long-acting injectables360

BREAKING DOWN THE BARRIERS TO UTILIZING LONG-ACTING INJECTABLE ANTIPSYCHOTICS FOR SCHIZOPHRENIA MANAGEMENT

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Faculty Disclosures

- **Desiree Matthews, PMHNP:** Speaker Bureau–Abbvie, Alkermes, Intracellular Therapies, Neurocrine Biosciences, Inc. Advisory Board–Alkermes, Neurocrine Biosciences, Inc.

- **Jonathan Meyer MD**: Advisory Board–Alkermes, Cerevel, ITCI, Karuna, Neurocrine Biosciences, Inc., Otsuka America Pharmaceutical, Inc., Relmada, Sunovion Pharmaceuticals Inc., Teva Pharmaceuticals; Speakers Bureau–Alkermes, ITCI, Neurocrine Biosciences, Inc., Noven, Sunovion, Teva Pharmaceuticals.

Disclosure

- 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).

- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.

- This activity has been independently reviewed for balance.

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 patient-centered communication, including motivational interviewing, to facilitate patient selection and patient acceptance of LAIs
- Utilize appropriate administration procedures, injection techniques, and patient monitoring to achieve optimal patient outcomes

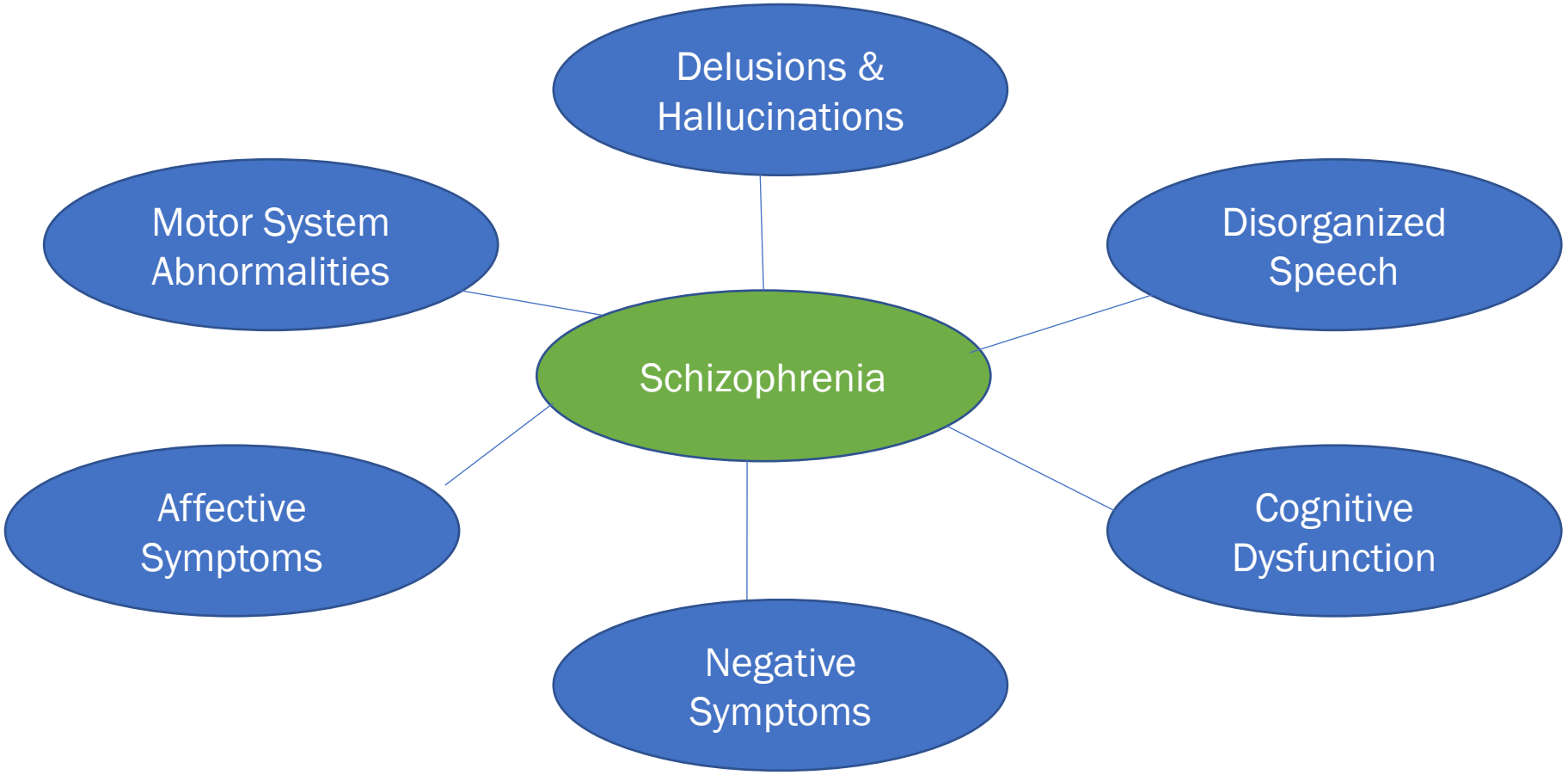
Clinician- and Patient-Related Barriers to Optimal Schizophrenia Outcomes

Desiree Matthews, PMHNP

Advanced Practice Provider Clinical Liaison

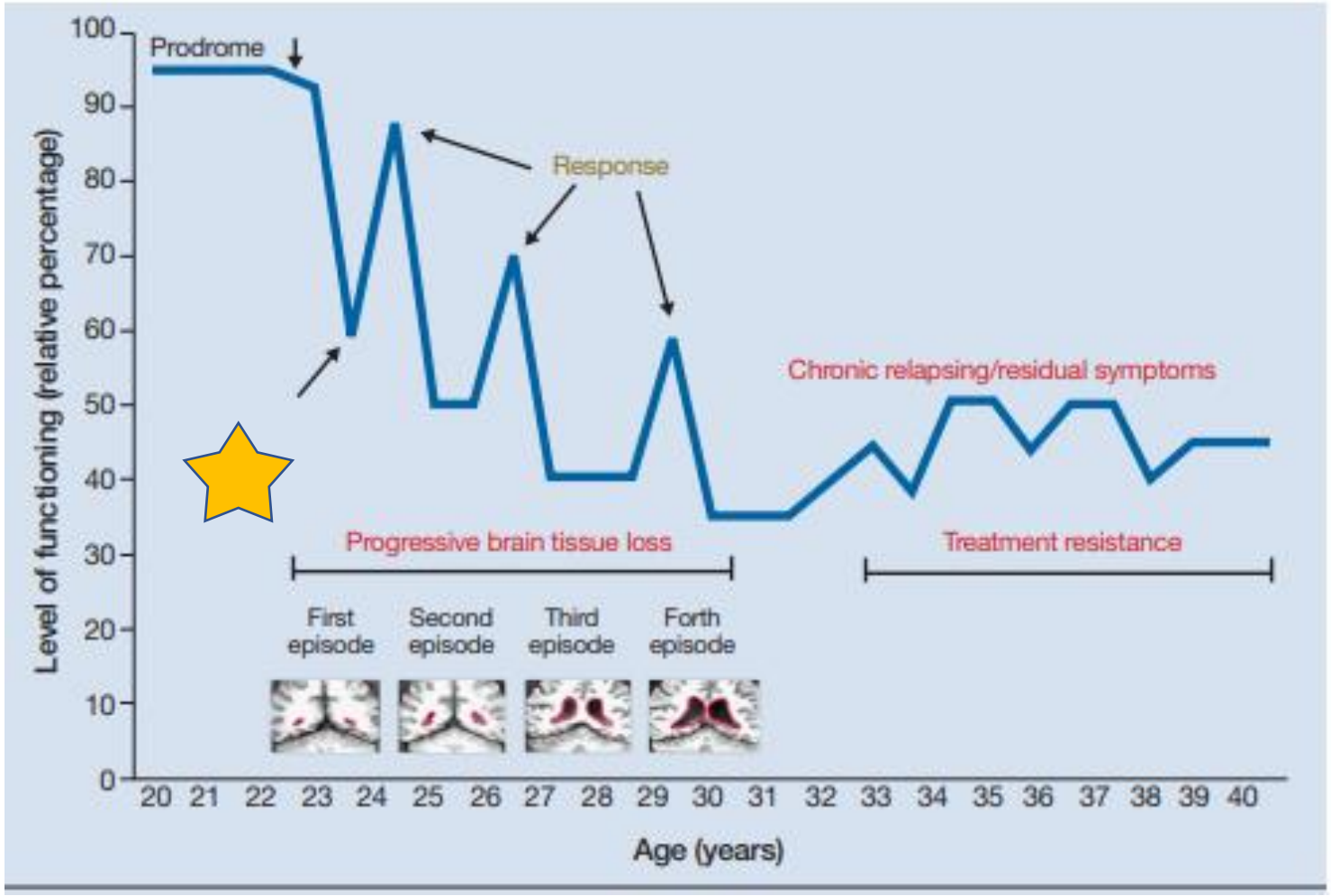
Monarch, Charlotte, NC

Domains of Schizophrenia



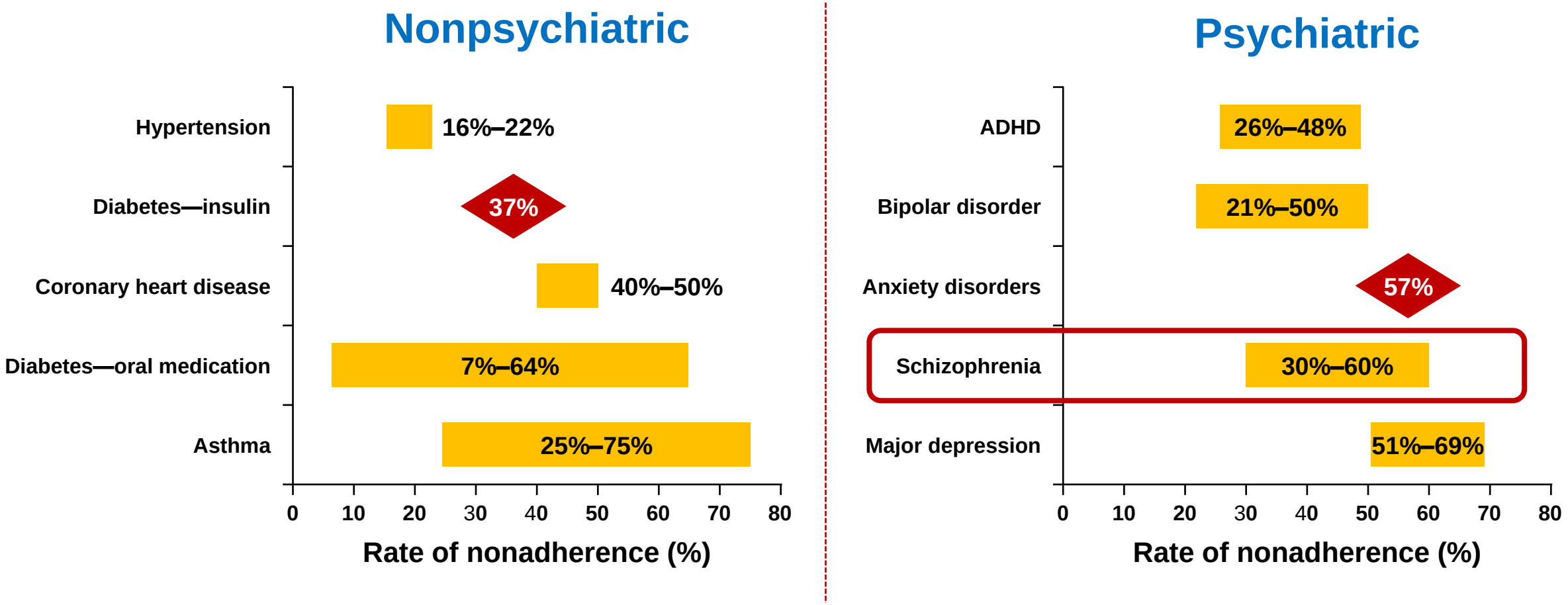
Viron M, et al. Schizophrenia for primary care providers: how to contribute to the care of a vulnerable patient population. *The American journal of medicine. 2012;125 3*, 223-30 .

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.

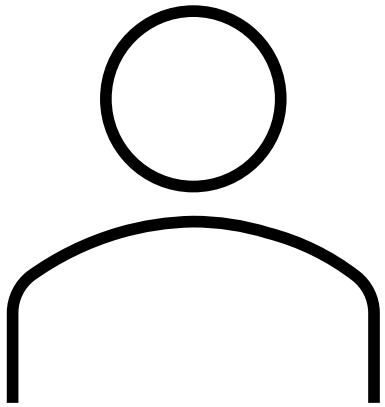
Many Chronic Conditions have High Rates of Medication Nonadherence



ADHD = attention-deficit/hyperactivity disorder.

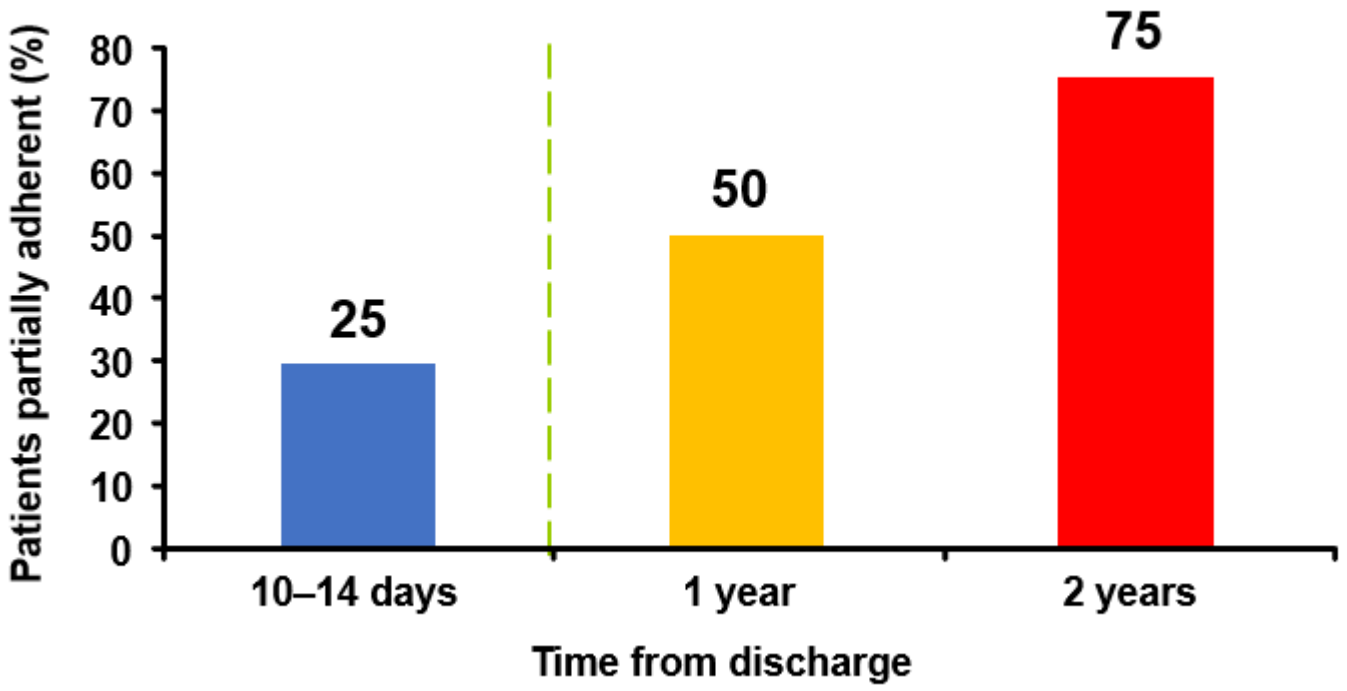
Parks J [www.thenationalcouncil.org]. “Clinical Strategies to Promote Medication Adherence.” Accessed August 2021. www.thenationalcouncil.org/wp-content/uploads/2020/04/Clinical-Strategies-to-Promote-Medication-Adherence-6.20.18.pdf?daf=375ateTbd56.

Case Study: Maria



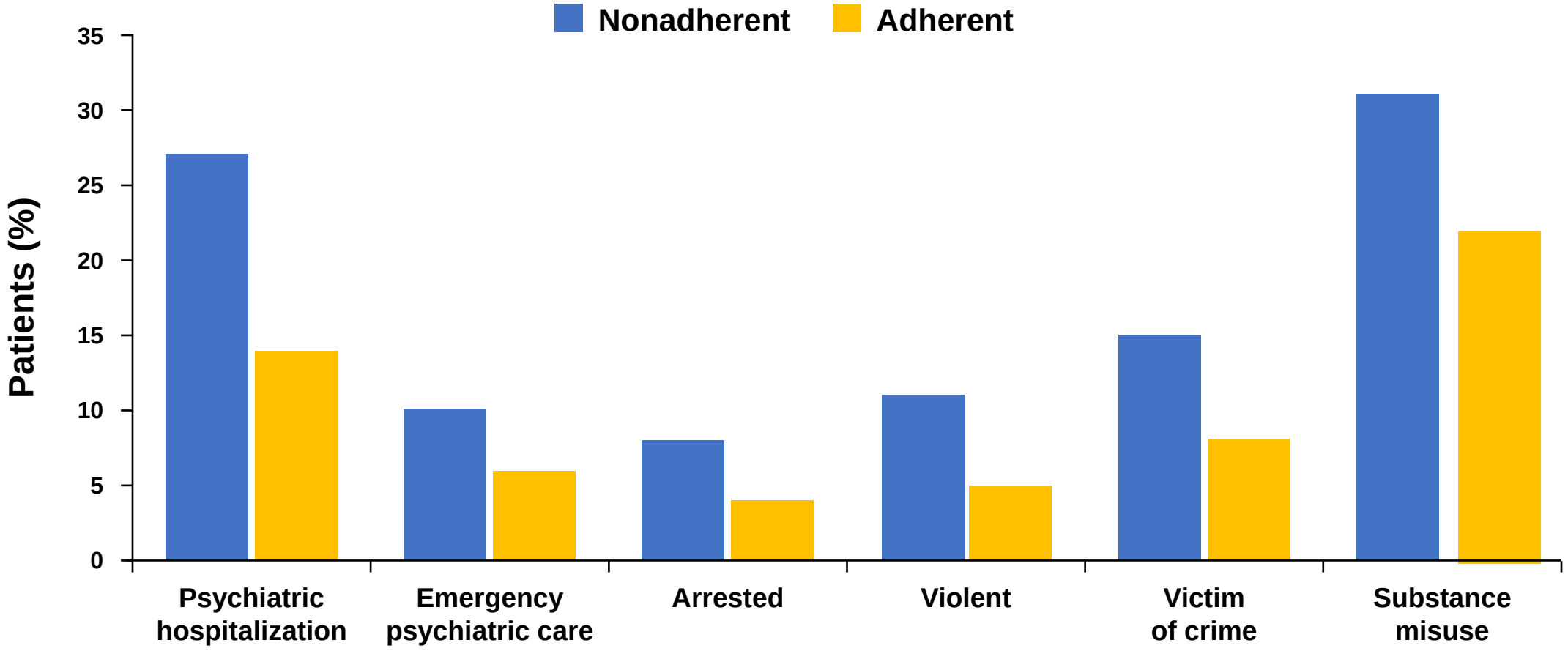
- 26 year old
- First Break psychosis at age 24.
- Is a mother to a 2 year old son, works part time in retail.
- Recently hospitalized due to relapse in psychosis & discharged and stable on oral antipsychotic
- On outpatient follow up “I am better now, I don’t need to take the medication every day”

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. *J Psychiatr Pract*. 1997;3:106-110.

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



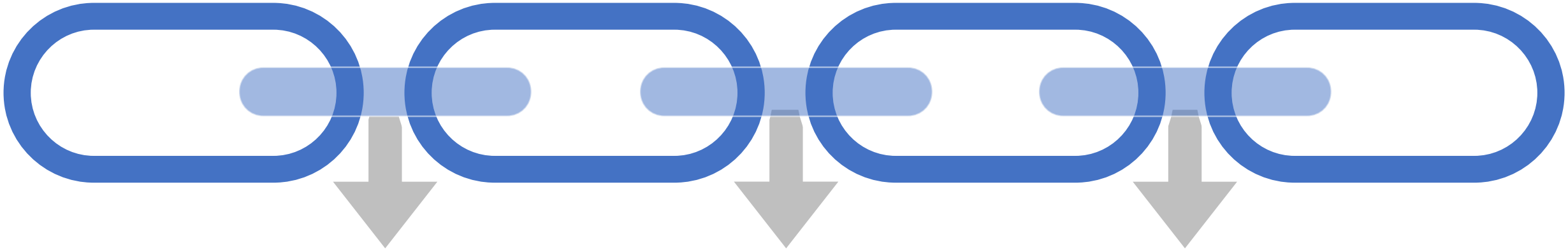
Haddad PM, et al. *Patient Relat Outcome Meas*. 2014;5:43-62.

Clinician Barriers to LAI's

Insufficient Knowledge or Experience

Negative Perceptions of LAIs

Limitations due to COVID-19



Inadequate training
Perceived lack of time
Unwillingness to do PA
Anxiety about discussion

Insufficient ancillary support
Overestimation of adherence
Lack of confidence
Stigma

Reduced face-to-face visits
Concern about contagion risk
Hesitancy to change treatments

PA = Prior Authorization

Lindenmayer JP, et al. *J Clin Psychopharmacol*. 2020;40(4):346-349. Weiden PJ, et al. *J Clin Psychiatry*. 2015;76(6):684-690. Velligan DI, et al. *Patient Prefer Adherence*. 2017;11:919-928.

Over Estimation of 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**

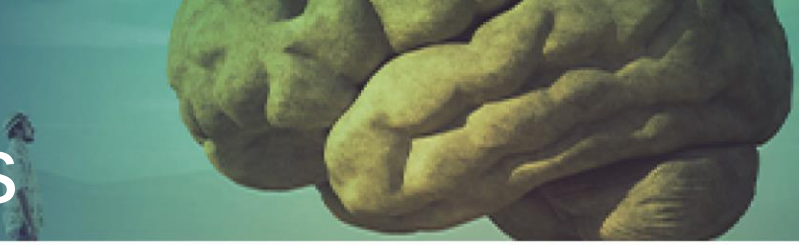
Velligan DI, et al. *Psychiatr Serv*. 2007;58(9):1187-1192.

Patient Barriers to LAI's

- Lack of Awareness
- Limited Insurance Coverage
- Sense of Coerciveness
- Frequent Clinic Visits
- Fear of Injections or Needles

Getzen H, et al. *Ann Clin Psychiatry*. 2014;26(1):33-38. Lindenmayer JP, et al. *J Clin Psychopharmacol*. 2020;40(4):346-349. Potkin S, et al. *BMC Psychiatry*. 2013;13:261.

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

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

Pharmacodynamic, Kinetic and Tolerability Concerns in Choosing an LAI Antipsychotic

Jonathan M. Meyer, MD

Clinical Professor of Psychiatry
University of California, San Diego

LAI Antipsychotics: Limited Choices Based on Pharmacodynamics

POTENCIES OF ANTIPSYCHOTIC AGENTS AT NEUROTRANSMITTER RECEPTORS

	DOPAMINE	SEROTONIN	MUSCARINIC	ADRENERGIC		HISTAMINE
	D_2	$5HT_{2A}$	M_1	α_{1A}	α_{1B}	H_1
First-generation agents (oral equivalent) (Leucht et al., 2020)						
Haloperidol 1 mg	1.2	57	>10,000	12	7.6	1700
Fluphenazine 1 mg	0.8	3.2	1100	6.5	13	14
Second-generation agents						
Aripiprazole [b]	*1.6* [b]	8.7	6800	26	34	28
Risperidone	3.2	0.2	>10,000	5.0	9.0	20
Paliperidone	4.2	0.7	>10,000	2.5	0.7	19
Olanzapine	31	3.7	2.5	110	263	2.2

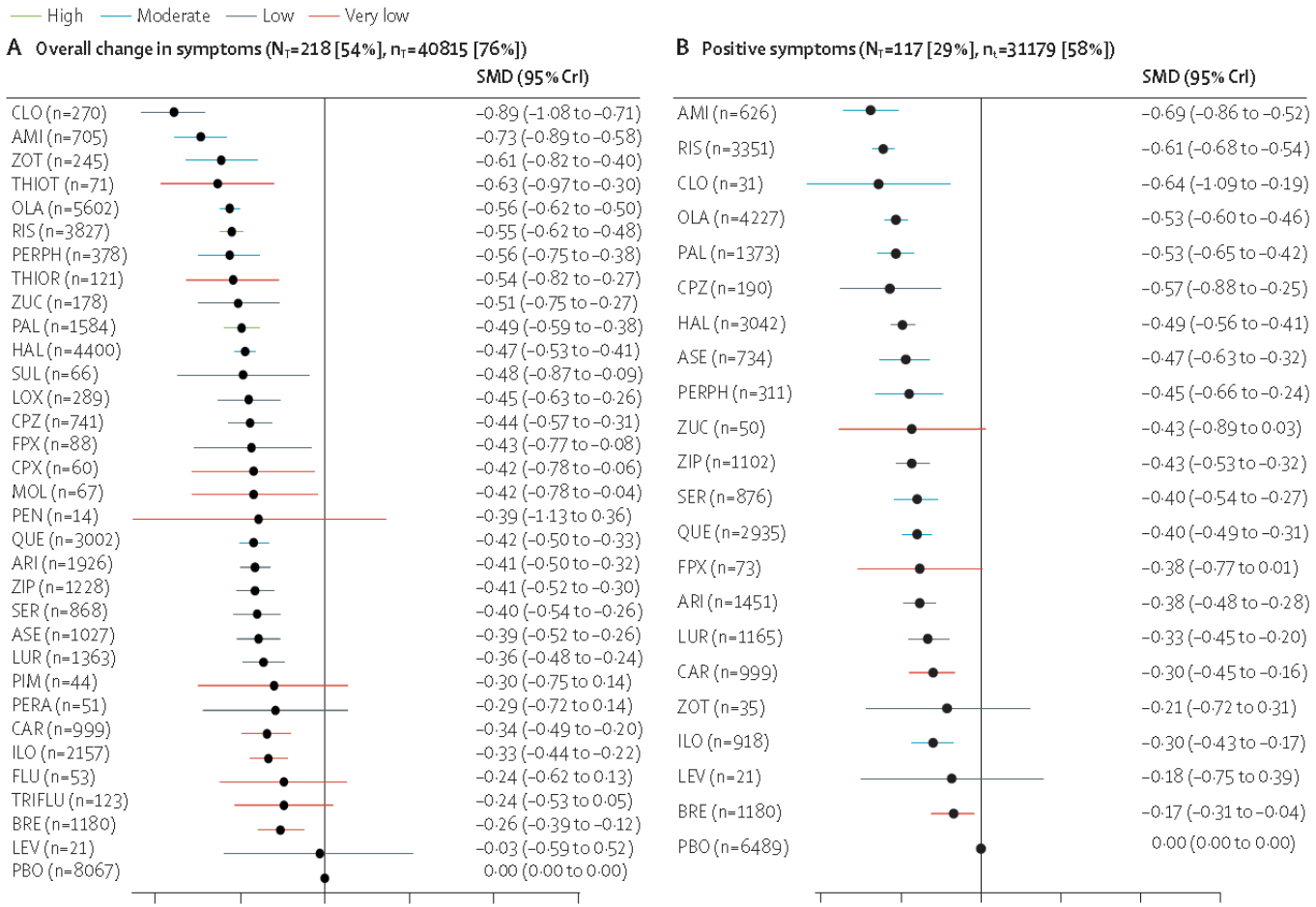
[a] Data are averaged K_i values (nM) from published sources determined by competitive binding at cloned human receptors. Data derived from receptor binding to human or rat brain tissue is used when cloned human receptor data are lacking.
[b] Partial agonist at D_2 receptor.

Source: PDSP Ki Database: http://pdsp.med.unc.edu/pdsp.php (accessed March 1, 2021).

Meyer JM. Pharmacotherapy of Psychosis and Mania. In: Brunton LL, ed. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 14th Edition. Chicago, Illinois: McGraw-Hill; 2022; ch 19.

Antipsychotic Efficacy – Comparable

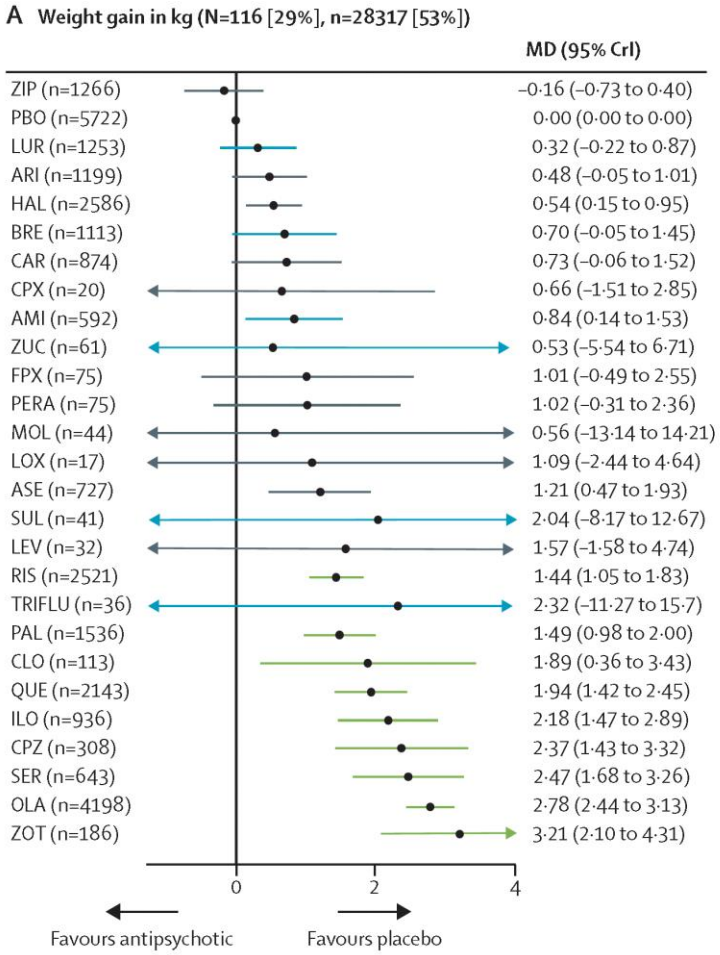
Network meta-analysis of 32 oral antipsychotics for adult schizophrenia

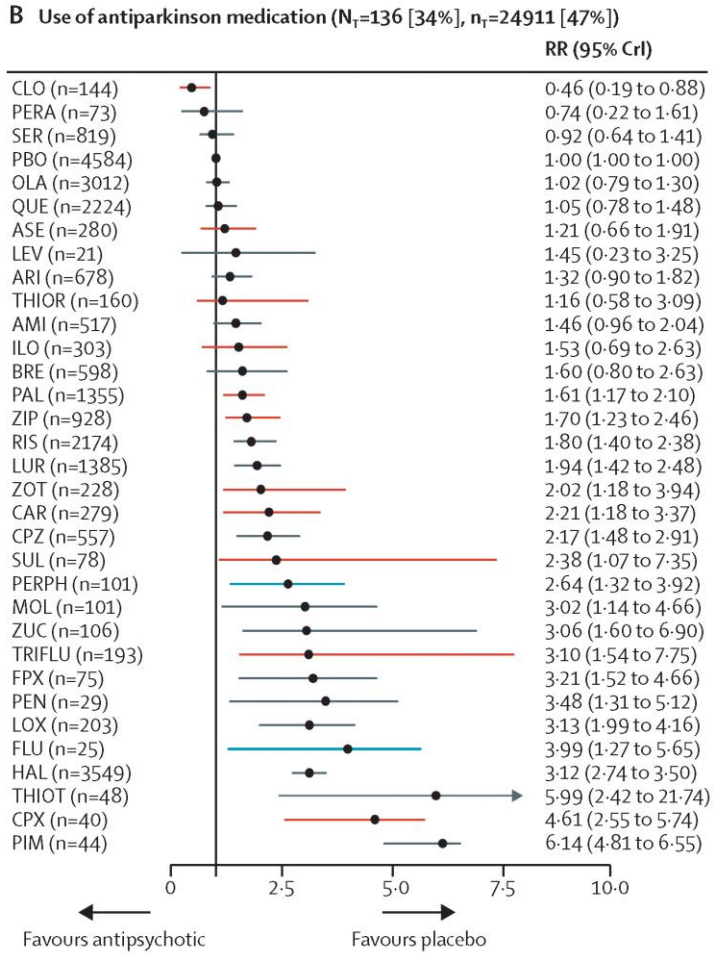


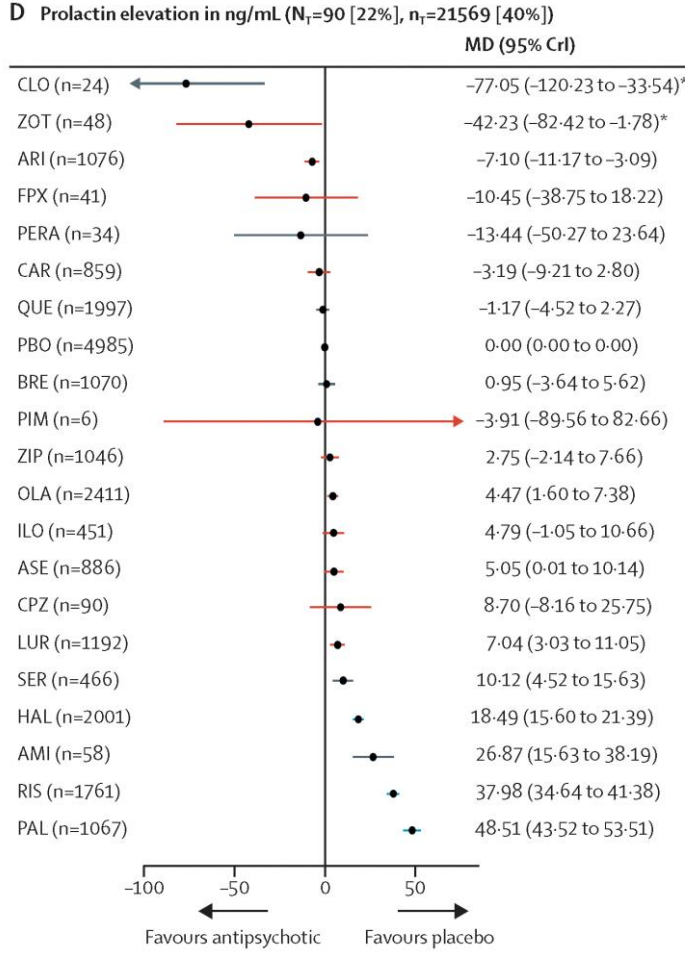
Huhn M, et al. *Lancet*. 2019; 394: 939–51

Antipsychotic Tolerability – Lots of Differences

Network meta-analysis of 32 oral antipsychotics for adult schizophrenia

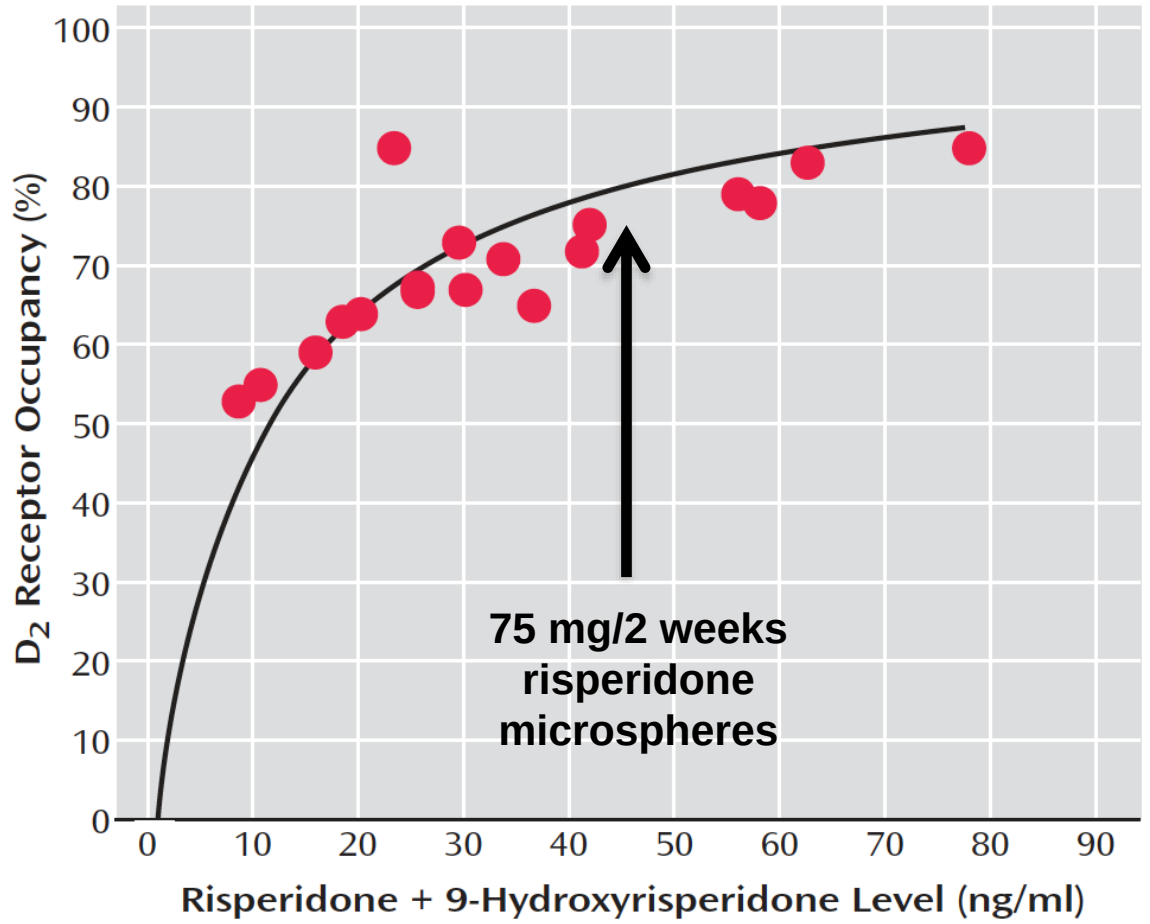






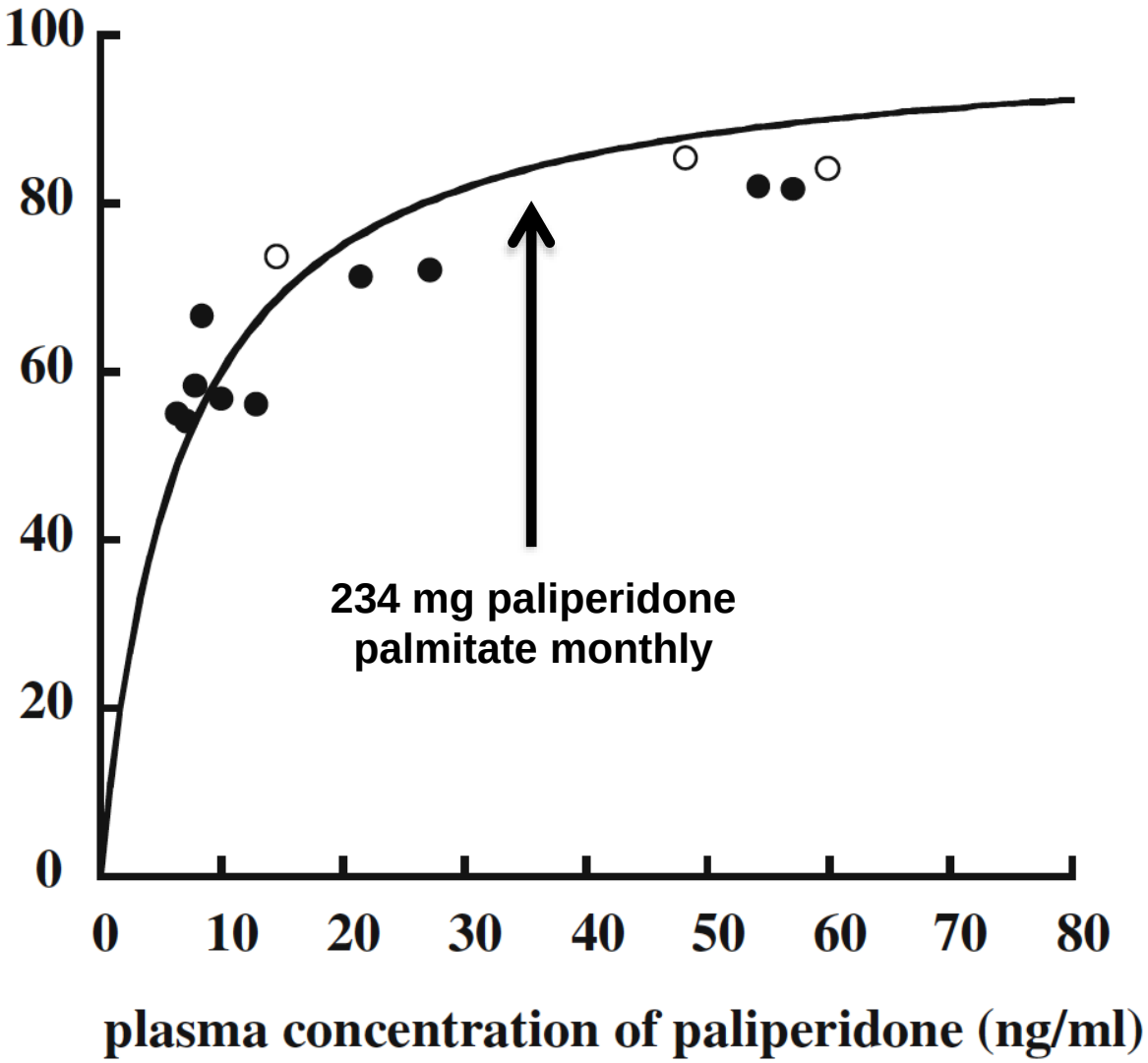
Huhn M, et al. *Lancet.* 2019; 394: 939–51.

LAI Risperidone D_2 Occupancy By Plasma Active Moiety Level (Risperidone + 9-OH Risperidone)



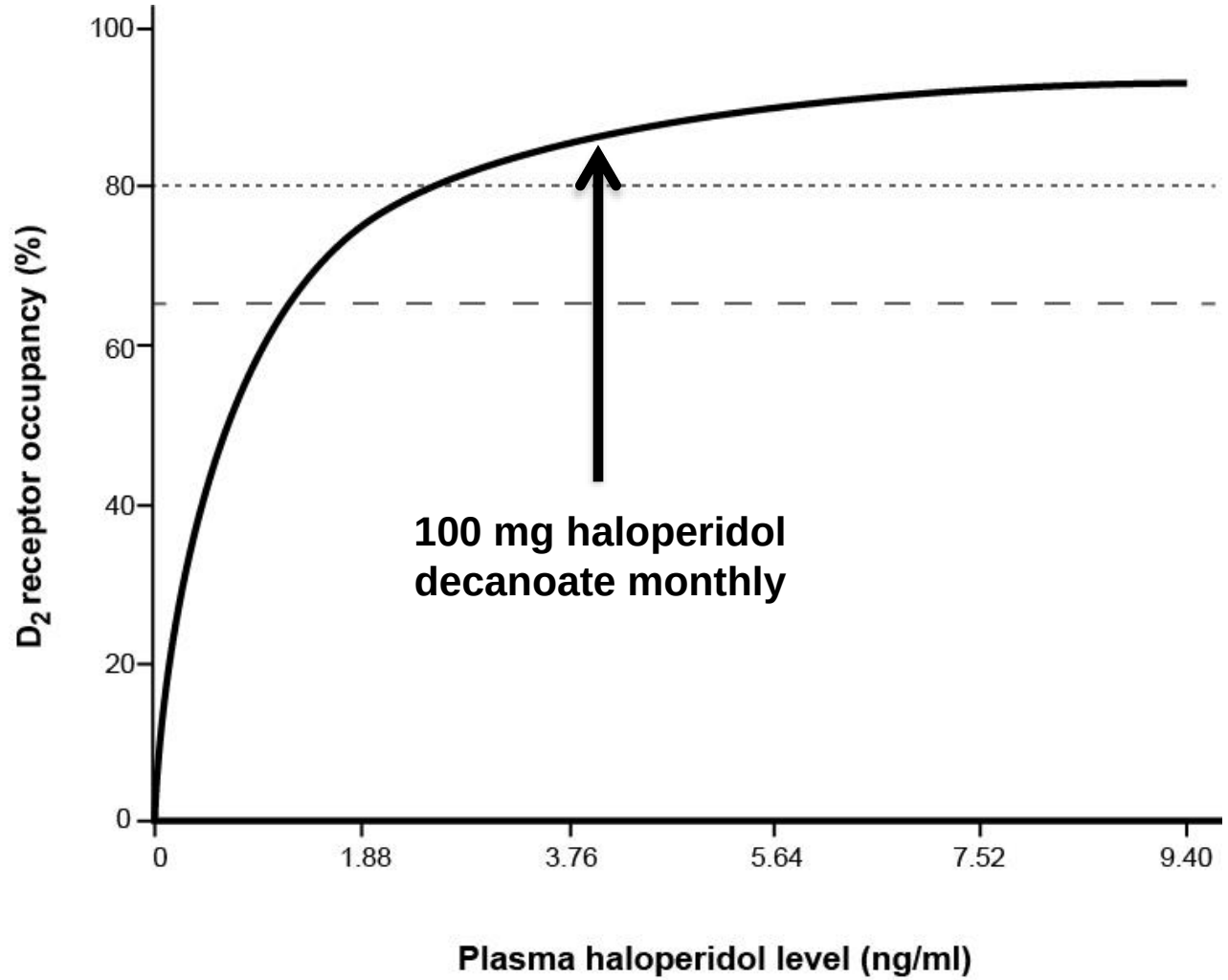
Remington G, Mamo D, Labelle A, et al. A PET study evaluating dopamine D2 receptor occupancy for long-acting injectable risperidone. *Am J Psychiatry.* 2006;163:396-401.

Striatal D_2 Occupancy vs Plasma Paliperidone Level



Arakawa R, Ito H, Takano A, et al. Dose-finding study of paliperidone ER based on striatal and extrastriatal dopamine D2 receptor occupancy in patients with schizophrenia. *Psychopharmacology.* 2008;197:229-35. Epub 2007 Dec 6.

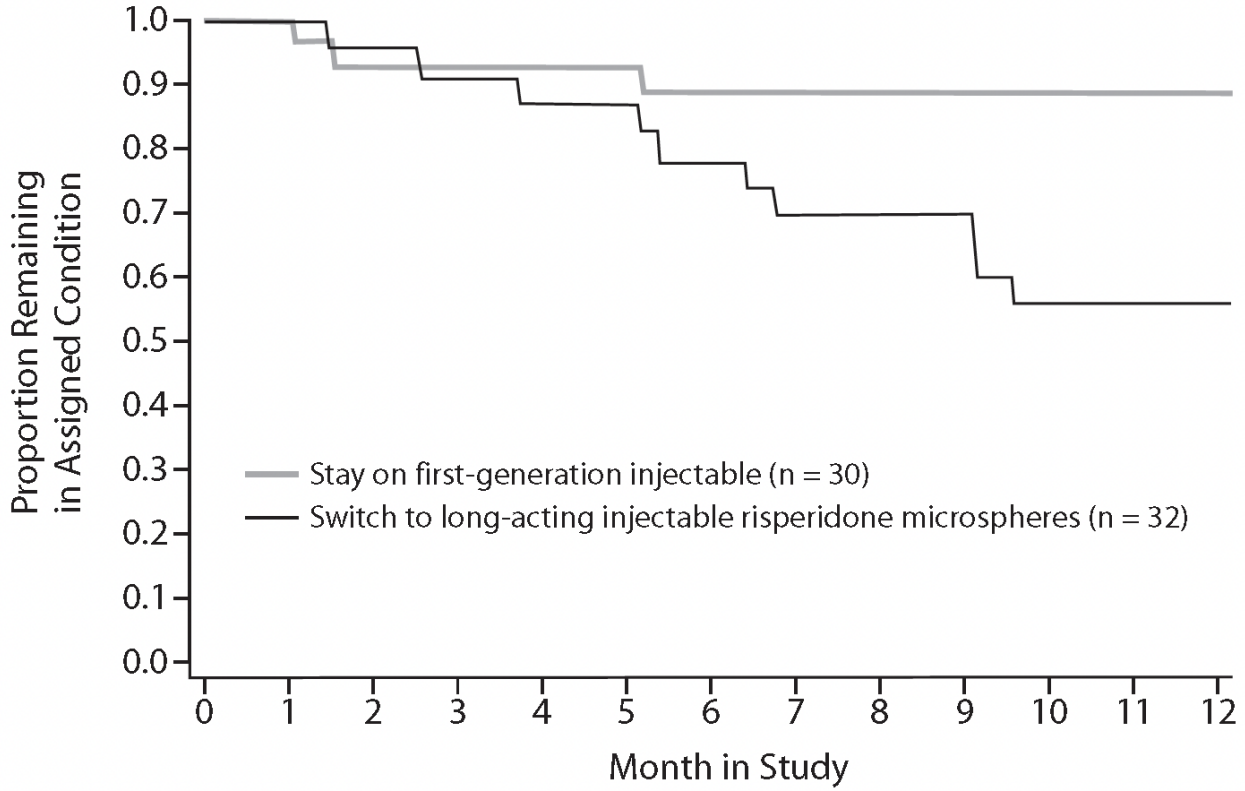
D_2 Occupancy vs Plasma Haloperidol Level



Regenthal R, et al. Haloperidol serum concentrations and D2 dopamine receptor occupancy during low-dose treatment with haloperidol decanoate. Int *Clin Psychopharmacol.* 1997; 12(5): 255-61.

FGA to Risperidone Microsphere Switch

- **Protocol:** 62 pts with SCZ spectrum disorders on haloperidol or fluphenazine dec were randomly assigned in an open label manner to stay or switch to risperidone microspheres and followed for 6 months per protocol, and another 6 months naturalistic F/U
- **Demographics:** 71% male, mean age 47.9 yrs, 38% White, BMI 31.2 kg/m^2, PANSS 67.7.
  - Baseline LAI dosages: haloperidol 117 mg/4 weeks; fluphenazine 35 mg/2 weeks.
- **Primary outcome:** all-cause discontinuation
- **Efficacy results:** No significant differences at 6 months in time to all-cause discontinuation, although more drop-outs among switchers for psychiatric Sx (n=3) than those who stayed (n=1). By month 12 the all-cause discontinuation rate was significantly different between stayers (10%) vs switchers (31%) (p=0.01).



[a]Groups did not differ at 6 months (Kaplan-Meier, Mantel-Cox $\chi^2_1 = 0.94$, $P = .33$). However, groups differed significantly at 12 months (Kaplan-Meier, Mantel-Cox $\chi^2_1 = 6.00$, $P = .01$). In Cox regression analyses, treatment group remained significant after controlling for gender and baseline decanoate (Wald $\chi^2_1 = 5.00$, $P = .03$).

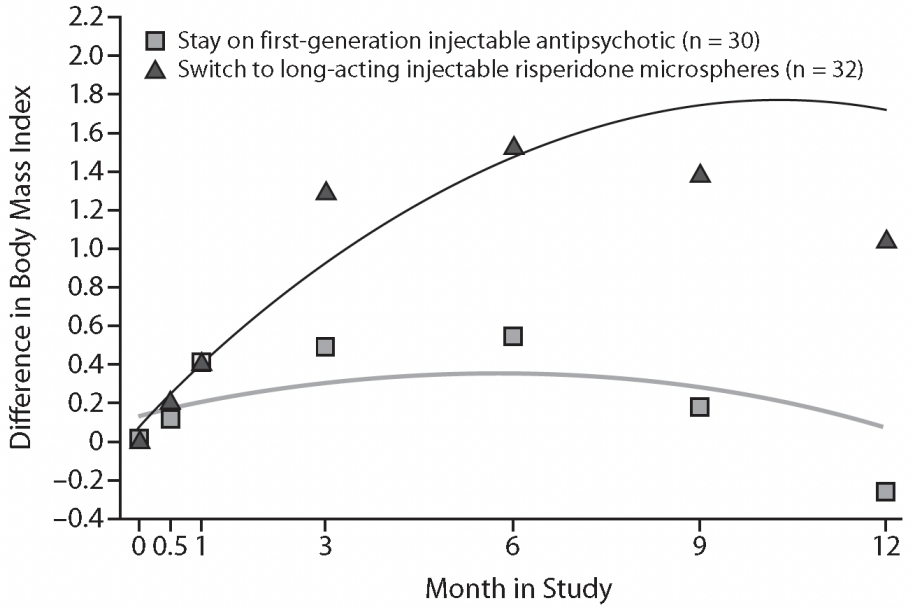
Covell NH, et al. Effectiveness of switching from long-acting injectable fluphenazine or haloperidol decanoate to long-acting injectable risperidone microspheres: an open-label, randomized controlled trial. Journal of Clinical Psychiatry 2012;73:669-75.

FGA to Risperidone Microsphere Switch

Tolerability issues

- **Weight:** Those on risperidone gained significantly more weight: BMI increase of 5% at month 6, 3% at month 12

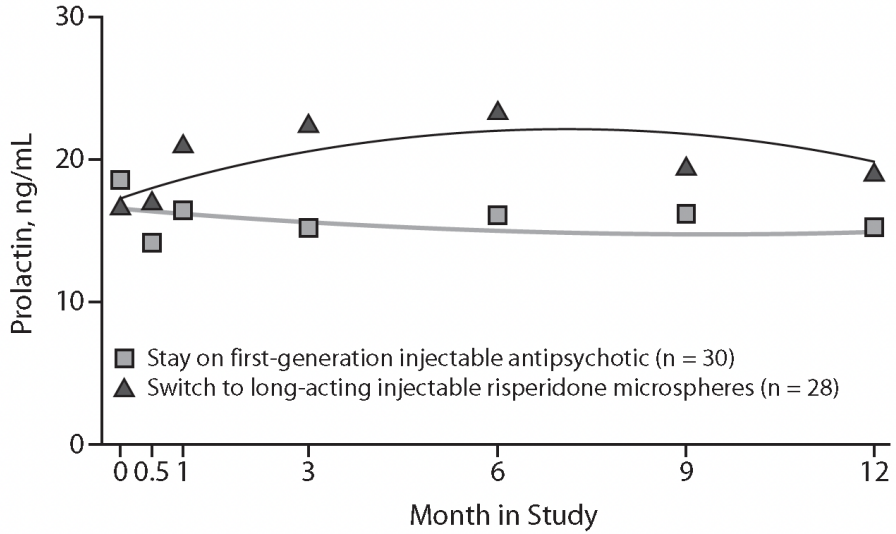
Figure 2. Difference in Body Mass Index Through Time[a,b]



Tolerability issues

- **Prolactin:** Risperidone was also associated with a greater proportion of patients with values 20 ng/ml.

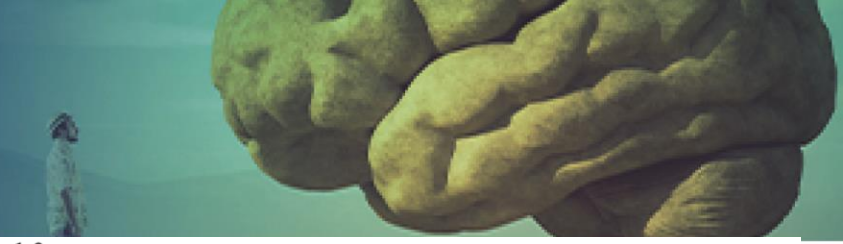
Figure 3. Prolactin Through Time[a,b]



EPS: No differences in new onset EPS or TD among those who did have these at baseline.

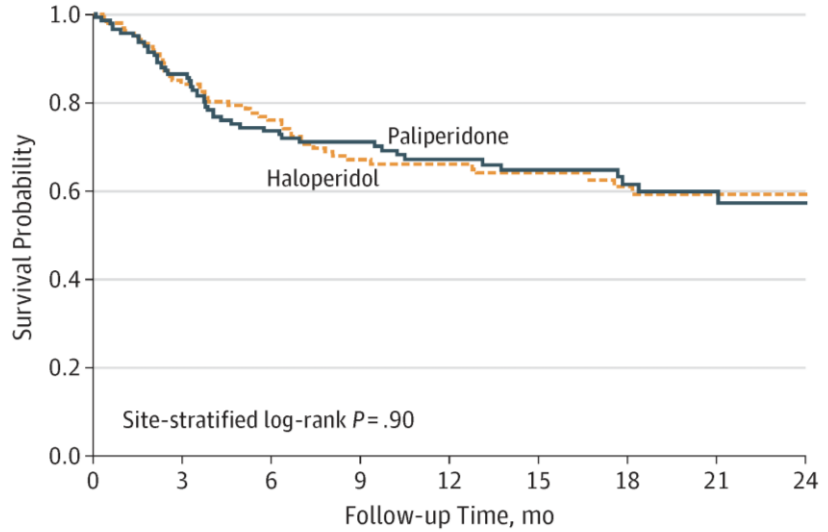
Covell NH, et al. Effectiveness of switching from long-acting injectable fluphenazine or haloperidol decanoate to long-acting injectable risperidone microspheres: an open-label, randomized controlled trial. Journal of Clinical Psychiatry 2012;73:669-75.

Double-Blind Study: Haloperidol Dec vs Paliperidone Palmitate 1 Month



- **Protocol: 311** pts with SCZ spectrum disorders **were randomly assigned** to haloperidol decanoate or PP1M, with blinded injectors and medication concealment
- **Dosing:** **PP1M**: 234 mg (D1)/156 mg (D8) (load): 117 mg/mo to start, flexible after
  HAL: 50 mg (D1)/50 mg (D1) (load): 75 mg/mo to start, flexible after
- **Primary outcome: Efficacy failure –** psych hospitalization or crisis stabilization, substantial increase in frequency of outpt visits, clinician's decision that oral AP could not be discontinued within 8 weeks after starting the LAI, or a clinician's decision to discontinue the assigned LAI due to inadequate therapeutic benefit.
- **Demographics:**

Characteristics	Paliperidone Palmitate (n = 145)	Haloperidol Decanoate (n = 145)
Demographic		
Age, mean (SD), y	43 (12.6)	45 (12.3)
Sex, No. (%)		
Men	106 (73.1)	110 (75.9)
Women	39 (26.9)	35 (24.1)
Race, No. (%)[a]		
White	56 (38.6)	54 (37.2)
Black	83 (57.2)	83 (57.2)
Other[b]	6 (4.1)	8 (5.5)
Spanish, Hispanic, or Latino ethnicity, No. (%)[a]	6 (4.1)	8 (5.5)
Clinical		
In hospital, No. (%)	24 (16.6)	28 (19.3)
Weight, mean (SD), kg	90 (21.7)	90 (22.5)
BMI, mean (SD)[c]	30 (7.4)	30 (7.3)



No. at risk									
Paliperidone	145	119	91	76	62	51	36	26	10
Haloperidol	145	107	88	71	64	51	39	30	13
No. with event									
Paliperidone	0	19	36	39	43	45	47	48	49
Haloperidol	0	21	31	41	42	44	46	47	47

Maintenance phase dosing: PP1M: 129 – 169 mg/mo
HAL: 67 – 83 mg/mo

Efficacy Results: Efficacy failure: 33.8% for PP1M vs 32.4% for HAL. This difference was not statistically significant (adjusted HR 0.98; 95% CI, 0.65-1.47).

McEvoy JP, et al. Effectiveness of paliperidone palmitate vs haloperidol decanoate for maintenance treatment of schizophrenia: a randomized clinical trial. *JAMA* 2014;311:1978-87.

Double-Blind Study: Haloperidol Dec vs Paliperidone Palmitate 1 Month

Significant Tolerability Differences

1. **Wt change:** HAL -3.88 kg vs PP1M + 6.04 kg
2. **Ever gained ≥ 15 lbs:** HAL 22.4% vs PP1M 33.1%
3. **Akathisia (BAS score ≥ 3):** HAL 10.6% vs PP1M 2.8%
4. **Peak prolactin:**
   - **Men:** HAL 15.41 ng/ml vs PP1M 34.56 ng/ml
   - **Women:** HAL 26.84 ng/ml vs PP1M 75.19 ng/ml

Outcome	Paliperidone Palmitate (n = 147)	Haloperidol Decanoate (n = 147)	*P* Value[a]
Weight change (least-squares mean) from baseline, mean (95% CI), kg			
Month 6	2.17 (1.25 to 3.09)	−0.96 (−1.88 to −0.04)	<.001[b]
Month 12	3.46 (1.83 to 5.09)	−1.93 (−3.56 to −0.31)	
Month 18	4.75 (2.36 to 7.14)	−2.91 (−5.28 to −0.53)	
Month 24	6.04 (2.88 to 9.20)	−3.88 (−7.02 to −0.73)	
Ever gained ≥15 lbs from baseline, No. (%)	48 (33.1)	32 (22.4)	.03[c]
At least 1 laboratory assessment after first injection, No. of patients	**129**	**126**	
Laboratory values, worst change from baseline			
Results, least-squares mean (95% CI)			
HbA_{1c}, %	0.34 (0.17 to 0.52)	0.23 (0.06 to 0.41)	.38[d]
Blood glucose, mg/dL	21.13 (12.59 to 29.67)	20.96 (12.38 to 29.54)	.98[d]
Total cholesterol, mg/dL	12.42 (7.20 to 17.63)	16.82 (11.56 to 22.07)	.25[d]
LDL cholesterol, mg/dL	11.70 (7.06 to 16.34)	13.49 (8.85 to 18.14)	.59[d]
Triglycerides, mg/dL	36.91 (22.40 to 51.43)	46.57 (31.93 to 61.21)	.36[d]
HDL cholesterol, mg/dL	−5.28 (−6.74 to −3.83)	−4.52 (−5.98 to −3.05)	.47[d]
Neurologic effects			
AIMS global severity score			
Incidence of AIMS ≥2, No. (%)	28 (21.4)	30 (23.8)	0.57[c]
Worst change from baseline, least-squares mean (95% CI)	0.43 (0.31 to 0.55)	0.50 (0.38 to 0.62)	.39[d]
BAS global score			
Incidence of BAS ≥3, No. (%)	4 (2.8)	15 (10.6)	.006[c]
Worst change from baseline, least-squares mean (95% CI)	0.45 (0.31 to 0.59)	0.73 (0.59 to 0.87)	.006[d]
SAS mean score			
Incidence of SAS ≥1, No. (%)	109 (79.0)	101 (74.8)	.45[c]
Worst change from baseline, least-squares mean (95% CI)	0.21 (0.16 to 0.27)	0.25 (0.20 to 0.30)	.34[d]
Serum prolactin levels			
Among men only			
Highest level after baseline, least-squares mean (95% CI), µg/L	34.56 (29.75 to 39.37)	15.41 (10.73 to 20.08)	<.001[e]
Worst ASEX after baseline, least-squares mean (95% CI)[f]	17.68 (16.36 to 19.00)	17.95 (16.66 to 19.25)	.77[e]
ASEX score ≥19, No. (%)	34 (37.8)	37 (39.4)	.72[c]
Incidence of gynecomastia or galactorrhea, No. (%)[g]	5 (4.7)	3 (2.8)	.46[h]
Among women only			
Highest level after baseline, least-squares mean (95% CI), µg/L	75.19 (63.03 to 87.36)	26.84 (13.29 to 40.40)	<.001[e]
Worst ASEX after baseline, least-squares mean (95% CI)[f]	23.41 (21.01 to 25.80)	22.83 (20.12 to 25.54)	.75[e]
ASEX score ≥19, No. (%)	24 (72.7)	19 (73.1)	.88[c]
Incidence of gynecomastia, galactorrhea, or menstrual irregularities, No. (%)[i]	10 (38.5)	5 (29.4)	.13[c]

McEvoy JP, et al. Effectiveness of paliperidone palmitate vs haloperidol decanoate for maintenance treatment of schizophrenia: a randomized clinical trial. JAMA 2014;311:1978-87.

Structural Brain Changes in Schizophrenia at Different Stages of the Illness in Longitudinal MRI Studies

Method: Reviewed findings from findings from longitudinal MRI studies investigating structural brain alterations and its impact on clinical outcome at different stages of the illness: (1) subjects at ultra-high risk of developing psychosis, (2) patients with a first episode psychosis, and (3) chronically ill patients. Also reviewed studies examining the longitudinal effects of medication on brain structure in patients with schizophrenia.

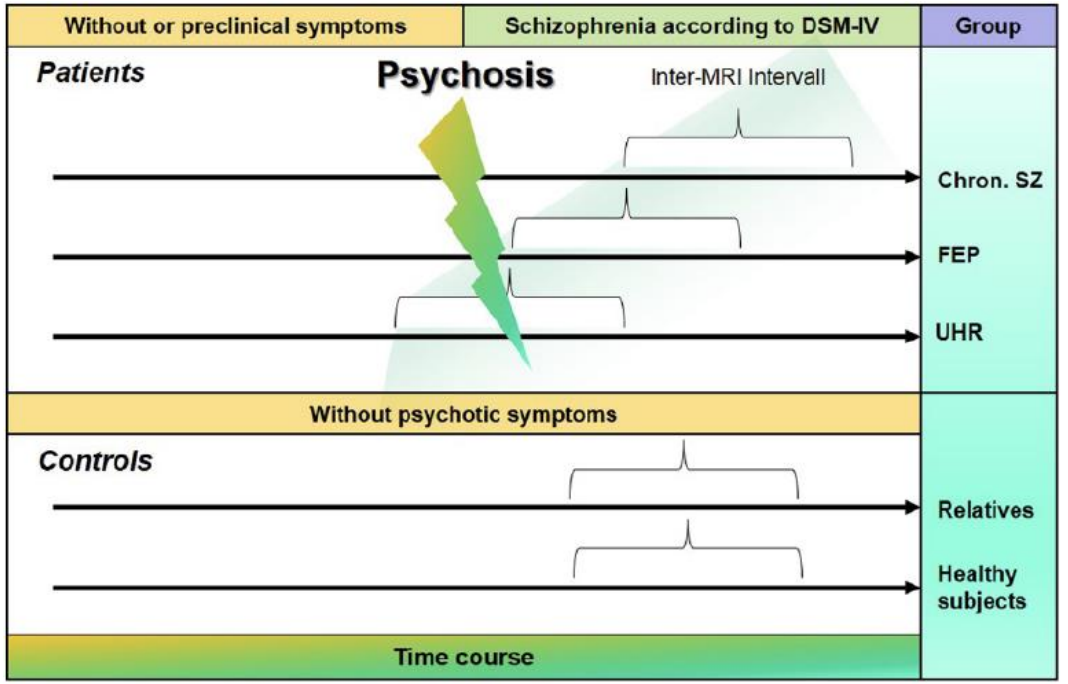
Conclusions:

i. **Pre-clinical stages to conversion:** more pronounced cortical gray matter loss (i.e. superior temporal & inferior frontal regions) in those who later made transition to psychosis.

ii. **First episode psychosis:** a decline in multiple gray matter regions (i.e. frontal regions and thalamus) and progressive cortical thinning in the superior and inferior frontal cortex.

iii. **Chronic schizophrenia:** gray matter decreased to a greater extent (i.e. frontal and temporal areas, thalamus, and cingulate cortices)—especially in poor-outcome patients.

Dietsche B, Kircher T and Falkenberg I (2017) Structural brain changes in schizophrenia at different stages of the illness: A selective review of longitudinal magnetic resonance imaging studies. Australian and New Zealand Journal of Psychiatry 51: 500–508.



Medication effects on MRI volume changes: Findings of med effects and differences between meds are unclear. Residual confounding may account for findings *so caution must be applied before drawing causal inferences from associations demonstrated in observational studies of moderate size*. Volume increases and decreases probably interact in a complicated way with the individual illness course. In general, it is yet not clear what kind of volume changes, decreases or increases, are potentially 'good' or 'bad' for the individual patient.

Do APs Impact Brain Volume and are There Differences Between FGA and SGA

- **Method:** Meta-analysis of *prospective studies* involving patients with schizophrenia and other psychotic disorder to examine longitudinal MRI changes. Use of prospective data removes some of the confounding issues inherent to retrospective analyses. Of 2639 papers only 4 met criteria for review.

- **Conclusions:** Bearing in mind the limited amount of prospective literature these results suggest no significant difference between FGA & SGA APs on brain structure (by MRI) and in comparison to healthy subjects. There does not seem to be any strong support to the opinion that APs cause loss of brain volume in patients with schizophrenia.

Author, year	Design	Duration	Arms	*N*	% of schizophrenia	Age	Mean dosage	Substance abuse	Males(%)	Comments
Lieberman et al. (2005)	Longitudinal, randomized, controlled, multisite, double-blind	104weeks	Haloperidol Olanzapine Controls	79 pts 82 pts 58 healthy	73.4 56.1 –	24.11 ± 4.64 23.60 ± 4.50 23.85 ± 4.56	2–20 5–20 –	SUD excluded	89.9 79.3 64.5	First-episode patients, most had received treatment in the past but for less than 16weeks
Garver et al. (2005)	Pseudorandomization	4weeks	Ris/Zipr Haloperidol Controls	7/6 pts 6 pts 7 controls	Unknown	31.6 ± 10.2 32.2 ± 14.8 29 ± 9	4/120 7 -	SUD excluded	69 67 71.4	Half were first-episode patients, overall patients had problematic adherence to medication in the past. Proportion of schizophrenia unknown Duration too short to arrive at conclusions
Crespo-Facorro et al. (2008)	Longitudinal, randomized, controlled, open	52 weeks	Haloperidol Risperidone Olanzapine Controls	18 pts 16 pts 18 pts 38 healthy	57.7	29.76 ± 7.88 24.99 ± 5.96 28.00 ± 5.09	244.09[a] 183.65 289.02 -	38.9 68.7 61.1 -	61.1 81.3 72.2 68.4	First-episode patients, mostly medication naïve.
Chopra et al. (2021)	Longitudinal, randomized, controlled, triple-blind	52 weeks	Risperidone Paliperidone Placebo Controls	25 pts 5 pts 30 pts 27 healthy	33.3%	19.5 ± 274 18.8 ± 272 21.9 ± 1.93	1 3		55.2 53.4 37.1	First-episode patients, the first and only study with a placebo arm

Fountalakis KN, Stahl SM. The effect of first- and second-generation antipsychotics on brain morphology in schizophrenia – A systematic review of longitudinal magnetic resonance studies with a randomized allocation to treatment arms JOP 2022

First Generation AP LAIs

DRUG	VEHICLE	DOSAGE	t_{max}	$t_{1/2}$ MULTIPLE DOSING	ABLE TO BE LOADED
First-generation antipsychotics					
Fluphenazine decanoate	Sesame oil	12.5–75 mg/2 weeks **Max:** 75 mg/week	0.3–1.5 days	14 days	Yes
Haloperidol decanoate	Sesame oil	25–300 mg/4 weeks **Max:** 300 mg/2 weeks	3–9 days	21 days	Yes

Advantages:

1. Deliver more D_2 blockade than can be achieved with any SGA LAI
2. Less metabolic effects than SGAs
3. Inexpensive
4. Easily loaded
5. Extensive knowledge of threshold plasma level and the point of futility

Disadvantages:

1. More D_2 related adverse effects than SGA LAI
2. Site reactions from sesame oil vehicle
3. Single injections cannot exceed 3 ml due to discomfort. Patients who require doses which exceed this volume will require more frequent injections (Ex: haloperidol decanoate 200 mg every 2 weeks in lieu of 400 mg monthly, fluphenazine decanoate 50 mg weekly in lieu of 100 mg every 2 weeks).

Meyer JM. Pharmacotherapy of Psychosis and Mania. In: Brunton LL, ed. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 14th Edition. Chicago, Illinois: McGraw-Hill; 2022; chapter 19.

SGA LAIs: Aripiprazole

DRUG	VEHICLE	DOSAGE	t_{max}	$t_{1/2}$ MULTIPLE DOSING	ABLE TO BE LOADED
Aripiprazole monohydrate (Abilify Maintena)	Water	300–400 mg/4 weeks **Max:** 400 mg/4 weeks	6.5–7.1 days	29.9–46.5 days	**No** (14 days oral overlap)
Aripiprazole lauroxil (Aristada)[e]	Water	441, 662, 882 mg/4 wks 882 mg/6 weeks 1064 mg/8 weeks **Max:** 882 mg/4 weeks	41 days (single dose) 24.4–35.2 days (repeated dosing)	53.9 – 57.2 days	No (start with AL_{NCD} 675 mg IM + 30 mg oral ***OR*** 21 days oral overlap)
Aripiprazole lauroxil nanocrystal (Aristada Initio)[f]	Water	675 mg once	27 days (range: 16–35 days)	15–18 days (single dose)	—

Advantages:

1. Low risk of metabolic and endocrine adverse effects
2. Aripiprazole lauroxil can be started using nanocrystal 675 mg IM + 30 mg oral dose in lieu of 3 weeks oral bridge (+ maintenance IM dose)
3. Aripiprazole lauroxil has 6- and 8-week options
4. Rates of akathisia are comparable to D_2 antagonist AP LAIs

Disadvantages:

1. A subset of schizophrenia patients may need a D_2 antagonist for optimal positive symptom control
2. Aripiprazole monohydrate requires 2 weeks of oral overlap

Meyer JM. Pharmacotherapy of Psychosis and Mania. In: Brunton LL, ed. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 14th Ed. Chicago, Illinois: McGraw-Hill; 2022; ch 19.

SGA LAIs: Risperidone

DRUG	VEHICLE	DOSAGE	t_{max}	$t_{1/2}$ MULTIPLE DOSING	ABLE TO BE LOADED
Risperidone subcutaneous (Perseris)	Water	90–120 mg/4 weeks **Max:** 120 mg/4 weeks	7–8 days	9–11 days	Not needed
Risperidone subcutaneous (TV-46000)	Water	50–125 mg/4 weeks 100–250 mg/8 weeks **Max:** 125 mg/4 weeks 250 mg/8 weeks	8–14 days	15–21 days	Not needed
Risperidone microspheres (Risperdal Consta)	Water	12.5–50 mg/2 weeks **Max:** 50 mg/2 weeks	21 days	See note[a]	**No** (21–28 days oral overlap)

Advantages:

1. Risperidone approved 1993 – well known
2. SC forms do not require oral overlap
3. TV-46000 can be administered in upper arm, will have 2 month option and max dose will be equivalent to 5 mg/d oral risperidone

Disadvantages:

1. Metabolic and endocrine adverse effects
2. Risp microspheres: unfavorable PK - long T_{max}, ≥ 3 weeks of oral overlap, injections are every 2 weeks
3. Risp SC (90 mg/120 mg): extensive mixing, injected in abdominal SC tissue, the 'implant' forms a nodule, 120 mg only equivalent to 4 mg/d oral risperidone
4. TV-46000 – not approved yet!

Meyer JM. Pharmacotherapy of Psychosis and Mania. In: Brunton LL, ed. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 14th Ed. Chicago, Illinois: McGraw-Hill; 2022; ch 19.

SGA LAIs: Paliperidone

DRUG	VEHICLE	DOSAGE	t_{max}	$t_{1/2}$ MULTIPLE DOSING	ABLE TO BE LOADED
Paliperidone palmitate (monthly) (Invega Sustenna)[b]	Water	39–234 mg/4 weeks (25–150 mg/4 weeks) **Max:** 234 mg/4 weeks (150 mg/4 weeks)	13 days	25–49 days	Yes
Paliperidone palmitate (3 month) (Invega Trinza)[c]	Water	273–819 mg/12 weeks (175–525 mg/12 weeks) **Max:** 819 mg/12 weeks (525 mg/12 weeks)	84–95 days (deltoid) 118–139 days (gluteal)	30–33 days	No
Paliperidone palmitate (6 month) (Invega Hafyera)[d]	Water	1092–1560 mg/26 weeks (700–1000 mg/26 weeks) **Max:** 1560 mg/26 weeks (1000 mg/26 weeks)	148–159 days (gluteal)	29–32 days	No

Advantages:

1. Can be loaded
2. Minimal drug-drug interactions (renally excreted via PGP)
3. Max dose equivalent to 6 mg/d oral risperidone
4. 3 month & 6 month options for pts on PP 1 month for ≥ 4 months

Disadvantages:

1. Metabolic and endocrine adverse effects

Meyer JM. Pharmacotherapy of Psychosis and Mania. In: Brunton LL, ed. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 14th Ed. Chicago, Illinois: McGraw-Hill; 2022; ch 19.

SGA LAI - Olanzapine

DRUG	VEHICLE	DOSAGE	t_{max}	$t_{1/2}$ MULTIPLE DOSING	ABLE TO BE LOADED
Olanzapine pamoate (Zyprexa Relprevv)	Water	150–300 mg/2 weeks 300–405 mg/4 weeks **Max:** 300 mg/2 weeks	7 days	30 days	Yes

Advantages:

1. Olanzapine's small efficacy advantage for some patients
2. Can loaded
3. Max dose equivalent to 20 mg/d oral olanzapine

Disadvantages:

1. Metabolic adverse effects
2. Postinjection delirium/sedation syndrome: requires 3 hours of observation after each injection

Meyer JM. Pharmacotherapy of Psychosis and Mania. In: Brunton LL, ed. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 14th Edition. Chicago, Illinois: McGraw-Hill; 2022; ch 19

Considerations in Choosing an LAI

Patient Factors

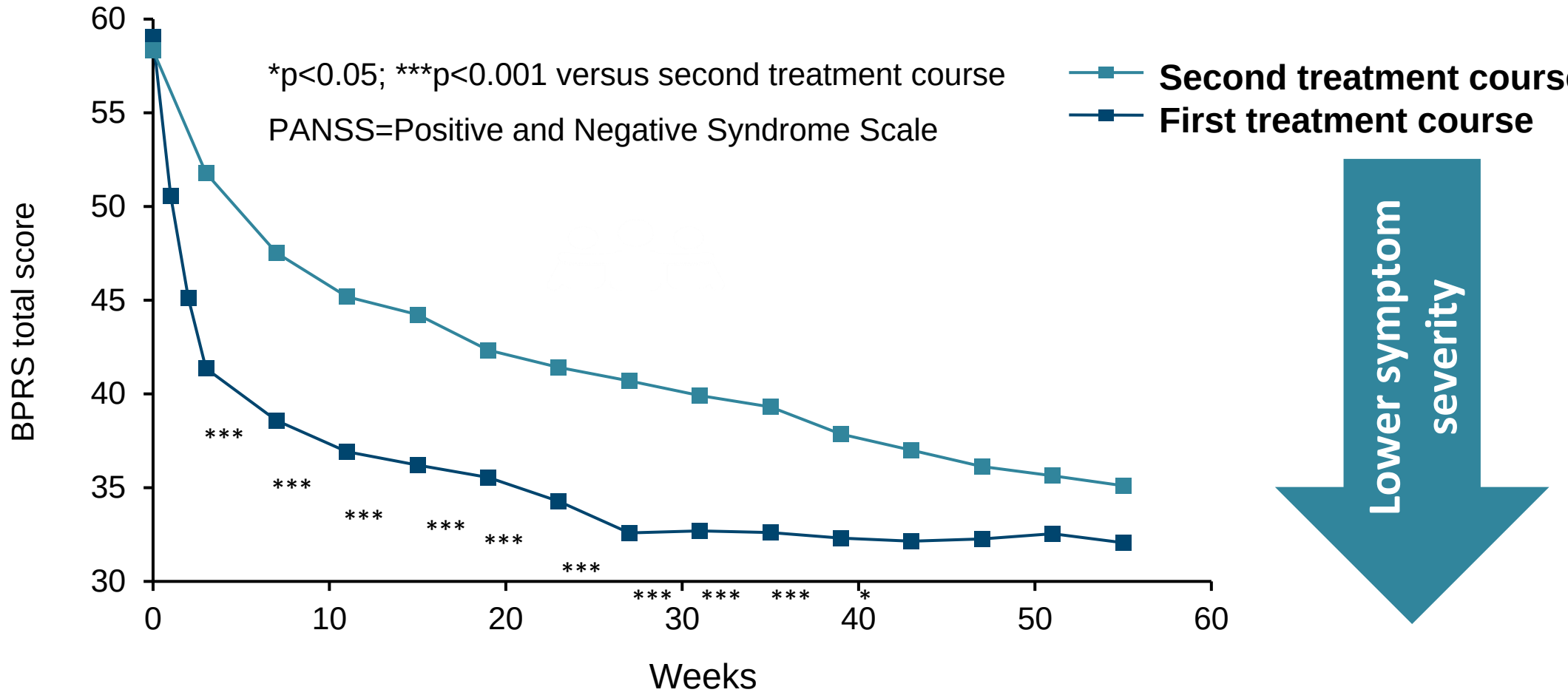
1. FEP/Younger patients: avoidance of ALL adverse effects is important as this is their first medication experience, esp. weight gain, sexual AEs, EPS
2. Preference for a dosing interval
3. Preference for non-gluteal injection
4. Need for more or less D_2 blockade based on prior Hx
5. Prior h/o AEs, medication sensitivity or injection site reactions
6. Schizophrenia Dx: **every** patient should be offered an LAI, especially early in the course of treatment, as relapse increases risk of treatment resistance
7. Bipolar I Dx: only two LAIs have indications in adults, and this may influence what the insurer will approve: risperidone microspheres (monotherapy & adjunct to lithium/VPA); aripiprazole monohydrate (monotherapy)

Medication Factors

1. Ability to load (haloperidol dec, fluphenazine dec, paliperidone palmitate, olanzapine pamoate) or initiate (e.g. aripiprazole lauroxil nanocrystal + maintenance + 30 mg single PO dose, subcutaneous risperidone) without oral bridging therapy
2. Need for extended interval as patient transitions between care sites (e.g. jail/prison or hospital -> community)
3. Ability to monitor for postinjection delirium/sedation syndrome when using olanzapine pamoate
4. Prior h/o injection site reaction from oil based LAIs

Takeuchi H, et al. Does relapse contribute to treatment resistance? Antipsychotic response in first- vs. second-episode schizophrenia. Neuropsychopharmacology 2019; 44: 1036–1042.

Treatment Response: Declines with Each Relapse



BPRS = Brief Psychiatric Rating Scale.

Agid et al. Neuropsychopharmacology 2014;39:S373–S374; 2. Zipursky et al. Poster at ACNP 2014.

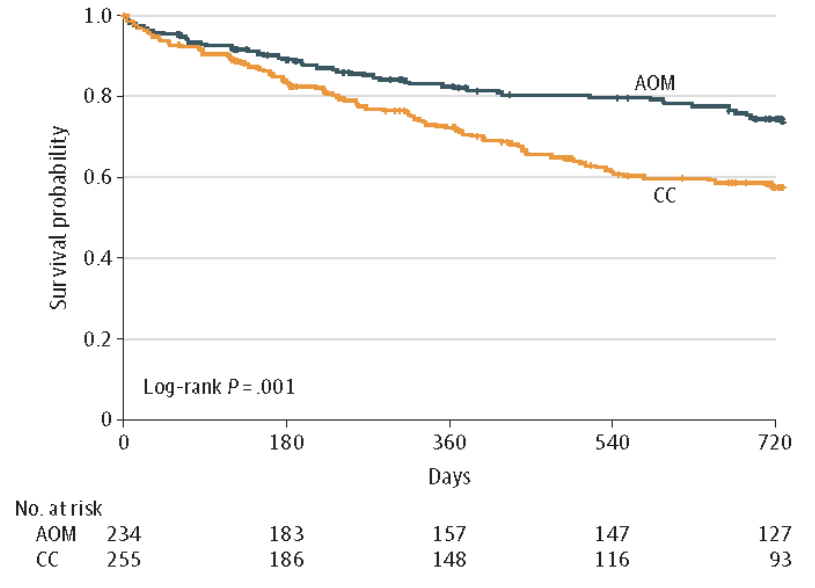
Case Study: Jasmine

- 21 year old AA female
- First break 3 months ago while at college, with one hospitalization for psychosis
- Now minimally symptomatic
- Patient thoughts:
  - “I guess I need the medicine but I feel better.”
  - “My current medicine made me gain a lot of weight and my periods have become irregular so I’ve skipped a few doses here and there.”
  - “I’d like to go back to college and finish. I also don’t want other people seeing me take my medicine.”

First Episode Patients and LAIs

- **Will FEP patients accept LAIs? Yes** - numerous studies indicate that FEP patients will accept LAIs, and may choose this option primarily for convenience, to avoid stigma of pill taking, or to minimize being reminded of their illness by daily pill taking.
- **Do FEP patients benefit from an LAI? Yes.** Retrospective & prospective studies show decreased hospitalization & relapse rates. An analysis of LAI use in FEP patients in Montréal noted that those who received an LAI as their first treatment were more likely to have baseline poor prognostic factors; however, their relapse rate was similar to those with good prognostic factors who only received oral antipsychotics. [7]
  - 2020 prospective, randomized study of once monthly aripiprazole (AOM) vs usual care (clinician's choice – CC) in 255 young adults with < 5 yrs of schizophrenia illness (figure).[10]
  - **For time to first hospitalization, the hazard ratio was 0.56** (95%CI, 0.34- 0.92; P = .02), favoring AOM. The number needed to treat to prevent 1 additional hospitalization was 7 participants treated with AOM compared with CC.

Figure 2. Time Remaining Without Having a First Hospitalization



Log rank test χ^2 = 11.373; df = 1; P < .001. AOM indicates aripiprazole once monthly; CC, clinician's choice.

1. Weiden PJ, et al. A randomized controlled trial of long-acting injectable risperidone vs continuation on oral atypical antipsychotics for first-episode schizophrenia patients: initial adherence outcome. Journal of Clinical Psychiatry 2009;70:1397-406.
2. Tiihonen J, et al. A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia.[Erratum appears in Am J Psychiatry. 2012 Feb;169(2):223]. American Journal of Psychiatry 2011;168:603-9.
3. Subotnik KL, et al. Long-acting injectable risperidone for relapse prevention and control of breakthrough symptoms after a recent first episode of schizophrenia : a randomized clinical trial. JAMA Psychiatry 2015;72:822-9.
4. Tiihonen J, et al. Real-world effectiveness of antipsychotic treatments in a nationwide cohort of 29823 patients with schizophrenia. JAMA Psychiatry 2017;74:686-93.
5. Medrano S, et al. Three-year naturalistic study on early use of long-acting injectable antipsychotics in first episode psychosis. Psychopharmacol Bull 2018;48:25-61.
6. Dufort A, Zipursky RB. Understanding and managing treatment adherence in schizophrenia. Clin Schizophr Relat Psychoses 2019.
7. Abdel-Baki A, et al. Impact of early use of long-acting injectable antipsychotics on psychotic relapses and hospitalizations in first-episode psychosis. International Clinical Psychopharmacology 2020;35:221-8.
8. Emsley R, et al. Predictors of psychosis breakthrough during 24 months of long-acting antipsychotic maintenance treatment in first episode schizophrenia. Schizophrenia Research 2020;225:55-62.
9. Taipale H, et al. Real-world effectiveness of antipsychotic doses for relapse prevention in patients with first-episode schizophrenia in Finland: a nationwide, register-based cohort study. The Lancet Psychiatry 2022.
10. Kane JM, et al. Effect of long-acting injectable antipsychotics vs usual care on time to first hospitalization in early-phase schizophrenia: a randomized clinical trial. JAMA Psychiatry 2020;77:1-8.

How to Administer an LAI

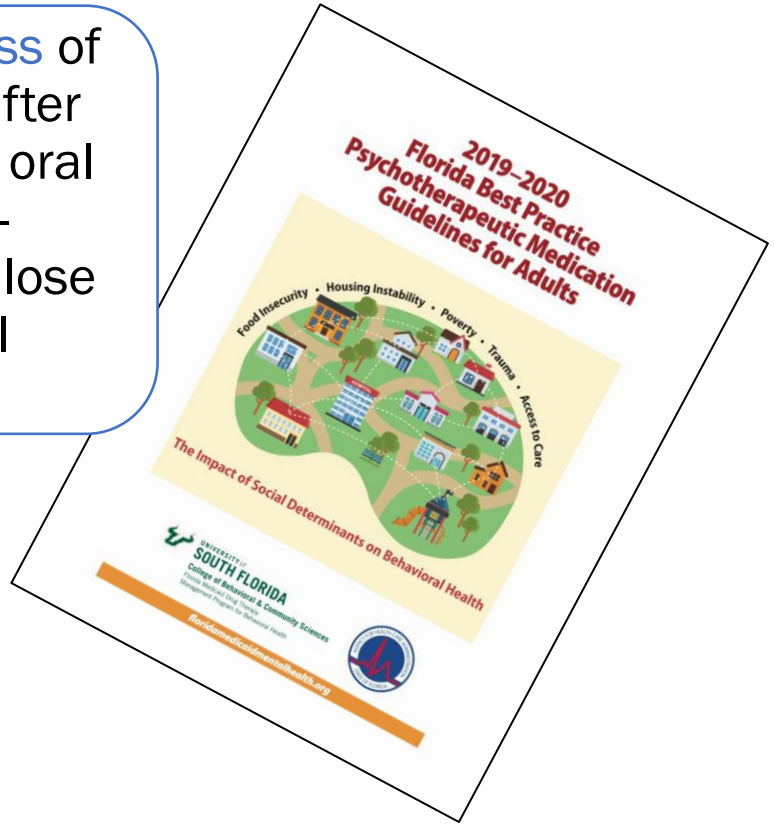
Desiree Matthews, PMHNP

Advanced Practice Provider Clinical Liaison

Monarch, Charlotte, NC

New Guidance on LAI Antipsychotic Medication

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"



LAI antipsychotic medication is advocated *if they **prefer** such treatment **or** if they have a history of poor or uncertain **adherence.***

FEP = first episode psychosis.

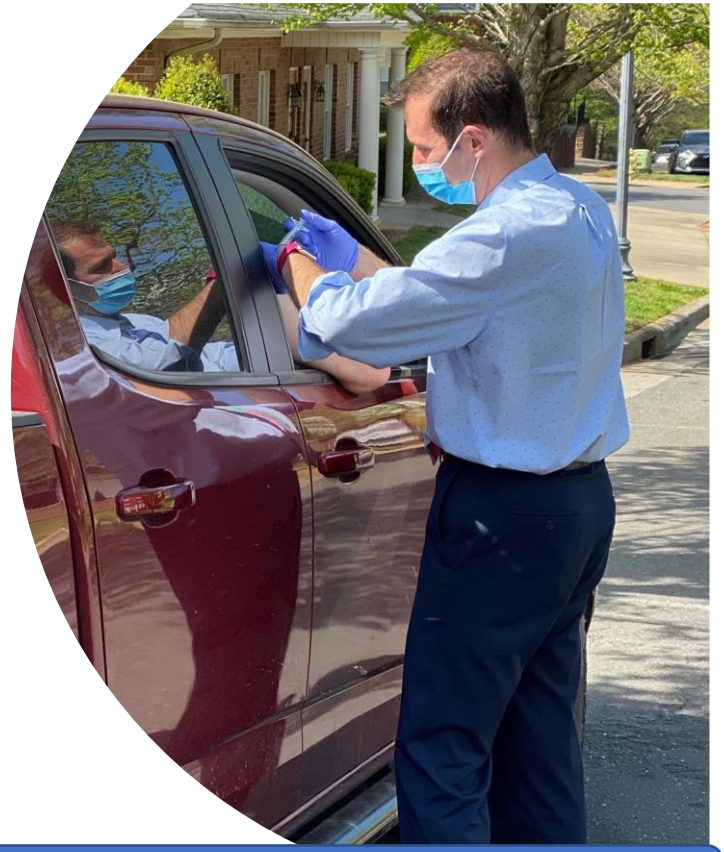
Keepers GA, et al. *Am J Psychiatry*. 2020;177(9):868-72. Florida Center for Behavioral Health Improvements and Solutions. *2019-2020 Florida Best Practice Psychotherapeutic Medication Guidelines for Adults*. Florida Center for Behavioral Health Improvements and Solutions; 2020.

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



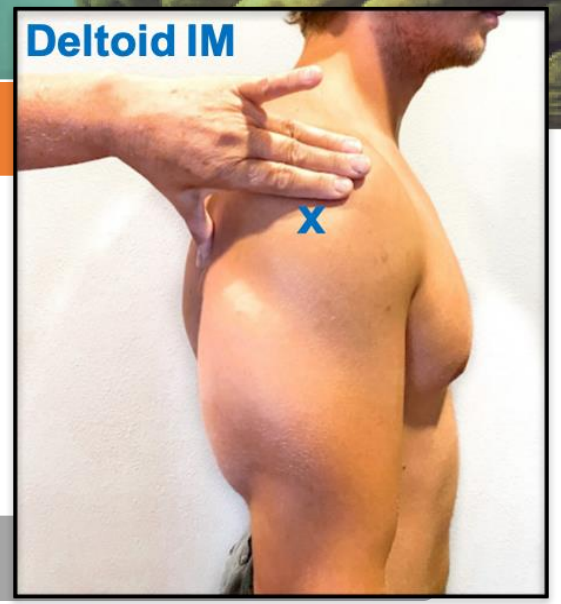
If we're creative and flexible, we can overcome any challenge to meeting our patients' needs!

American Psychiatric Association [www.psychiatry.org]. Last updated 2020. Accessed February 5, 2022. https://www.psychiatry.org/File%20Library/Psychiatrists/APA-Guidance-Long-Acting-Injectables-COVID-19.pdf. Chepke C. *Current Psychiatry.* 2020;19(5):29-30.

Administering the Injection

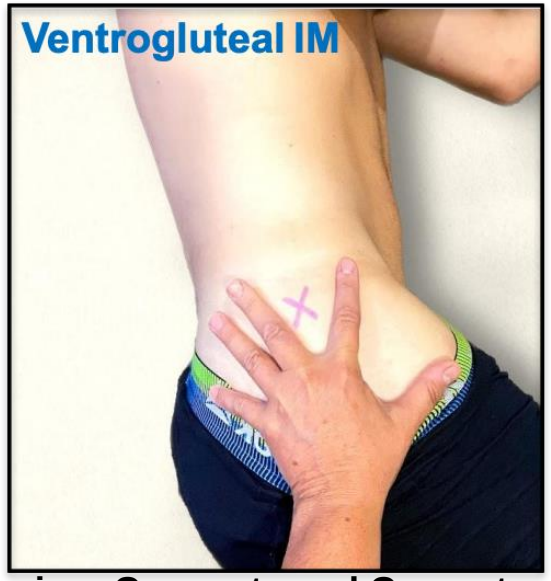
Deltoid Injections

- 2-3 fingerbreadths below the acromial process
- Stretch skin tight
- Insert needle at 90° angle with quick firm motion
- Dispense solution then remove needle



Gluteal Injections

- Find trochanter (top of femur) and place palm of hand there
- Point index finger toward iliac crest
- Spread index finger and middle finger, making a V
- Injection should be given between knuckles of index finger and middle finger
- Stretch skin tight
- Insert needle at 90° angle with quick firm motion
- Dispense solution then remove needle

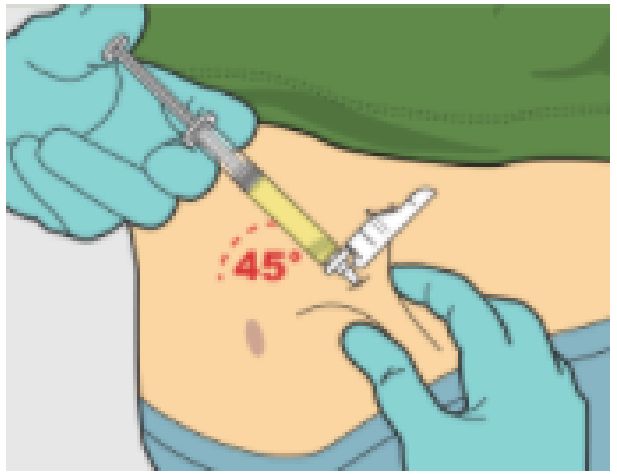


Hopkins U, et al. Oncology Nurse Advisor. 2013;4(1):32-37. 82-90. Craven RF, et al. Fundamentals of Nursing: Concepts and Competencies for Practice.9th Ed. Lippincott Williams & Wilkins, 2019.

Administering the Injection

Subcutaneous Injections

- Have patient positioned supine
- Find adequate subcutaneous abdominal tissue
- Pinch enough skin to accommodate needle size
- Insert needle at 45° angle
- Inject medication slow and steady
- Remove needle from same angle as insertion
- Release the skin

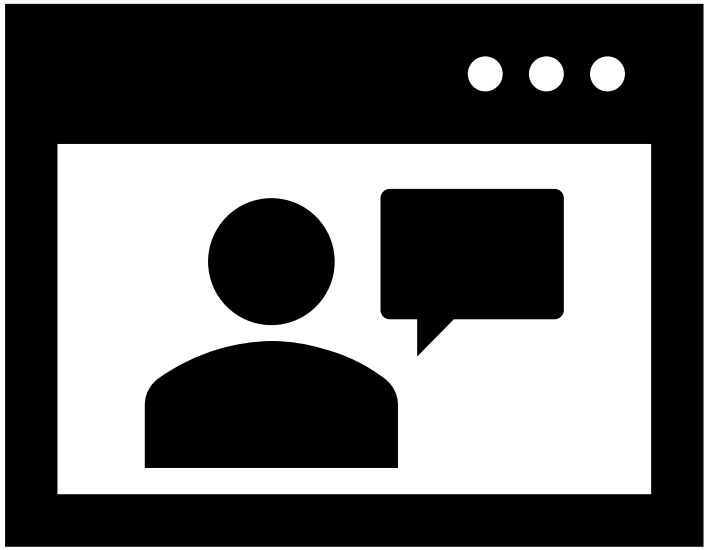


PERSERIS [prescribing information]. North Chesterfield, VA: Indivior Inc; 2019. 2. Data on file. Indivior Inc. North Chesterfield, VA; 2018.

Boosting Confidence for Administration

Observe an experienced colleague.

Watch an instructional video / demo.

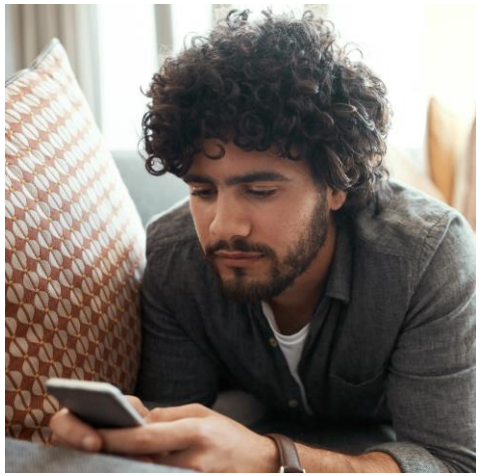


Practice on a training model.

The Art of the Jab: Countering Needle Pain/Anxiety

Encourage breathing exercises

Distract the patient by engaging in conversation



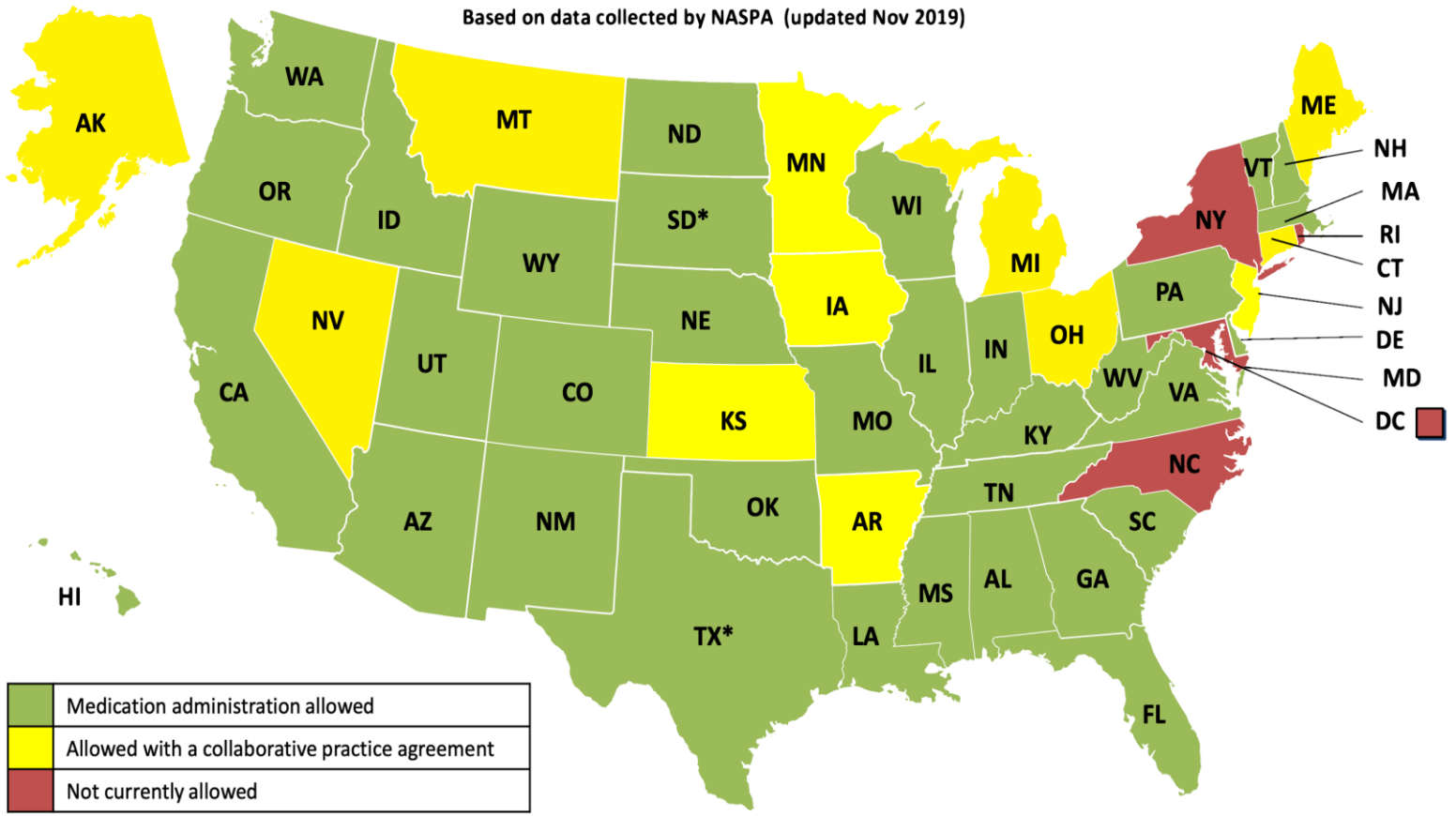
Insert needle quickly, in a dart-like fashion

Avoid needle clogs by injecting slowly (except aripiprazole lauroxil)

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

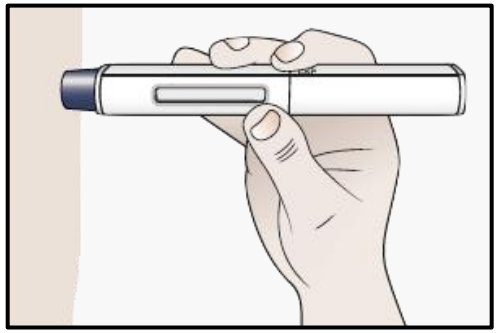
Taddio A, et al. *CMAJ.* 2015;187(13):975-982. Usach I, et al. *Adv Ther*. 2019;36(11):2986-2996. Advisory Committee On Immunization Practices (ACIP) [www.cdc.gov]. Last updated February 15, 2022. Accessed February 5, 2022. https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/downloads/general-recs.pdf. 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



Pharmacist authority to administer LAIs

Partnering with PCPs



Maybe one day?

PCP = primary care provider.

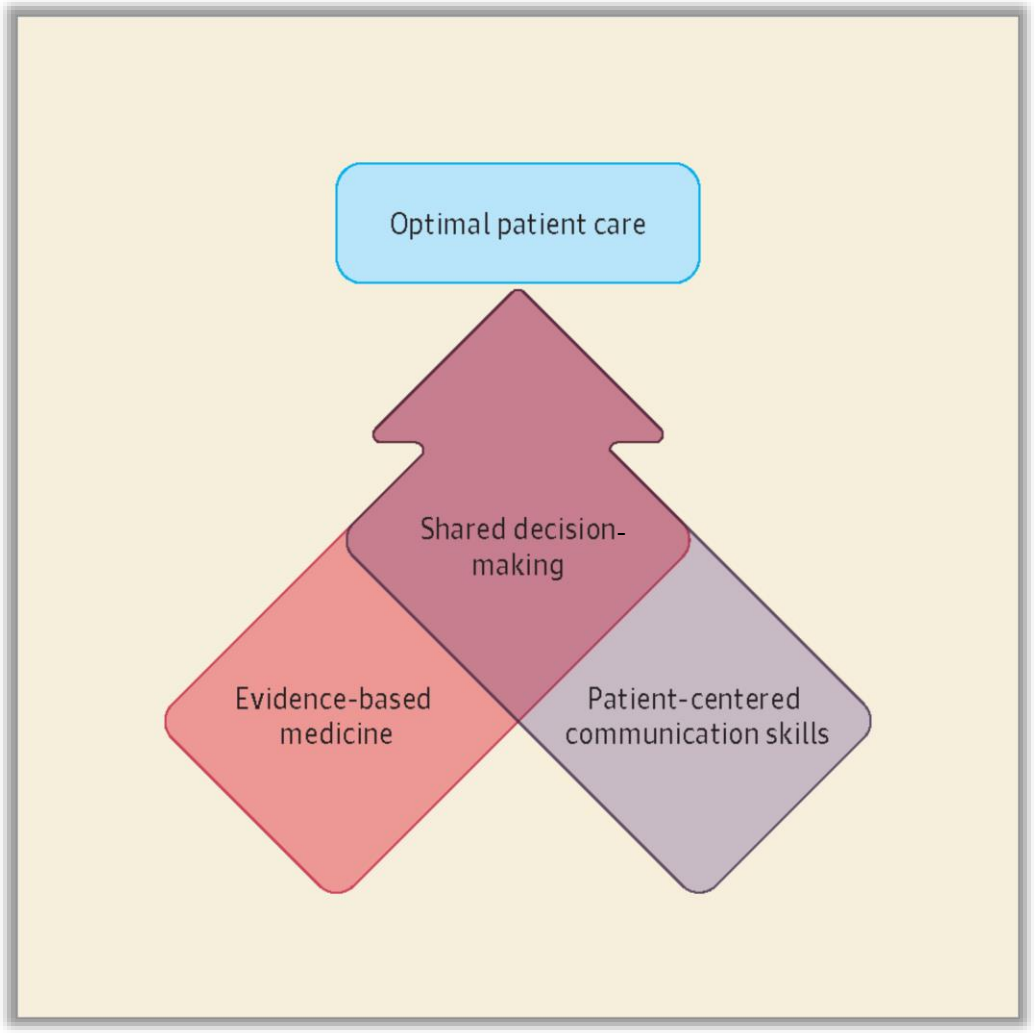
National Alliance of State Pharmacy Associations (NASPA) [www.naspa.us]. Last updated 2017. Accessed February 5, 2022. https://naspa.us/wp-content/uploads/2017/07/Pharmacists-Authority-to-Administer-Medications.pdf. Keepers GA, et al. *Am J Psychiatry*. 2020;177(9):868-72.

Best Practices to Assess Patient Preferences, Optimize Treatment Selection, Encourage Acceptance, and Address Barriers to Adherence

Jonathan M. Meyer, MD

Clinical Professor of Psychiatry
University of California, San Diego

Connection Between Evidence-Based Medicine & Shared Decision-Making



Hoffman TC et al. JAMA 2014;312(13):1295-6.

Always a risk: benefit assessment

- Psychiatric condition/diagnosis, target symptoms
- History: response, adherence, AEs
- Comorbidities

Shared decision-making

- Patient-centered approach to making treatment decisions
- Options with consequences explored with decision aids during clinical encounters
- Informed decisions reflecting patient values and goals made with clinicians

Use Shared Language to Reach Shared Goals

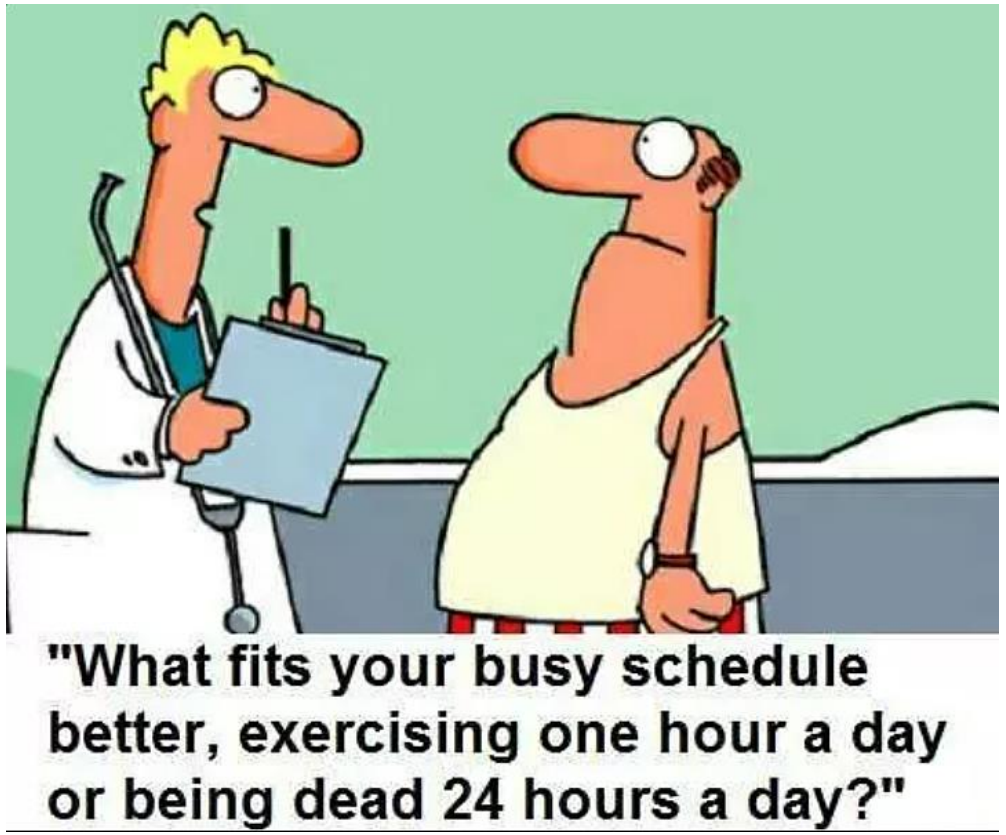
A-C-E

Autonomy	VERSUS	**A**uthority
Collaboration		**C**oercion
Evocation		**E**ducation

Westra HA, et al. *Psychotherapy.* 2013;50:273-278.

What is the Shared Goal?

Advantages
• No need for daily administration • Guaranteed administration and transparency of adherence [Gerlach, 1995; Remington and Adams, 1995] • Allows healthcare professionals to be alerted and to intervene appropriately if patients fail to take their medication [NICE, 2009] • Less probability for rebound symptoms and rapidly occurring/abrupt relapses • Overcome partial adherence or overt nonadherence • If a relapse occurs, it is due to other reasons beyond noncompliance [Waddell and Taylor, 2009] • Reduced risk of unintentional or deliberate overdose [Gerlach, 1995; Remington and Adams, 1995] • Lower relapse rates [Walburn *et al.* 2001; De la Gándara *et al.* 2009; Gabel *et al.* 2010; Kane *et al.* 2010] • Minimal gastrointestinal absorption problems, circumventing first-pass metabolism [Dencker, 1984; Marder *et al.* 1989] • More consistent bioavailability [Waddell and Taylor, 2009] • More predictable correlation between dosage and plasma levels [Rocca *et al.* 2013] • Reduced peak-trough plasma levels [McEvoy, 2006] • Improved patient outcomes [Olfson *et al*, 1999] • Improved patients' and physicians' satisfaction [Peuskens *et al.* 2010] • Regular contact between the patient and mental healthcare team [Pandarakalam, 2003]



Brissos S, et al. The role of long-acting injectable antipsychotics in schizophrenia: a critical appraisal. *Ther Adv Psychopharmacol.* 2014; 4(5): 198–219.

Motivational Interviewing

A style of dialogue between two parties, which is intended to motivate one party into making positive changes by **compassionately** challenging the status quo and helping them explore alternatives.

Rollnick S, et al. *Behavioural Cognitive Psychotherapy*. 1995:23;325-334

Motivational Interviewing: Principles & Skills

- **Autonomy**
  - Patient has the right to self-direction
  - Caregiver affirms this, but also provides input
- **Collaboration**
  - Patient is their own expert
  - Caregiver builds partnership
- **Evocation**
  - Patient has the resources to change
  - Caregiver elicits the change

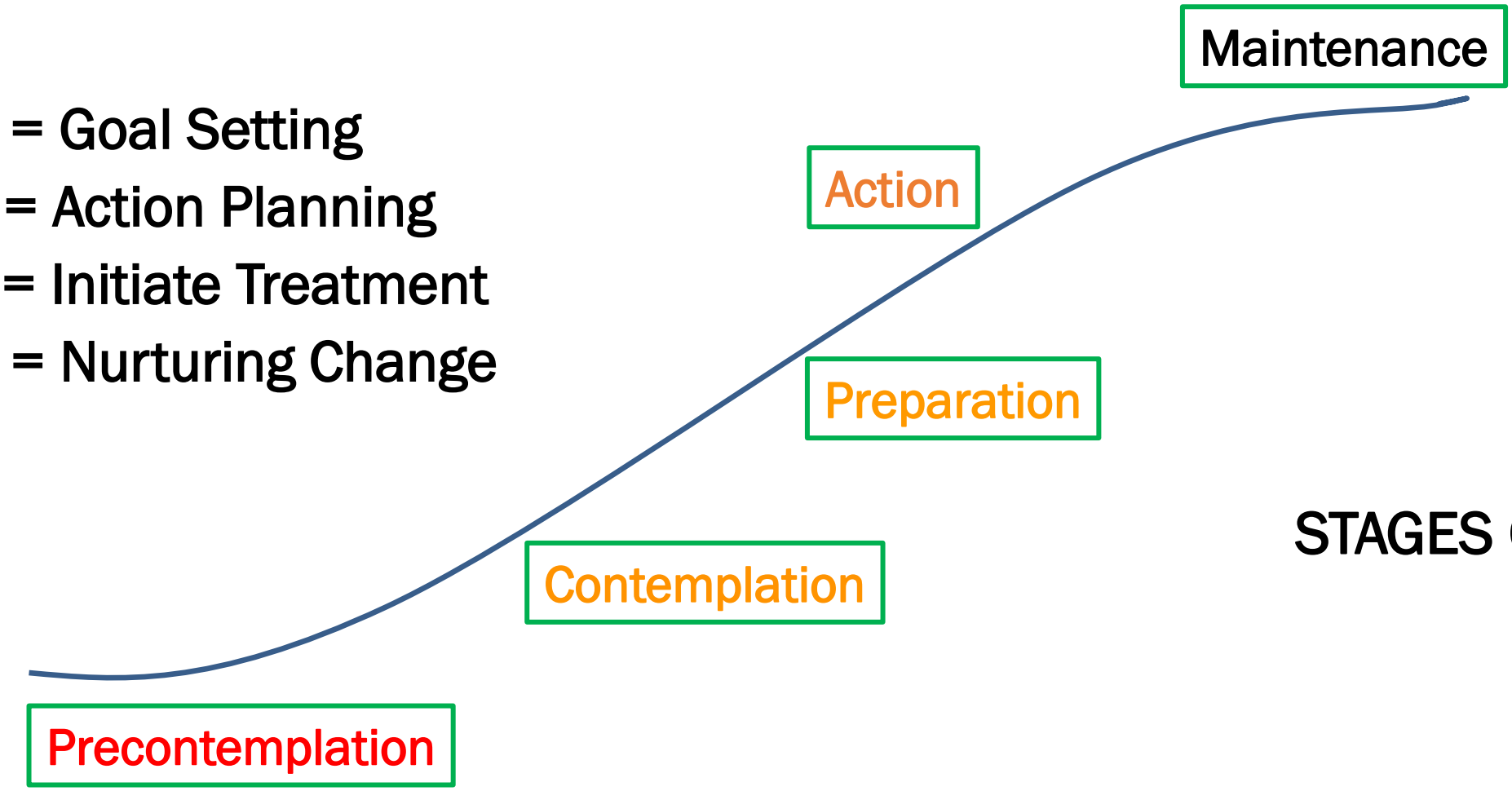
To practice motivational interviewing, we must:

- Connect with our patients and listen actively
- Understand patients' values, fears, qualities, and skills
- Be non-judgmental, collaborative, challenging, genuine, flexible, empathic, and respectful
- Identify and work with stages of change

Rollnick S, et al. *Behavioural Cognitive Psychotherapy*. 1995:23;325-334.

The GAIN Model of Change Facilitation

G = Goal Setting
A = Action Planning
I = Initiate Treatment
N = Nurturing Change



STAGES OF CHANGE

Lasser RA, et al. *Psychiatry.* 2009;6:22-27.

How Does This Apply to the LAI Conversation?

- **Identify what the patient's goals are:** job, relationship, school, fear of Sx or rehospitalization
- **Identify their motivation for receiving any antipsychotic treatment or acceptance of diagnosis** (i.e. their attitude and stage of change)
  - For patients who are still in the precontemplation stage with respect to meds in general or the value of LAIs, this is an ongoing discussion. No clinician should accept the first 'no' as the end of the discussion.
  - As events occur (e.g. relapse, etc.), the patient's motivational stage may change
- **Educate:** discuss how LAIs may benefit the patient with respect to the their goals, and present the options for various LAIs without pejorative language (i.e. "You don't want a shot, do you?")
- **Identify their treatment concerns:** side effects (especially if these have been experienced by the patient), convenience, stigma, pain from the injection, etc.
  - Have methods to address concerns, whether it is alternate medications or injection schedules, ways to overcome the fear of the injection itself, peer counselors who can relate their experience with the injection
- **Rinse and repeat:** These steps will occur periodically throughout the illness course in those who are struggling with the need to take meds or try an LAI.

Be Systematic in Asking Patients About Antipsychotic Side Effects

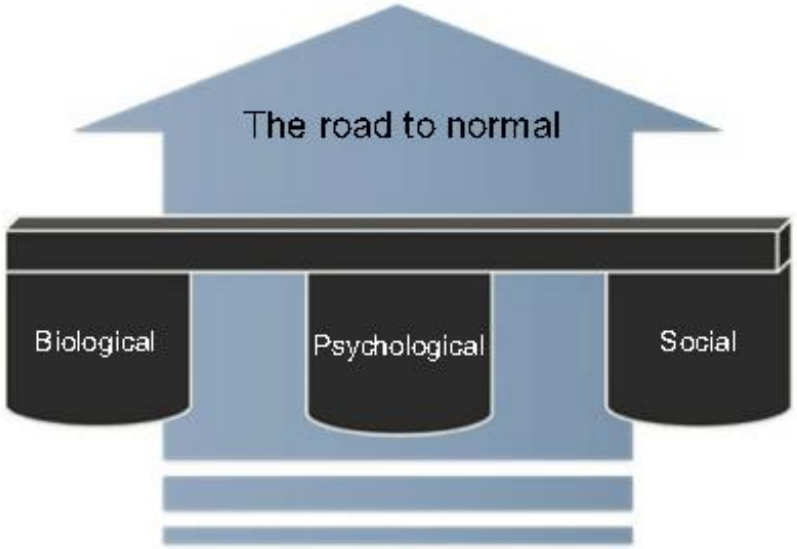
Table 1. Potential side effects of antipsychotics addressed by questions in the SMARTS checklist.

SMARTS checklist questions (Are you troubled by...)	Potential side effect addressed
1. Difficulties in your movement such as shaking, stiffness or muscle aches?	Parkinsonism, tremor
2. Changes in your weight or appetite?	Weight and appetite change
3. Problems with your sex life?	Sexual dysfunction (may reflect raised prolactin and/or other pharmacological mechanisms)
4. Changes in your periods or changes in your breasts?	Hyperprolactinaemia
5. Dizziness or light-headedness?	Postural hypotension
6. Tiredness or sleepiness?	Sedation
7. Restlessness or feeling fidgety?	Akathisia
8. Constipation, diarrhoea, nausea, stomach problems or dry mouth?	Gastrointestinal side effects (e.g. antimuscarinic side effects)
9. Difficulty passing water or passing water very frequently?	Urinary symptoms (e.g. antimuscarinic action may cause urinary retention; type 2 diabetes may cause polyuria)
10. Problems with your concentration or memory?	Sedation
11. Feeling anxious or depressed?	Affective side effects
12. Any other problems that you think may be related to your medication? Please state	Miscellaneous side effects

Haddad PM, et al. SMARTS (Systematic Monitoring of Adverse events Related to TreatmentS): The development of a pragmatic patient completed checklist to assess antipsychotic drug side effects. Ther Adv Psychopharmacol 2014; 4(1) 15–21.

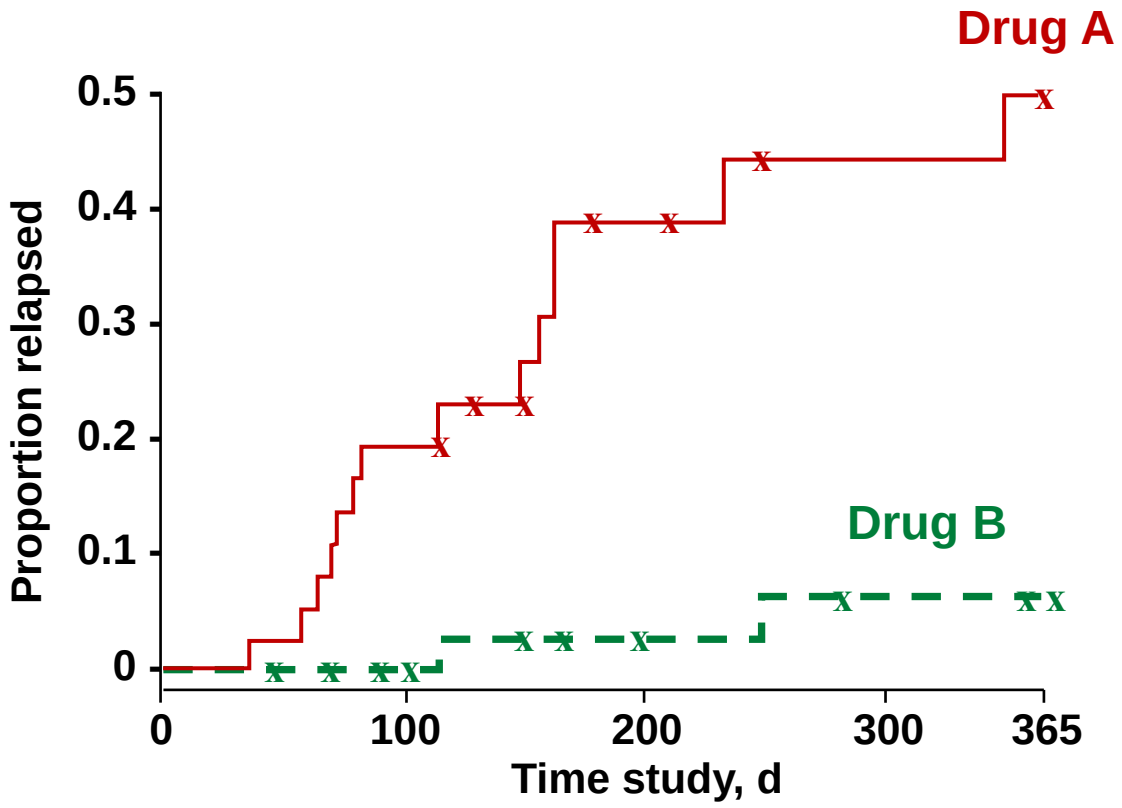
Effective Motivation Makes it the Patient's Goal

"The new screen saver was created by a motivation expert. It's a slide show of former employees who were fired for poor performance."



Chiu L-L, et al. Patients' experiences of long-acting injectable antipsychotics - a qualitative study. Neuropsychiatric Disease and Treatment 2019:15 1797–1804.

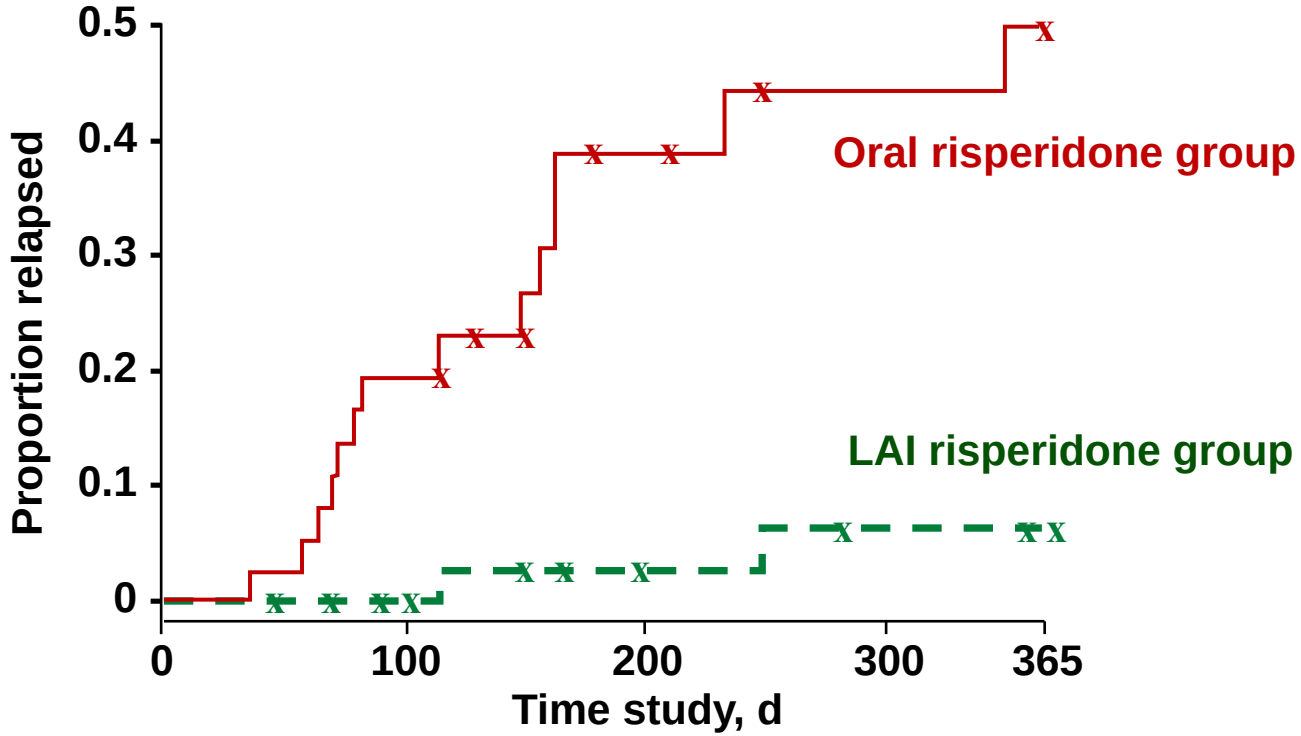
Which Medicine Would You Choose?



Subotnik KL, et al. JAMA Psychiatry. 2015;72(8):822–829.

LAI Risperidone vs Oral Risperidone After a Recent First Episode of Schizophrenia: A Randomized Clinical Trial

Time to first psychotic exacerbation and/or relapse as a function of form of medication administration in 83 patients



No. of Patients					
Oral risperidone group:	43	32	30	30	18
LAI risperidone group:	40	35	30	29	28

Risk of exacerbation and/or relapse over time was significantly lower for the LAI risperidone group than for the oral risperidone group; x indicates censored data.

Subotnik KL, et al. *JAMA Psychiatry*. 2015;72(8):822–829.

Summary Points

- Schizophrenia remains a severe, relapsing, and often debilitating disorder with high rates of nonadherence.
- LAIs represent an important tool that should be offered to ALL schizophrenia patients to **help them reach their functional goals**
  - **Know how to use all of the LAI tools, their kinetics, advantages and disadvantages**
  - **Know how to administer LAIs and techniques to maximize patient comfort**
- Effective treatment depends on effective communication. Motivational interviewing skills can facilitate engagement and an effective shared decision-making process.
- Aiming at enhancing patient autonomy depends on helping patients make healthy decisions, not allowing the illness to stay in charge

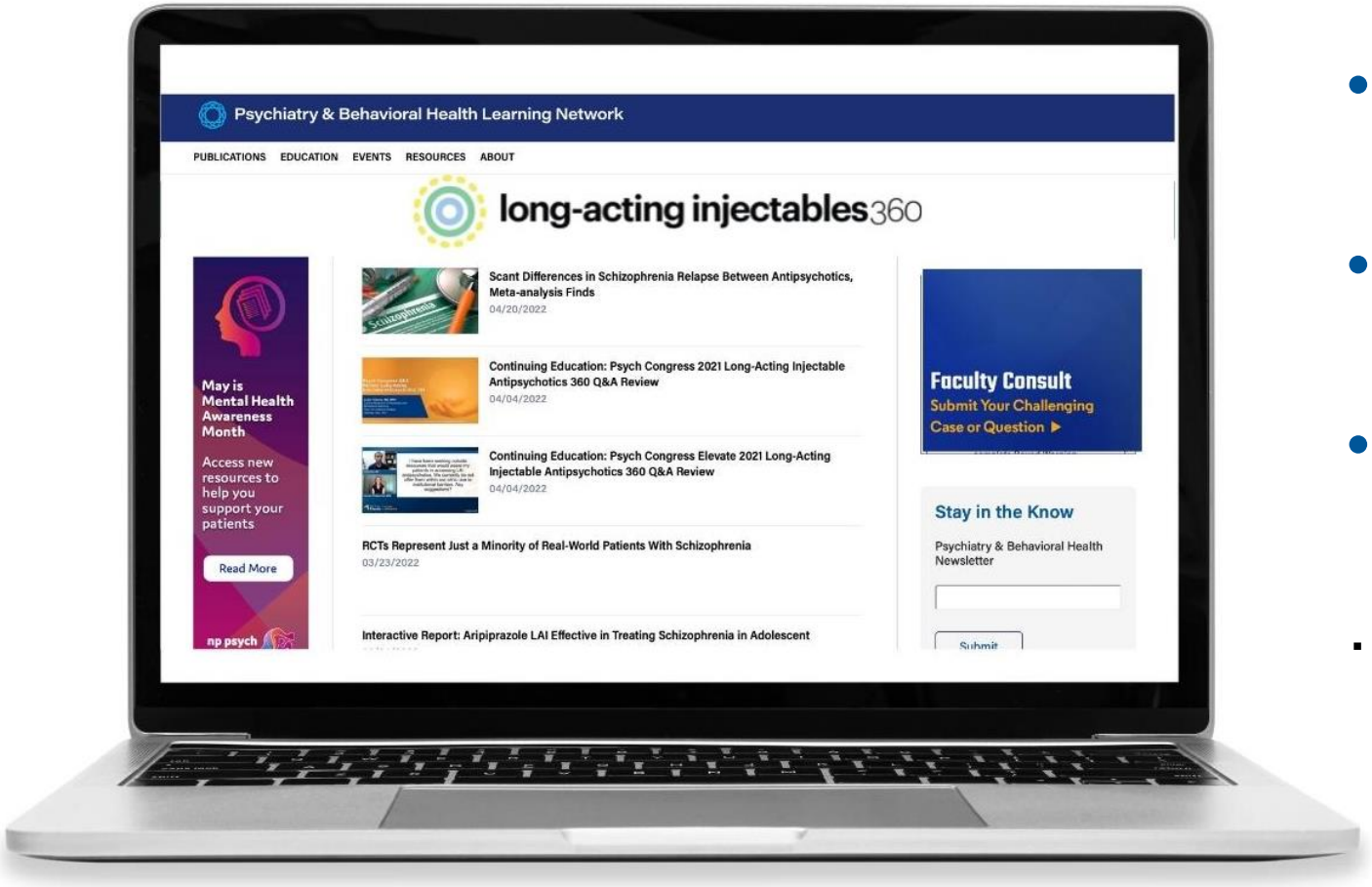
Practice Makes Perfect!

- Visit the Exhibit Hall on TODAY from 1:45 PM – 3:15 PM and attend the **LAI and Motivational Interviewing Workshop**!

- Practice administering LAIs on prosthetics as well as interact with patients and faculty experts to learn more about best Motivational Interviewing techniques.

- Located in the back of the Exhibit Hall, at the end of the 900 aisle

long-acting injectables360 | Visit the Resource Center



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Q&A