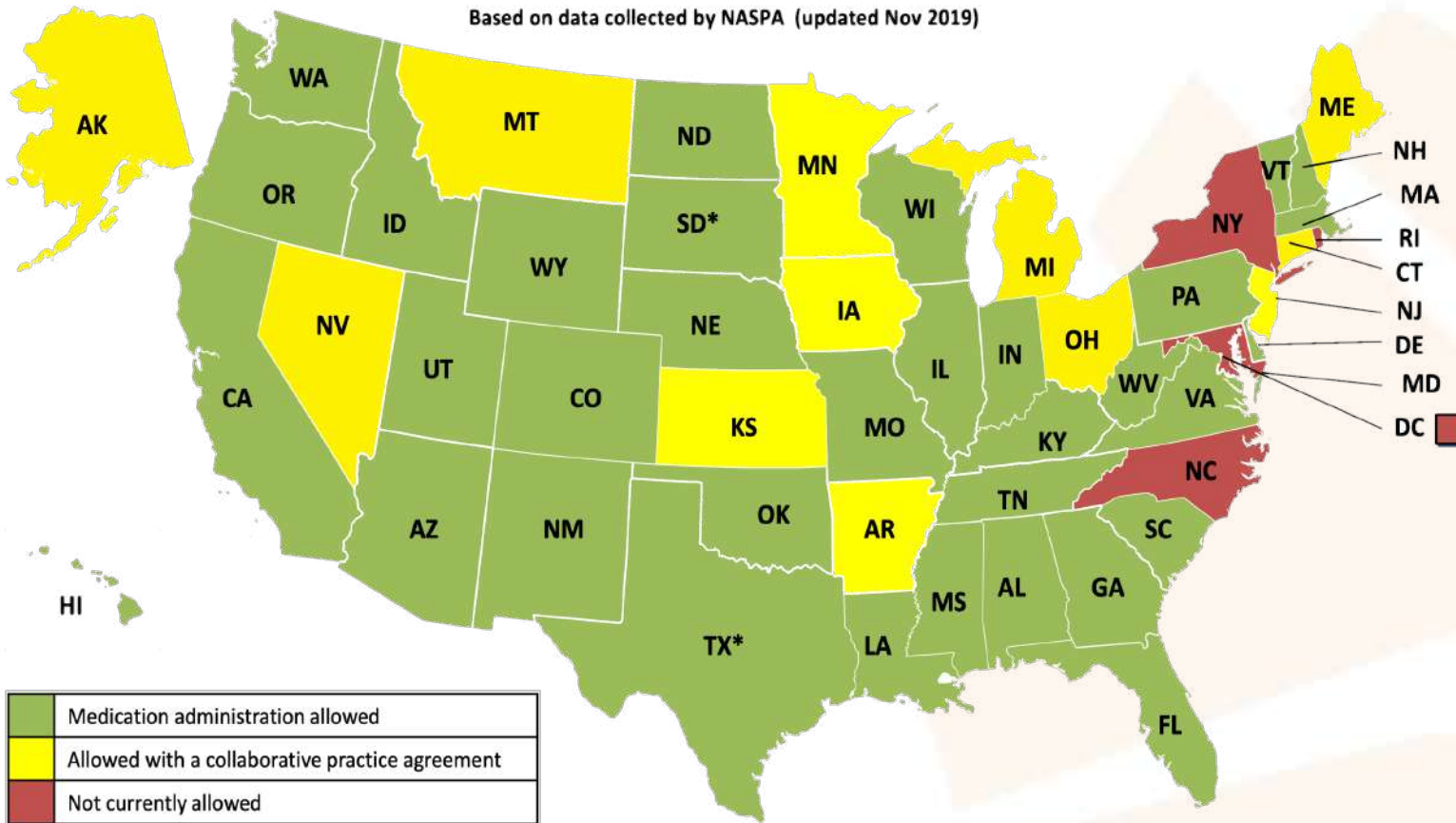
Avoid needle clogs by injecting slowly (except aripiprazole lauroxil)

Injection volumes under 0.5-0.8ml are no more painful than needle insertion itself

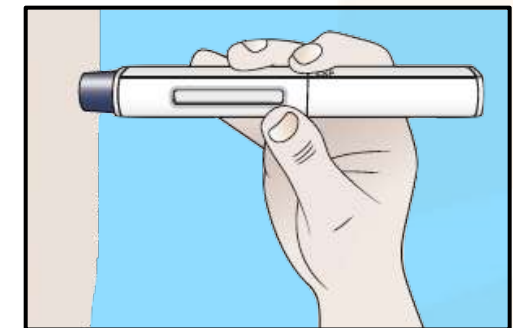


Taddio A, et al. *CMAJ*. 2015;187(13):975-982. Usach I, et al. *Adv Ther*. 2019;36(11):2986-2996. Advisory Committee On Immunization Practices (ACIP) [www.cdc.gov]. Last updated February 15, 2022. Accessed February 5, 2022. <https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/downloads/general-recs.pdf>. Farwick S, et al. *J Psychiatr Pract*. 2019;25(2):82-90. Potter PA, et al. *Fundamentals of Nursing*. 10th ed. Elsevier; 2020.

Utilizing LAIs as a Non-Injector



Partnering with PCPs



Maybe one day?

Pharmacist authority to administer LAIs

PCP = primary care provider.

National Alliance of State Pharmacy Associations (NASPA) [www.naspa.us]. Last updated 2017. Accessed February 5, 2022.

<https://naspa.us/wp-content/uploads/2017/07/Pharmacists-Authority-to-Administer-Medications.pdf>. Keepers GA, et al. *Am J Psychiatry*. 2020;177(9):868-72.

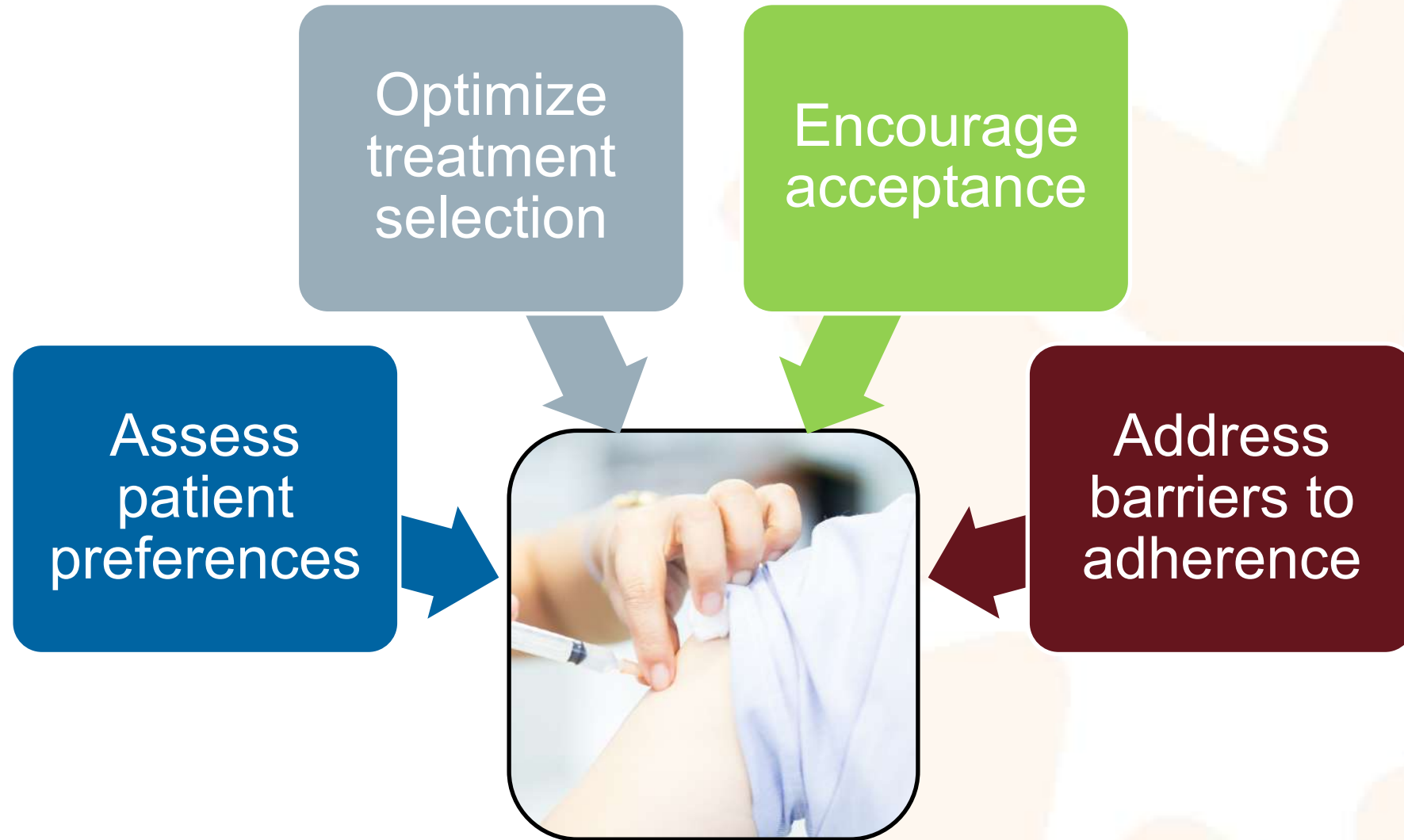
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Meet Lesley

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Strategies for Patient Acceptance of LAIs and Improved Outcomes

Getting from Idea to Injection Takes Communication



Missed Connections?

75% of psychiatrists in one study reported routinely informing their patients about LAIs



...but only 33% of LAI-naïve patients felt educated



A study analyzing the language psychiatrists used to discuss LAIs revealed:

91% emphasized the fact that it was a "shot" or "injection"; only 9% emphasized clinical benefits

33%
Accepted

96%
Would have

What if we talked about dating the way we talk to patients about LAIs?

"How about we eat at the same time and place and talk to each other between chewing?"

"Going on a date with me is an option ... I just wanted to mention it so you would know."

"I'd like to take you on a date ... but nobody's going to force that on you! It's your choice!"

"Going out with me wouldn't bother you at all? Okay. And why not?"

How to ~~Talk to~~ Communicate with ~~Schizophrenics~~ People with Schizophrenia

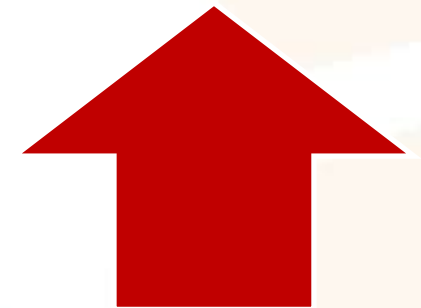
Practicing and trainee psychotherapists were randomized to receive versions of the Community Attitudes towards the Mentally Ill (CAMI) rating scale which either used the terms “schizophrenics” or “people with schizophrenia”

Those whose CAMI scale used the term “schizophrenics” scored:



Significantly **lower**
on measures of
benevolence

Significantly **higher**
on measures of
authoritarianism



Are We Giving Them a Chance?

“Just because someone has schizophrenia doesn’t mean they aren’t capable of being a part of their treatment...”



Maxwell, 38,
lived experience
of schizophrenia

“[Psychosis] is a small window of this illness ... 99% of the time my husband is rational, and he can make those decisions.”



Samantha, 55, supports
husband who lives with
schizophrenia

“There is just no interest ... absolutely no interest in [my son] or his well-being. Just none.”

Alfred, 72, supports
son who lives with
schizophrenia



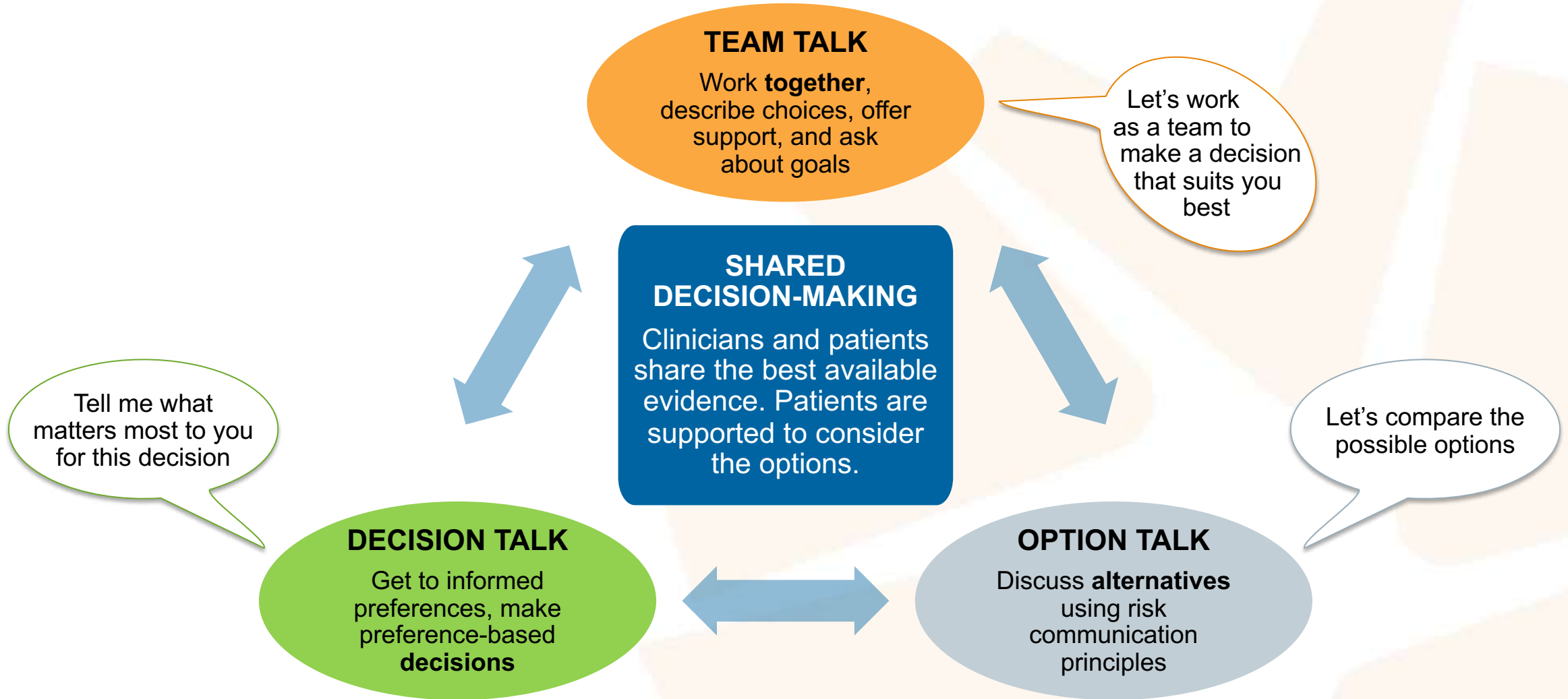
When clinicians view people with lived experience as having expertise

“I felt like she listened better and she cared about me rather than just medicating me.”

Shannon, 46,
lived experience
of schizophrenia



Relationships Create Results



Elwyn, Glyn, et al. *BMJ* 359 (2017).

Elwyn, Glyn, et al. *Journal of general internal medicine*. 27.10 (2012): 1361-1367.

Back to Lesley

Supporting Change



Motivational interviewing

Arranging conversations so that people talk themselves into change, based on their values and interests.

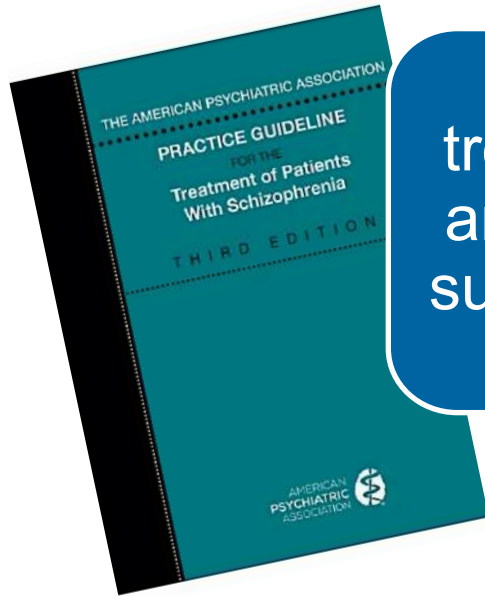
G.A.I.N. Approach to Motivational Interviewing

<u>G</u>oal setting	<u>A</u>ction planning	<u>I</u>nitiating treatment	<u>N</u>urturing motivation
Be curious about their life and goals	Confidently discuss your belief that LAIs could help them achieve their goal	Project a positive and enthusiastic attitude	Inquire about and celebrate progress toward their short-term goals
Link identified goals with barriers posed by potential relapse	Explain how LAIs work and potential benefits as well as risks	Normalize concerns and correct any misconceptions	Explore barriers to treatment and develop a plan to overcome
Prioritize goals and document them	Link the specific goals with consistency of medication	Explain logistics but proceed quickly to reduce anxiety	As short-term goals are achieved, switch focus to long-term goals
Partner on a plan of action and be willing to compromise		Tell them you're excited to hear their feedback next time!	

Multidisciplinary Care Optimizes Use of LAIs



Updated LAI Therapy Guidelines

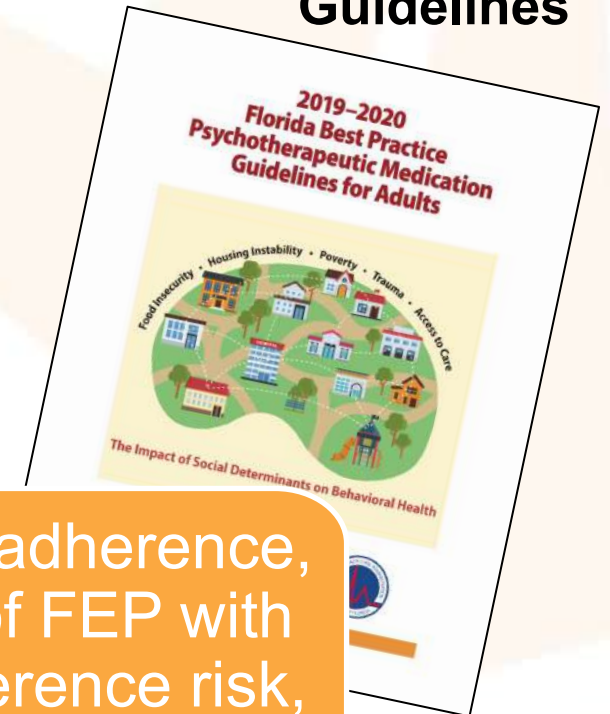


APA Practice Guidelines for the Treatment of Patients with Schizophrenia

APA suggests that patients receive treatment with a long-acting injectable antipsychotic medication if they prefer such treatment or if they have a history of poor or uncertain adherence.

Recommended regardless of adherence, as well as after stabilization of FEP with oral AP: “high future non-adherence risk, most to lose from future potential relapse”

Florida Medicaid Guidelines



FEP = first episode psychosis.

Keepers GA, et al. *Am J Psychiatry*. 2020;177(9):868-72. Florida Center for Behavioral Health Improvements and Solutions. 2019-2020 *Florida Best Practice Psychotherapeutic Medication Guidelines for Adults*. Florida Center for Behavioral Health Improvements and Solutions; 2020.

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LONG-ACTING INJECTABLES