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Treatment Strategies for Patients with Schizophrenia: Finding the Right Mix of Drug and Delivery to Prevent Relapse

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Disclosures

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- ***Consultant:*** Alkermes, Teva Pharmaceuticals

Learning Objective 1

Implement treatment planning with a goal of recovery in at least 50% of patients with schizophrenia

Learning Objective 2

Weigh the pros and cons of oral therapies versus long acting injectables (LAIs) in achieving recovery when developing a treatment plan in patients with schizophrenia

Schizophrenia

Positive Symptoms
- Hallucinations
- Delusions
- Disorganized Thought

Negative Symptoms
- Affective Blunting
- Alogia
- Avolition
- Anhedonia

FUNCTIONING

Cognition
- New Learning
- Memory
- Attention/Concentration

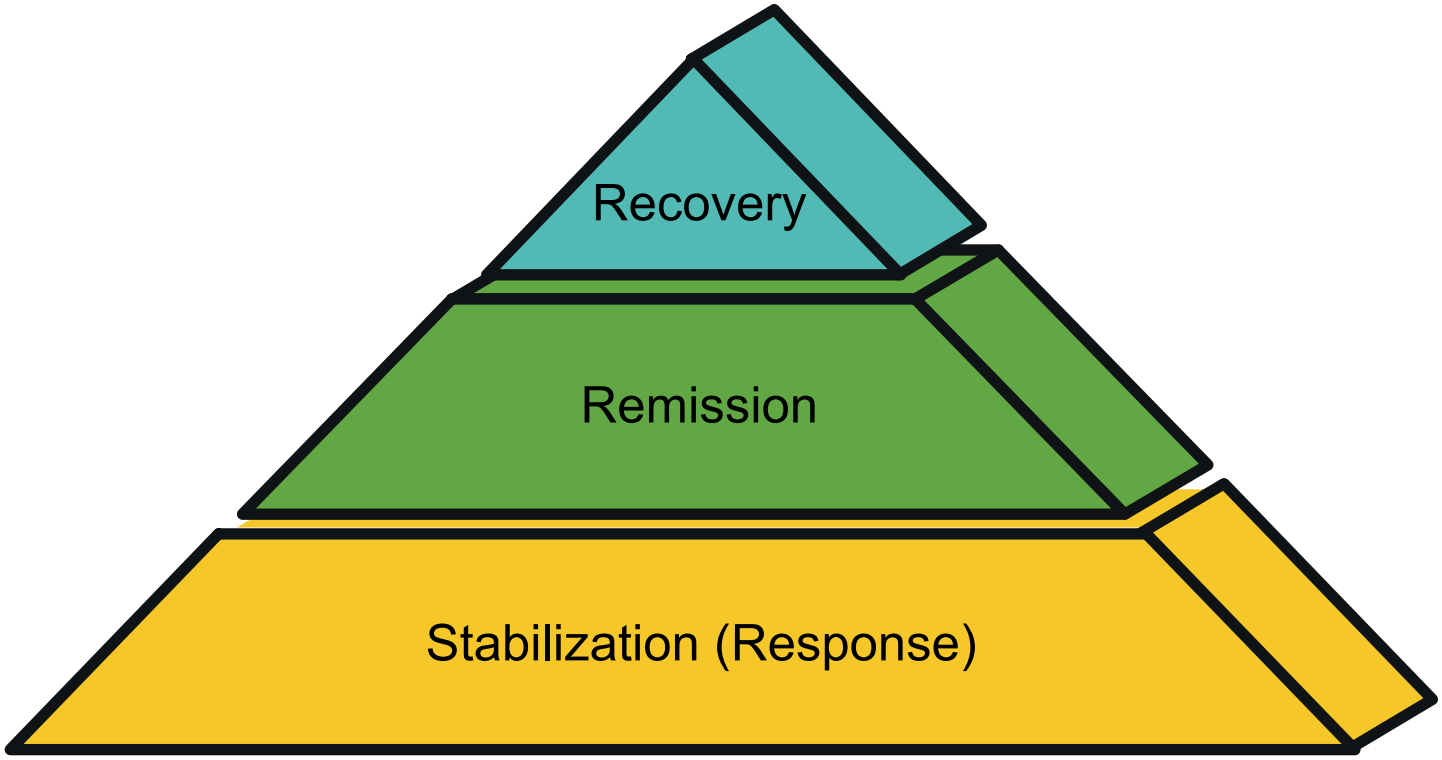
Mood Symptoms
- Dysphoria
- Demoralization
- Suicide

Course in Schizophrenia

- Remission and exacerbation
- Positive symptoms are less severe
- 20-30% recover sufficiently
- 20-30% moderate symptoms
- 40-60% permanent impairment

Ammerman RT, et al. *Handbook of Prescriptive Treatments for Adults*. 2013.

Response, Remission, Recovery



Weiden P. *J Clinical Psychiatry*. 1996;57(Suppl 11):53-60.

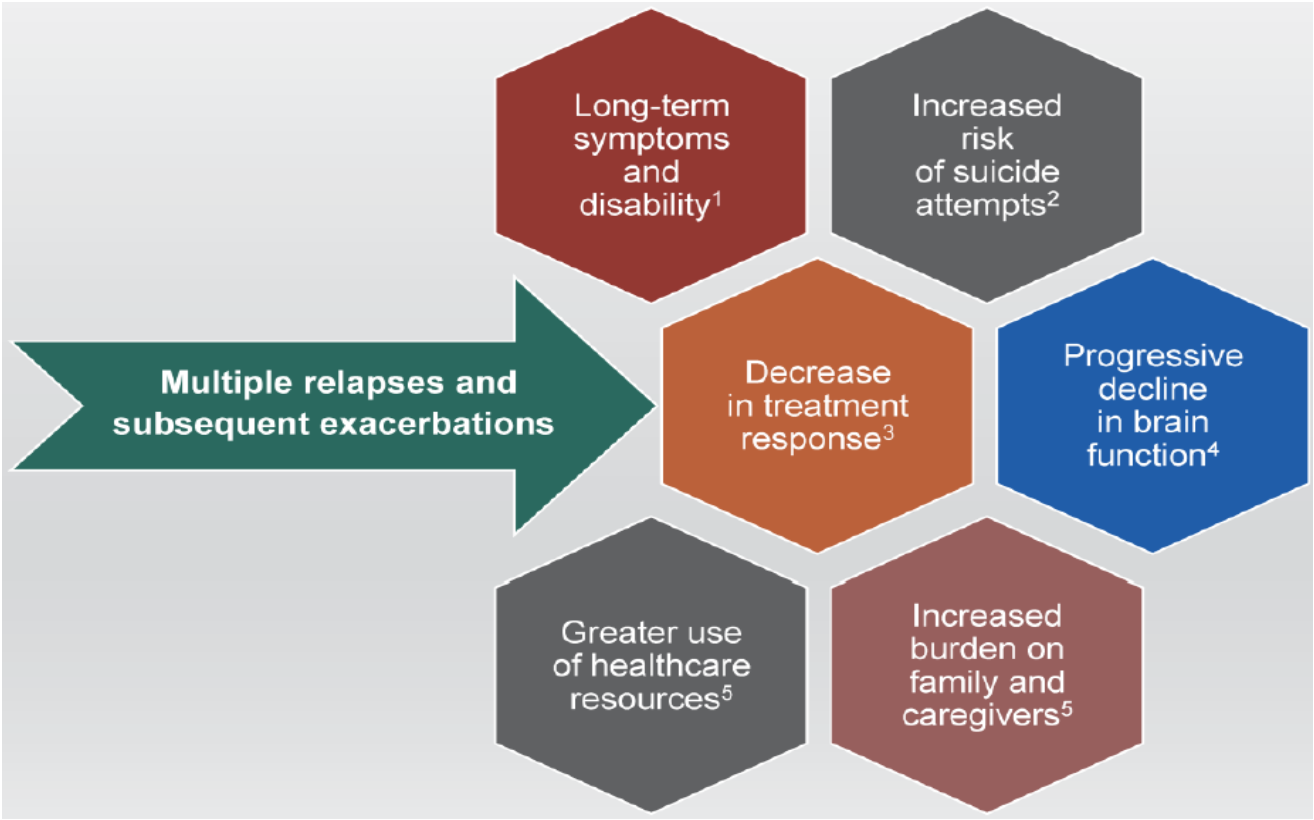
Criteria for Recovery: UCLA Criteria

- Symptom remission
- Vocational functioning
- Independent living
- Peer relationships
- Duration ≥ 2 years

Is recovery best viewed as an *outcome* or a *process*?

Liberman RP, et al. *Int Rev Psychiatry*. 2002;14(4):256-272; Liberman RP, et al. *Psychiatr Serv*. 2005;56:735-742.

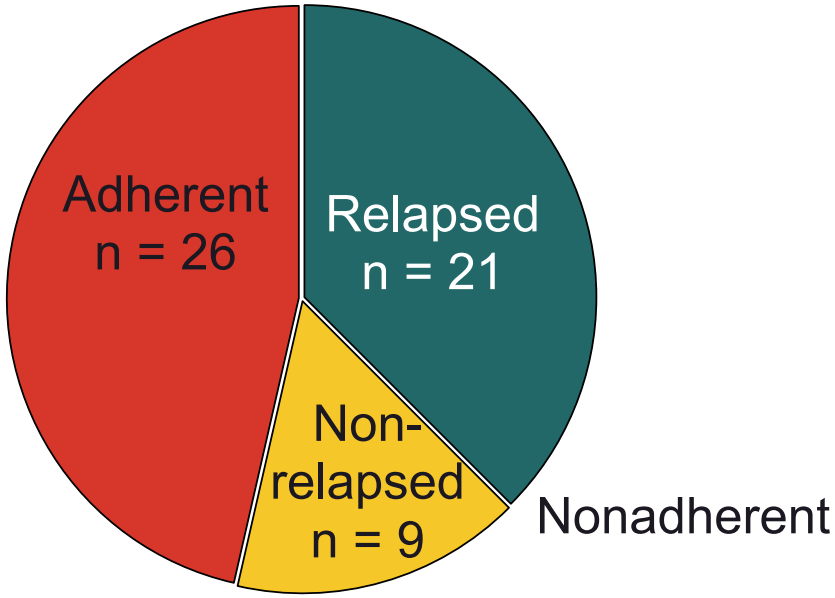
What is the Importance of Relapse Prevention?



1. Harrison G, et al. *Br J Psychiatry*. 2001;178(6):506-517. 2. Herings RM, et al. *Pharmacoepidemiol Drug Saf*. 2003;12(5):423-424; 3. Lieberman JA, et al. *Neuropsychopharmacology.* 1996;14:13S-21S. 4. Lieberman JA, et al. *Psychiatr Serv*. 2008;59(5):487-496. 5. Kane JM. *J Clin Psychiatry.* 2007;68(Suppl 14):27–30.

A Significant Proportion of Patients Who Are Nonadherent Will Relapse Within the First Year

70% of patients who discontinue antipsychotics will relapse within the first year



- 56 male patients with first-episode schizophrenia, schizophreniform, or schizoaffective disorder were followed up for 1 year post-discharge
- 30 patients discontinued (54%); of them, 21 relapsed (70%)

Novak-Grubic V, et al. *Eur Psychiatry*. 2002;17:148-154.

Predictors of Relapse

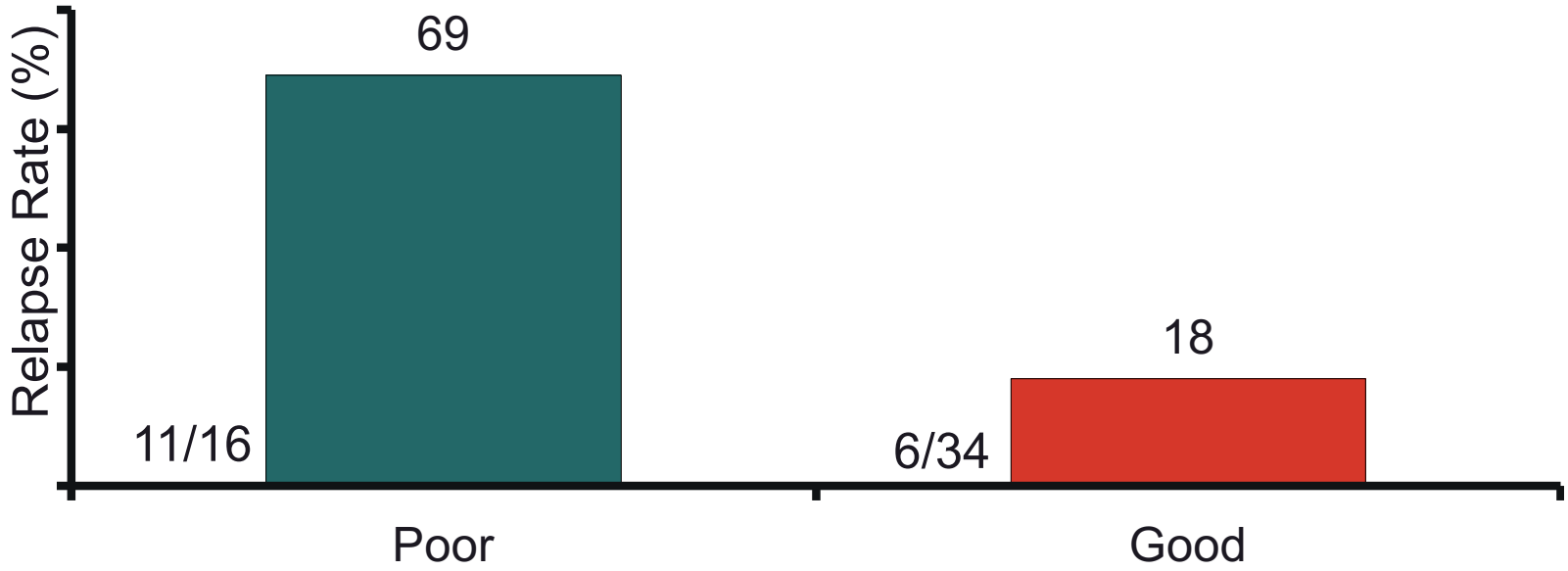
- Antipsychotic medication status
- Gender difference
- Social functioning at baseline

Alphs L, et al. *Int Clin Psychpharmacol*. 2016;31:202-209; Haro JM, et al. *Prog Neuropsychopharmacol Biol Psychiatry.* 2008;32:1287-1292; Emsley R, et al. *Schizophr Res.* 2007;89:129-139.

Patients With Poor Adherence Show High Relapse Rates

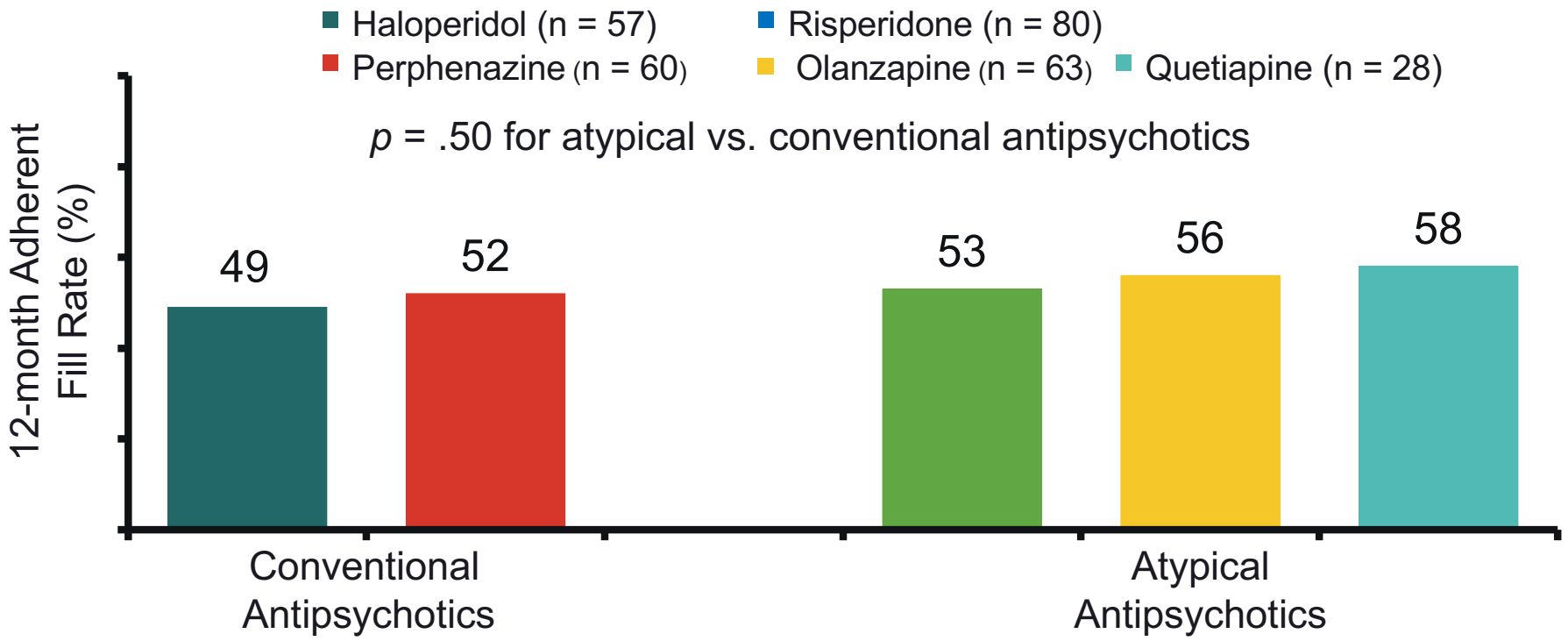
Study population included patients with recent onset of schizophrenia, schizophreniform, or schizoaffective disorders

Adherence With Oral or Depot Antipsychotics (N = 50)



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

Oral Atypical Medications Have Not Solved the Issue of Nonadherence



Reprinted with permission from Dolder CR, et al. *Am J Psychiatry*. 2002;159:103-108.

Factors that Contribute to Nonadherence

Patient-related Factors

- Persecutory delusions
- Lack of insight
- Health care beliefs
- History of substance abuse
- Previous nonadherence

Medication-related Factors

- Lack of efficacy
- Distressing side effects
- High doses
- Medication type
- Regimen complexity

Environmental Factors

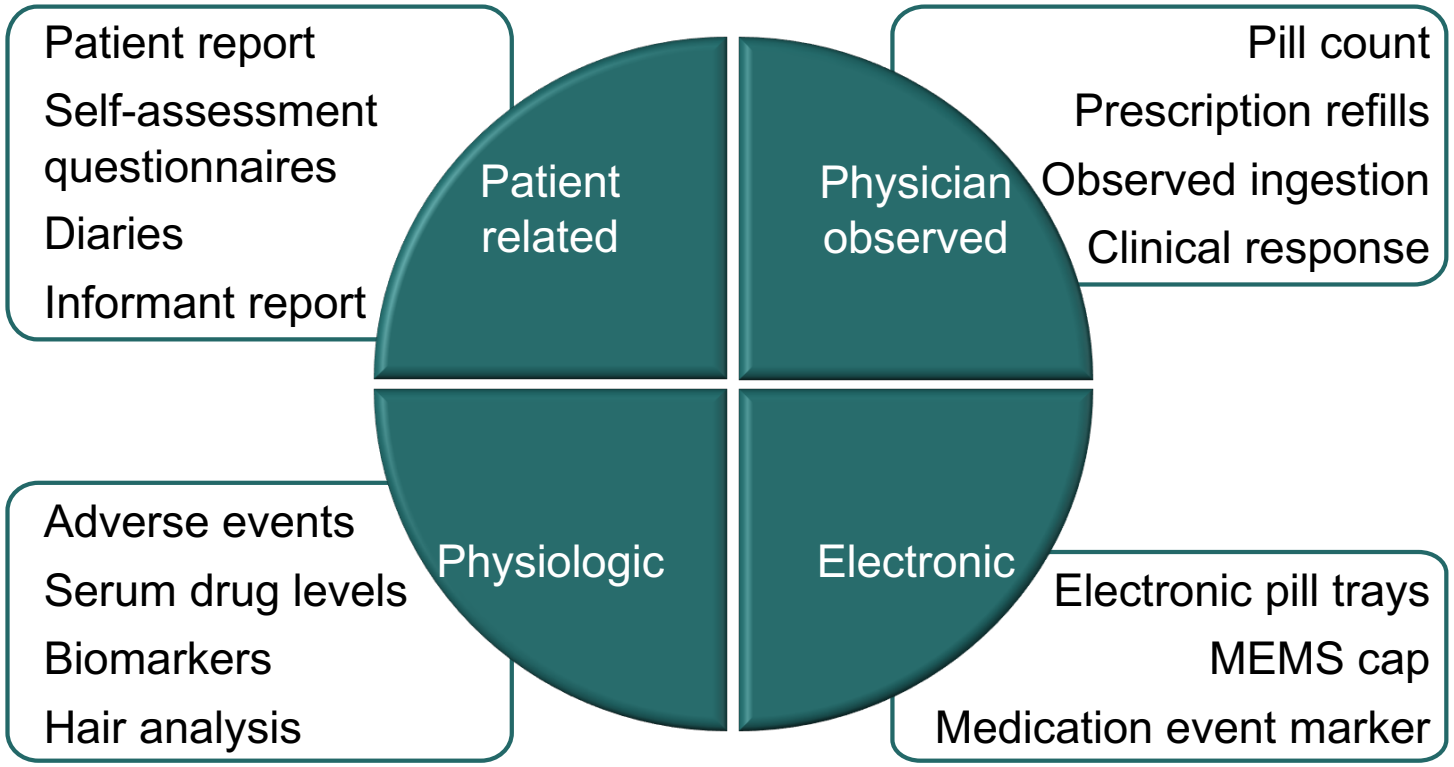
- Caregiver support
- Family and social support
- Financial cost
- Practical barriers

Clinician-related Factors

- Poor therapeutic alliance
- Attitude of staff

Fenton WS, et al. *Schizophr Bull*. 1997;23(4):637-661; Lacro J, et al. *J Clin Psychiatry*. 2002;63(10):892-909.

Methods for Monitoring Medication Adherence



MEMS = medication event monitoring system

Kane JM, et al. *World Psychiatry*. 2013;12(3):216-226.

Does Delivery Matter?

Pros and Cons of Long-Acting Antipsychotics

Perceived advantages

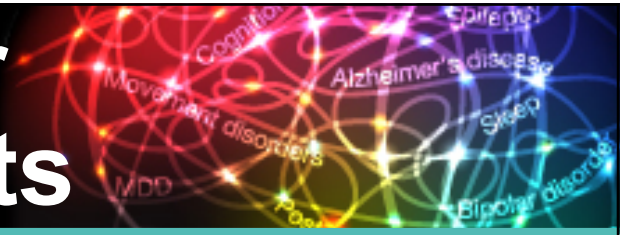
- No need for daily medication
- Ease of compliance monitoring
- Stable plasma levels
- Elimination of discussing compliance issues
- Security for carers
- Reduced risk for relapse/ rehospitalisation
- Less side effects

Perceived disadvantages

- Low acceptance
- Injection-site complications
- Reduction in patient autonomy
- No rapid dose adjustment
- Invasive/coercive
- Expensive
- More side effects

Fleischhacker WW, et al. *Managing Schizophrenia: The Compliance Challenge*. 2nd edition; 2007.

Atypical Antipsychotics for Schizophrenia – Oral Agents



Drug	Formulation (Approval)	FDA-Approved Dose Range
Clozapine	Oral (1989)	300-900 mg/day
Risperidone	Oral (1993)	2-8 mg/day recommended Approved for up to 16 mg/day
Olanzapine	Oral (1996)	10-20 mg/day
Quetiapine	Oral (1997, 2007)	150-800 mg/day
Ziprasidone	Oral (2001)	80-160 mg/day
Aripiprazole	Oral (2002)	10 - 30 mg/day

[Package Inserts]. Drugs@FDA Website.

Atypical Antipsychotics for Schizophrenia – Oral Agents (cont.)

Drug	Formulation (Approval)	FDA-Approved Dose Range
Paliperidone	Oral (2006)	3 - 12 mg/day
Asenapine	Oral – sublingual (2009)	5 - 10 mg twice daily
Iloperidone	Oral (2009)	6 - 12 mg twice daily
Lurasidone	Oral (2010)	40 - 160 mg/day
Brexpiprazole	Oral (2015)	1 - 4 mg /day
Cariprazine	Oral (2015)	1.5 - 6 mg/day

[Package Inserts]. Drugs@FDA Website.

Atypical Antipsychotics LAIs for Schizophrenia

Drug	Formulation (Approval)	FDA Approved Dose Range
Risperidone	Long-Acting IM (2003)	25, 37.5, or 50 mg IM every 2 weeks
Olanzapine	Long-Acting IM (2009*)	150-300 mg IM every 2 weeks
Aripiprazole monohydrate	Long Acting IM (2013)	300-400mg per month
Aripiprazole lauroxil	Long Acting IM (2015)	441, 662 or 882mg per 4-6 weeks, 1064 per 2 months
Paliperidone	Long-Acting IM (2009)	117 to 234 mg per month
Paliperidone	Long-Acting IM (2015)	273-819 mg every 12 weeks

*Includes Risk Evaluation and Mitigation Strategy (REMS) with approval

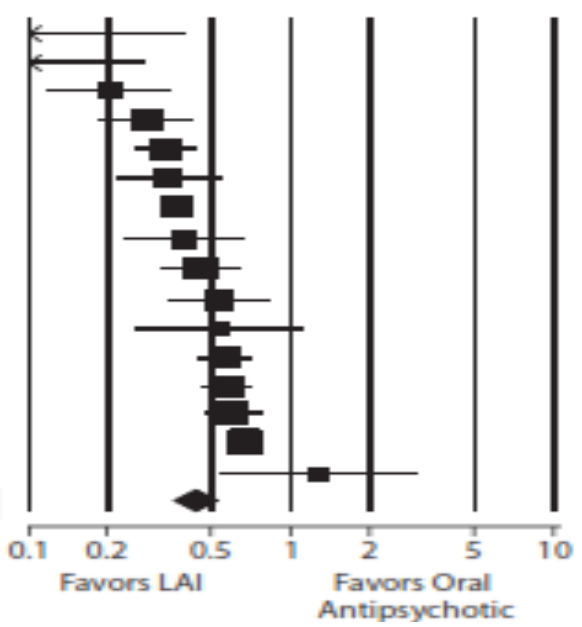
LAI = Long-acting injectable

[Package Inserts]. Drugs@FDA Website.

In Mirror-Image Studies, LAIs Reduce Risk of Hospitalizations vs. Oral Antipsychotics

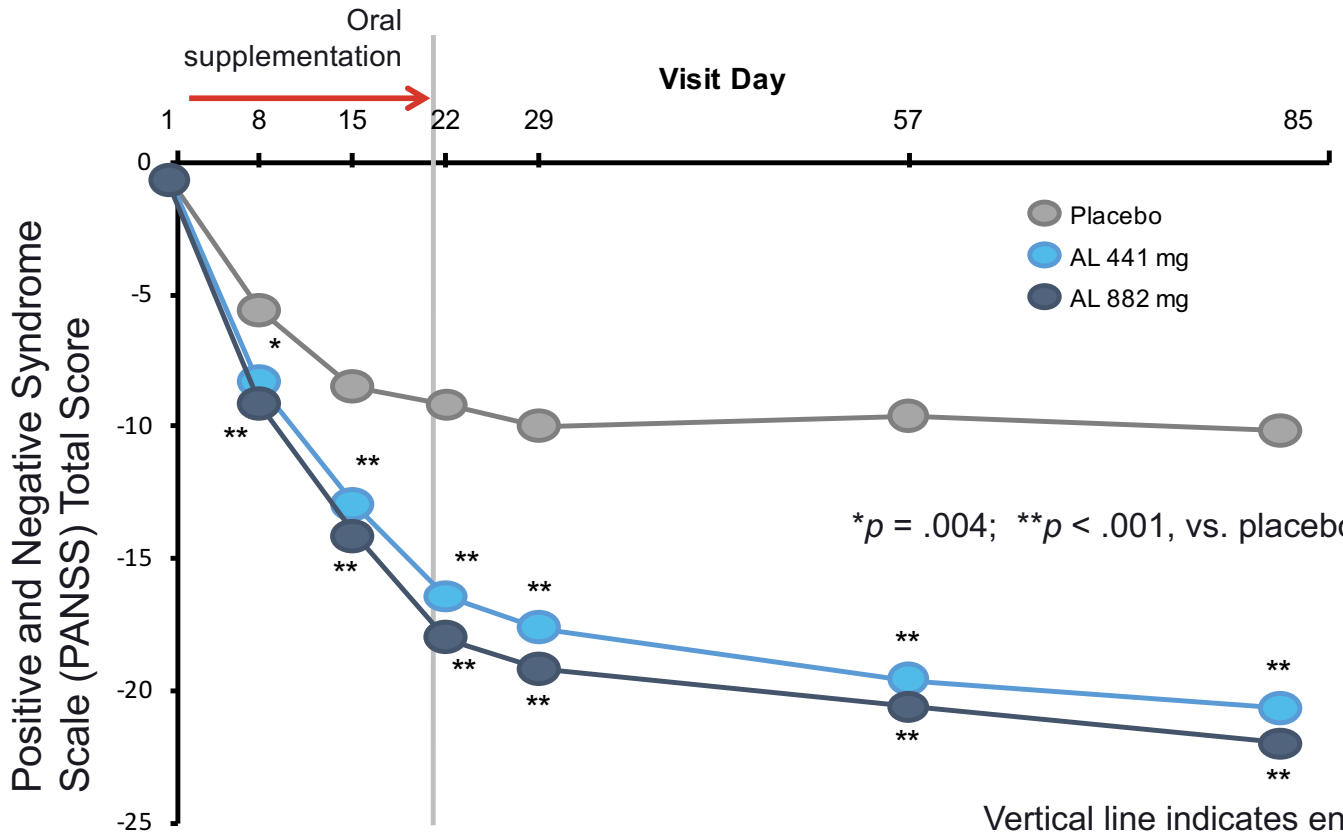
Hospitalization Risk

Study	Risk Ratio	Lower Limit	Upper Limit	*Z* Value	*P* Value
Girardi et al, 2010[22]	0.024	0.001	0.397	–2.609	.0091
Beauclair et al, 2005[26]	0.092	0.030	0.282	–4.166	.0000
Arató and Erdós, 1979[32]	0.204	0.119	0.350	–5.761	.0000
Devito et al, 1978[33]	0.281	0.183	0.430	–5.844	.0000
Denham and Adamson, 1971[39]	0.333	0.254	0.438	–7.884	.0000
Morritt, 1974[37]	0.343	0.214	0.550	–4.440	.0000
Lam et al, 2009[24]	0.369	0.327	0.415	–16.569	.0000
Lindholm, 1975[35]	0.391	0.232	0.660	–3.515	.0004
Peng et al, 2011[20]	0.452	0.321	0.636	–4.554	.0000
Gottfries and Green, 1974[36]	0.529	0.341	0.822	–2.831	.0046
Rosa et al, 2012[17]	0.529	0.251	1.116	–1.672	.0944
Chang et al, 2012[16]	0.557	0.437	0.711	–4.697	.0000
Johnson and Freeman, 1972[38]	0.570	0.461	0.704	–5.203	.0000
Crivera et al, 2011[18]	0.597	0.463	0.768	–4.003	.0001
Ren et al, 2011[19]	0.663	0.611	0.720	–9.746	.0000
Svestka et al, 1984[28]	1.286	0.541	3.056	0.569	.5694
	0.430	0.350	0.527	–8.074	.0000



Kishimoto T, et al. *J Clin Psychiatry*. 2013;74:957-965.

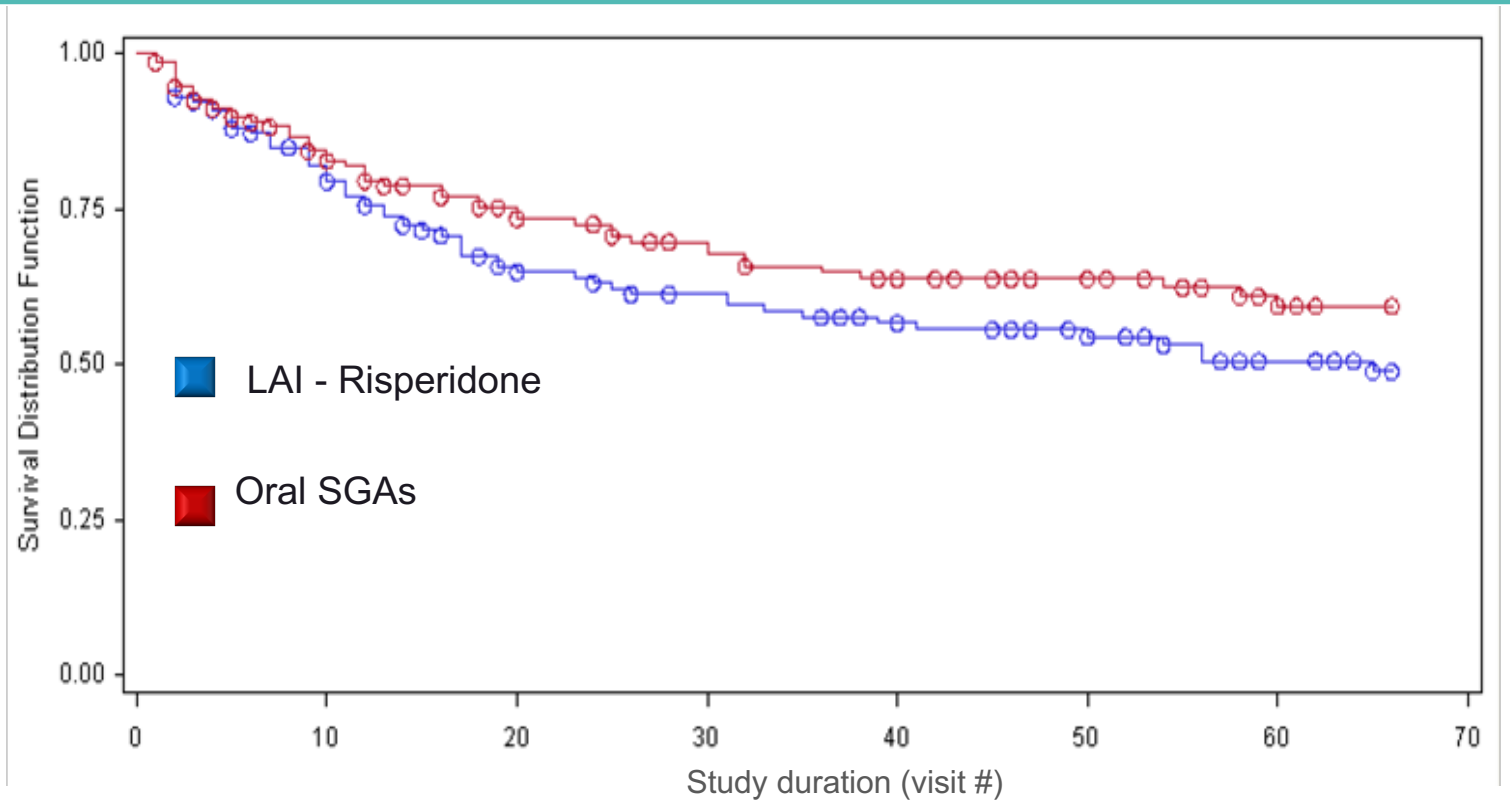
Efficacy of Aripiprazole Lauroxil in Improving Schizophrenia Symptoms



Vertical line indicates end of oral aripiprazole supplementation.

Meltzer HY, et al. *J Clin Psychiatry*. 2015;76(8):1065-1090.

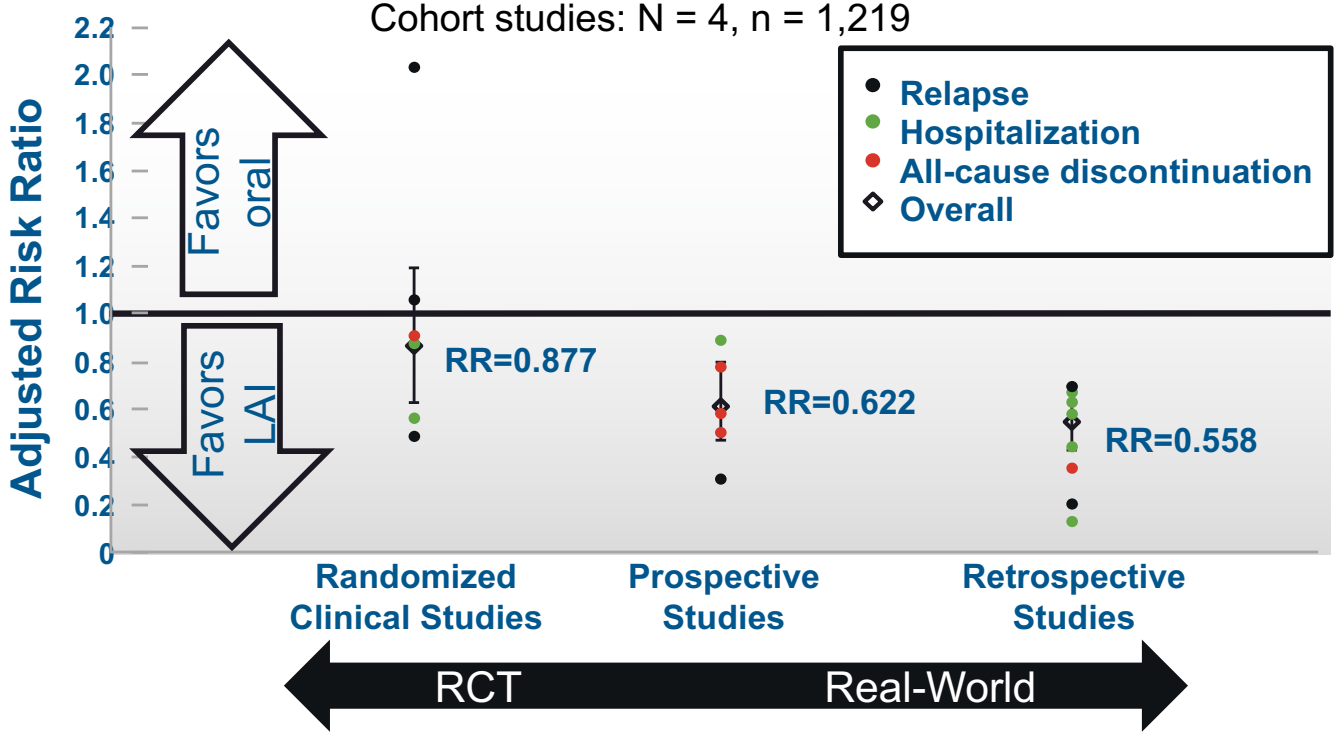
PROACTIVE Study: LAI Risperidone Confers No Advantage over Oral SGAs



Buckley PF, et al. *Schizophr Bull*. 2015;41(2):449-459.

RCT vs Real-World Data: RWD Demonstrates Superiority of LAIs over Oral Antipsychotics (OAPs)

Search: 01/01/2010-12/31/2011: RCTs: N = 5, n = 2,983; Mirror-image studies: N = 4, n = 2,125; Cohort studies: N = 4, n = 1,219



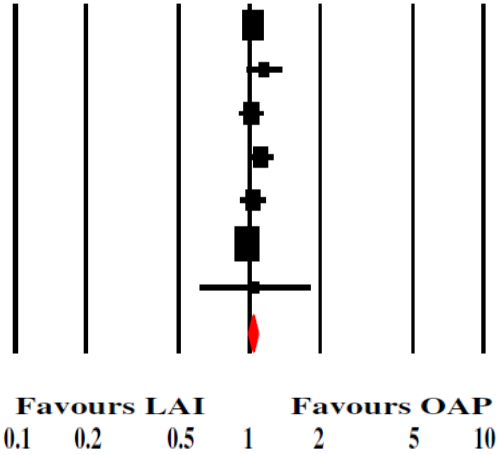
OAP = oral antipsychotic; RCT = Randomized controlled trial; RR = Risk ratio

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

Adverse Effects with LAI vs. Same OAPs (N = 16, n = 4,902)

No Difference in Frequency of at Least One Adverse Effect

Study name	Subgroup within study	Risk ratio	Lower limit	Upper limit	p-Value	Events / Total LAI	Events / Total OAP
Fleischhacker, 2014	ARI LAI vs ARI	1.032	0.951	1.120	0.448	219 / 265	213 / 266
Ishigooka, 2015	ARI LAI vs ARI	1.156	0.972	1.374	0.102	130 / 228	112 / 227
Detke, 2011	OLA LAI vs OLA	1.018	0.906	1.144	0.759	182 / 264	176 / 260
Starr, 2014 PP vs PAL/RIS	PAL LAI vs PAL/RIS	1.121	0.988	1.271	0.075	181 / 208	66 / 85
Chue, 2005	RLAI vs RIS	1.038	0.915	1.178	0.561	195 / 319	189 / 321
Kamijima, 2009	RLAI vs RIS	0.970	0.904	1.041	0.398	137 / 147	49 / 51
NCT00992407	RLAI vs RIS	1.058	0.612	1.827	0.841	11 / 20	13 / 25
Overall		1.026	0.984	1.071	0.231	1055 / 1451	818 / 1235



- Out of all 119 adverse events, LAIs and OAPs did not differ significantly regarding 115 (96.6%).
- LAIs were associated with more akinesia, low-density lipoprotein cholesterol change and anxiety.
- LAIs were associated with significantly lower prolactin change.

ARI = aripiprazole; OLA = olanzapine; PAL = paliperidone; RIS = risperidone

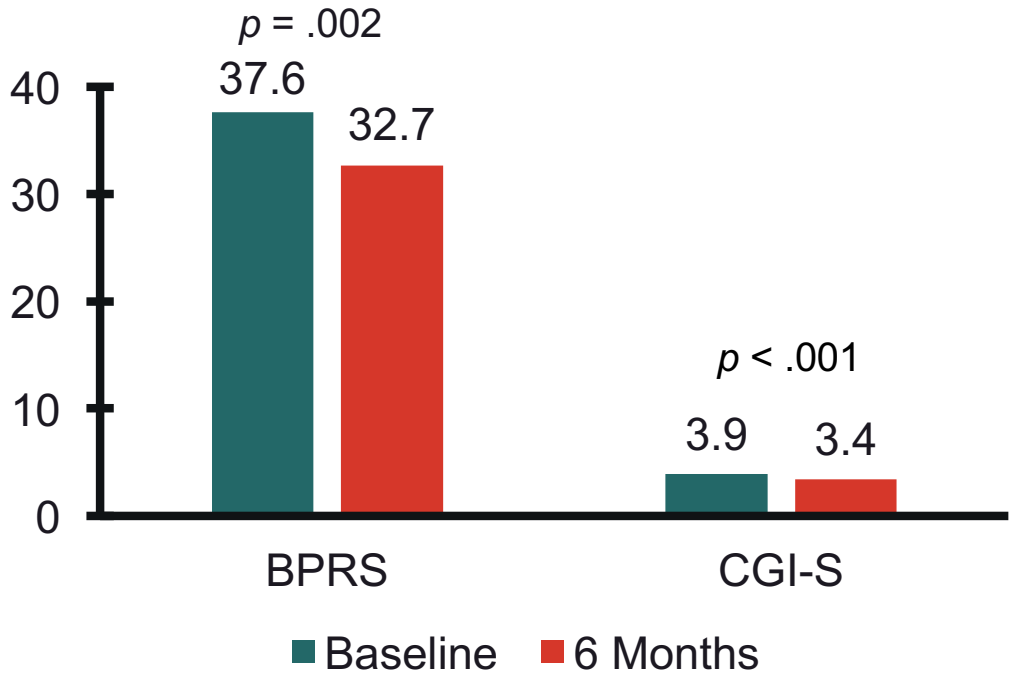
Misawa F, et al. *Schizophr Res*. 2016 Oct;176(2-3):220-230.

Advantages of Having More Than One LAI

- We are used to switching oral antipsychotics based on efficacy and tolerance (not all antipsychotics work the best on the individual patient or are tolerated as well)
- We tend not to try another long-acting agent
  - Historically not enough to pick from
  - Now we can try a number of LAIs, based on unique parent compound, with different frequencies of injections, etc.

Aripiprazole Lauroxil Effective in Patients with Inadequate Response to Paliperidone Palmitate

- Patients (N = 34) received at least 3 consecutive doses of paliperidone palmitate, half at the highest dose, prior to switch to aripiprazole lauroxil
- Reasons for switch:
  - Insufficient control of symptoms (66%)
  - Intolerability (18%)
  - Breakthrough negative symptoms (16%)



BPRS, Brief Psychiatric Rating Scale; CGI-S, Clinical Global Impression-Severity

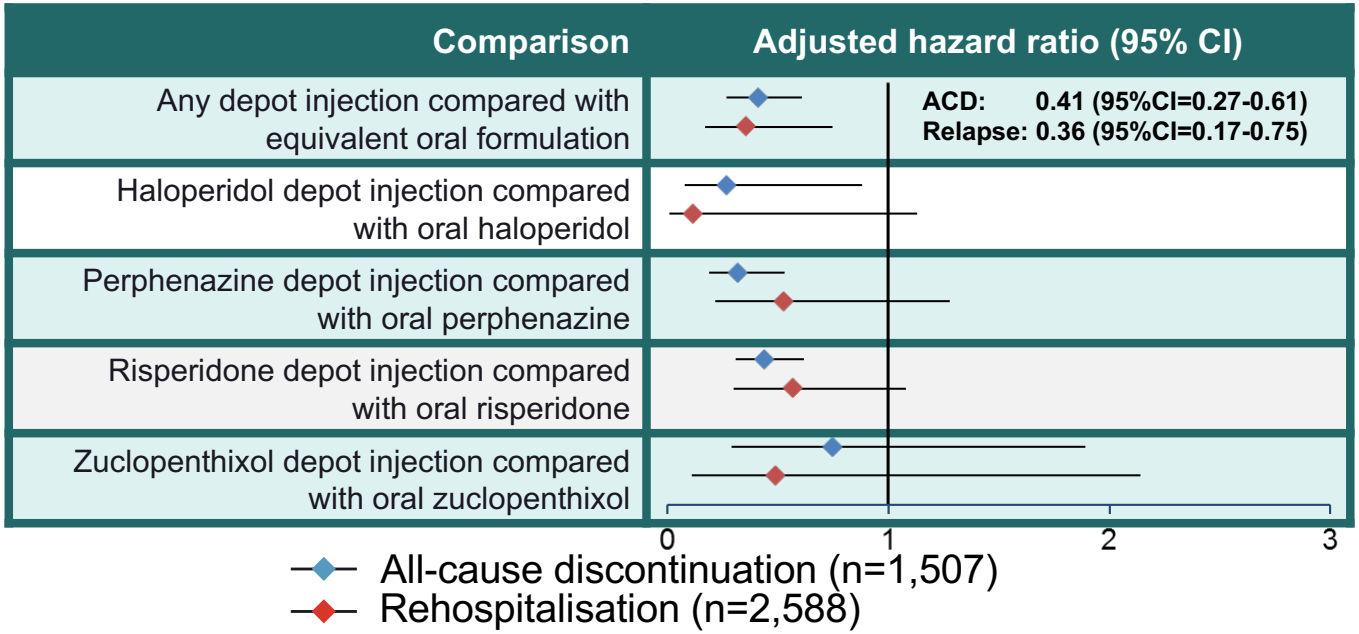
Potkin SG, et al. Psych Congress 2017. Poster 259.

Is There a Role in Select Populations?

First Episode
High-Risk Populations

LAIs Significantly Improve Treatment Outcomes in Patients with Schizophrenia

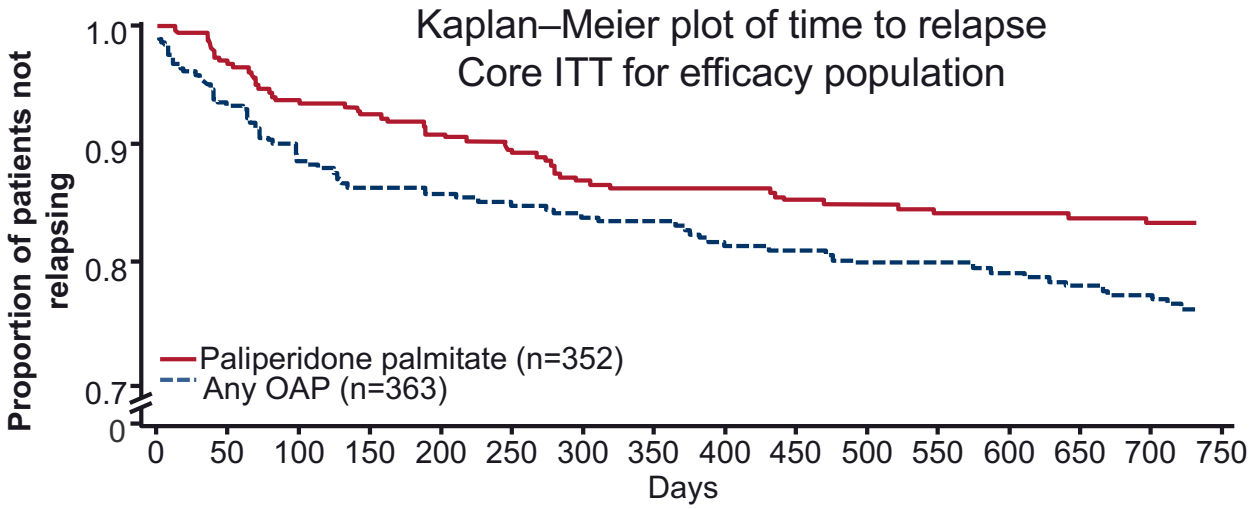
Risk of discontinuation or rehospitalization after a first hospitalization for schizophrenia, by antipsychotic treatment (n = 2,588)



2000–2007; nationwide register study; follow-up after 1st admission for schizophrenia
Tiihonen J, et al. *Am J Psychiatry.* 2011;168(6):603–609.

LAI Paliperidone Palmitate Superior to OAP in Time to Relapse

- Time to relapse* significantly longer in the PP group compared to the OAP group (p = .0191, HR [95% CI] 1.5 [1.1; 2.2])†
- The 85th percentile for time to relapse was 469 days in PP group vs 249 days in OAP group



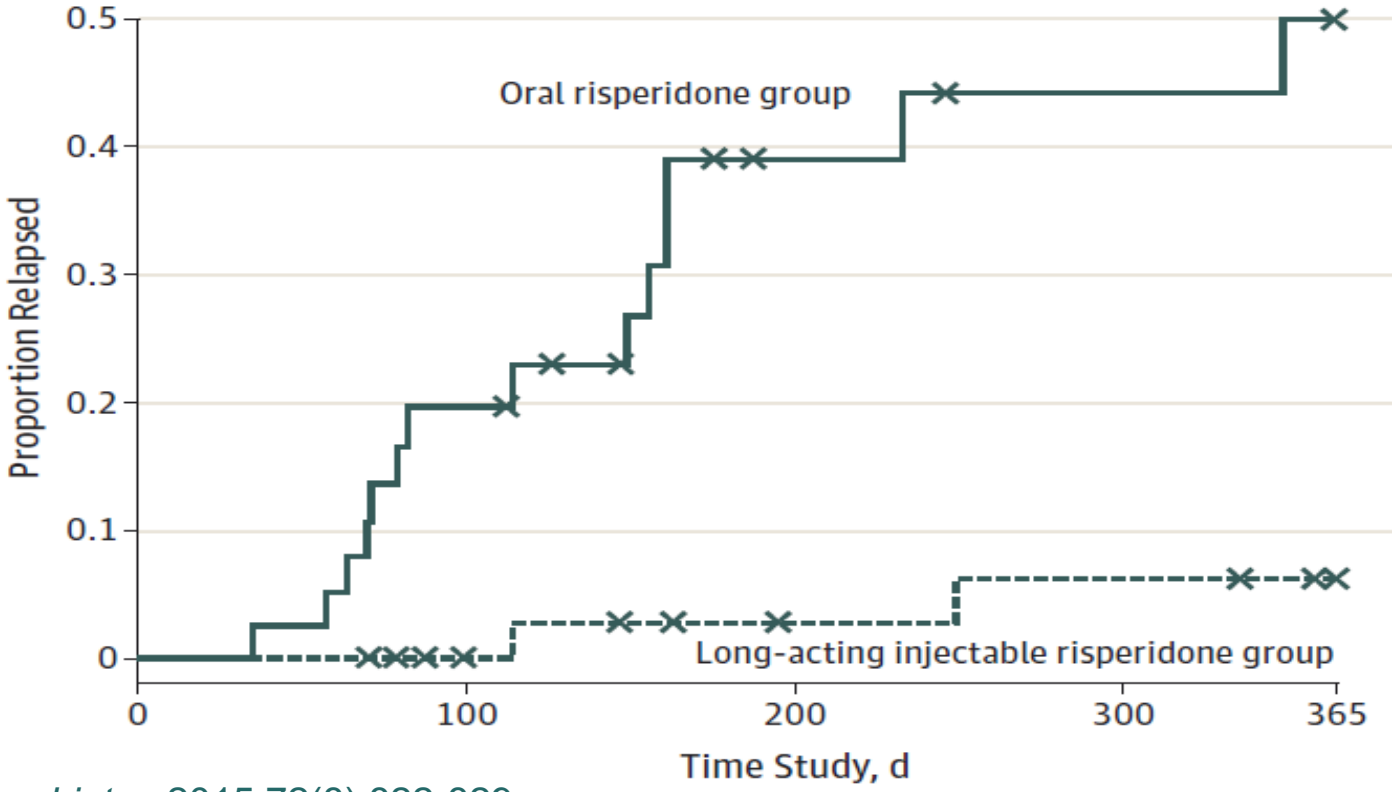
ITT, intent-to-treat; PP, paliperidone palmitate.
*According to Csernansky criteria †log-rank test
Schreiner A, et al. *Schizophr Res*. 2015;169(1-3):393-399.

By the end of the 24-month treatment phase, 52 (14.8%) patients met relapse criteria in the PP group vs 76 (20.9%) patients in the OAP group (p = .0323).

This represents a 29.4% relative risk reduction in favor of PP.

Risperidone LAI Superior to Oral Risperidone in Relapse Prevention

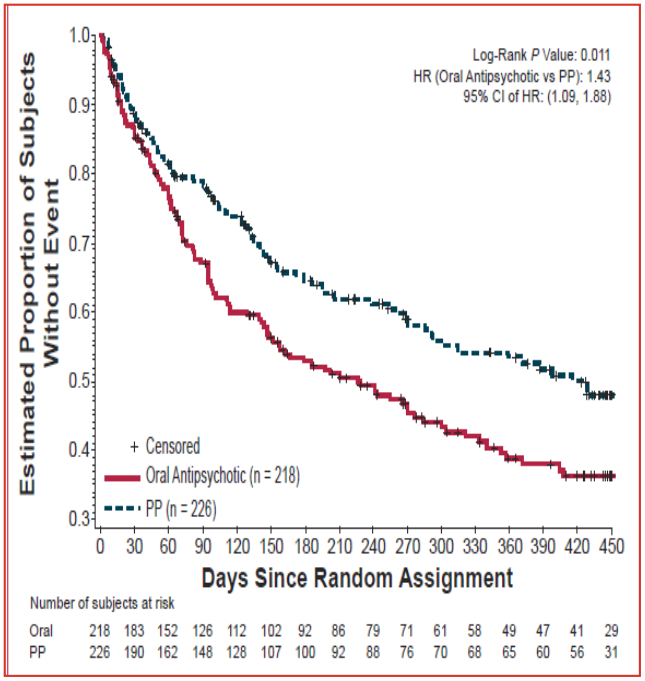
35% vs. 5% relapse in 86 first episode schizophrenia patients randomized to Oral RIS vs. RIS LAI



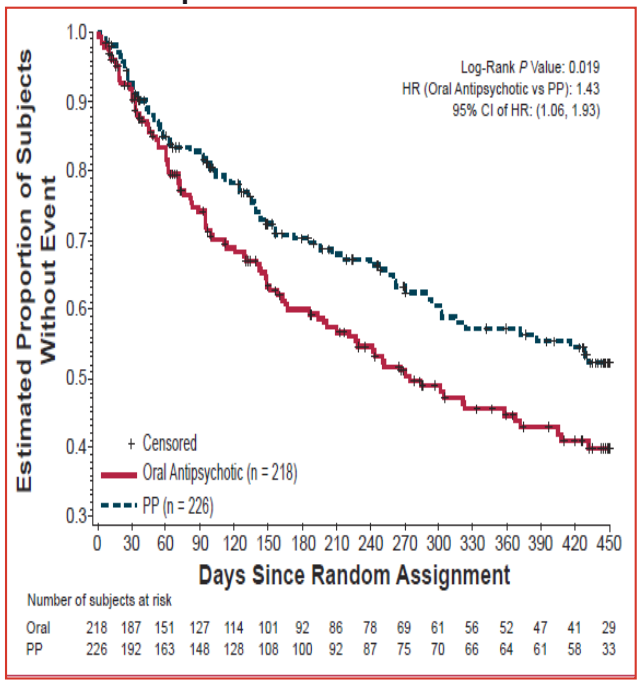
Subotnik KL, et al. *JAMA Psychiatry*. 2015;72(8):822-829.

Paliperidone LAI vs Oral Antipsychotics in Schizophrenia Patients with History of Incarceration and Substance Abuse

Estimated Time to First Treatment

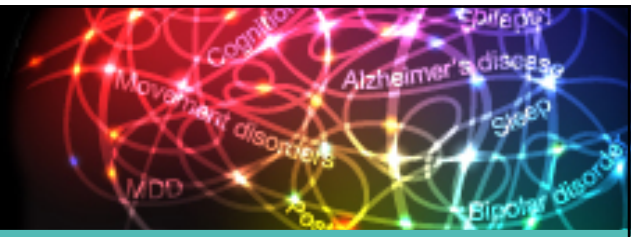


Estimated Time to First Psychotic Hospitalization or Arrest



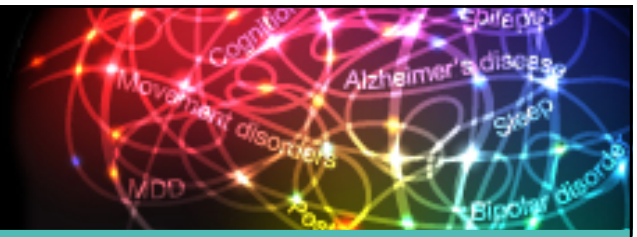
Alphs. L, et al. *J Clin Psychiatry*. 2015;76(5):554-561; Alphs L, et al. *Schizophr Res*. 2016;170(2-3):259-264; Kim E, et al. *CNS Spectr*. 2016;21(6):466-477.

Summary



- Recovery is the goal, relapse prevention the way to achieving it.
- There are pros and cons of oral therapies versus long acting injectables (LAIs) in achieving recovery when developing a treatment plan in patients with schizophrenia.
- Specific populations may be the best candidates for LAIs.
- Incorporate into practice, management strategies that engage the patient and family/caregivers in improving adherence and reducing the risk of relapse in schizophrenia

Call to Action



- Proactively address relapse prevention and recovery in schizophrenia by increasing the utilization of LAIs, particularly earlier in treatment
- When choosing a LAI to promote recovery in schizophrenia, assess the risk/benefit balance of available therapies

Questions & Answers

Don’t forget to fill out your evaluations to collect your credit.