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Moving the Needle for Optimal Outcomes in Schizophrenia Management: *An Update on Long-Acting Injectables and Strategies for Shared Decision-Making*

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Learning Objective 1

Assess treatment adherence and effective medication strategies to improve probability of remission and recovery.



Learning Objective 2

Incorporate shared decision-making to facilitate using long acting injectables (LAIs) in clinical practice.



Who Would You Give a Long-Acting Antipsychotic To?



- 22-year-old college student with onset of psychosis in the past year and two “back to back” inpatient admissions
- 44-year-old man with continued psychotic symptoms but stable in a supportive apartment
- 33-year-old woman with history of schizophrenia recently released from jail
- 66-year-old who has been taking clozapine for 15 years

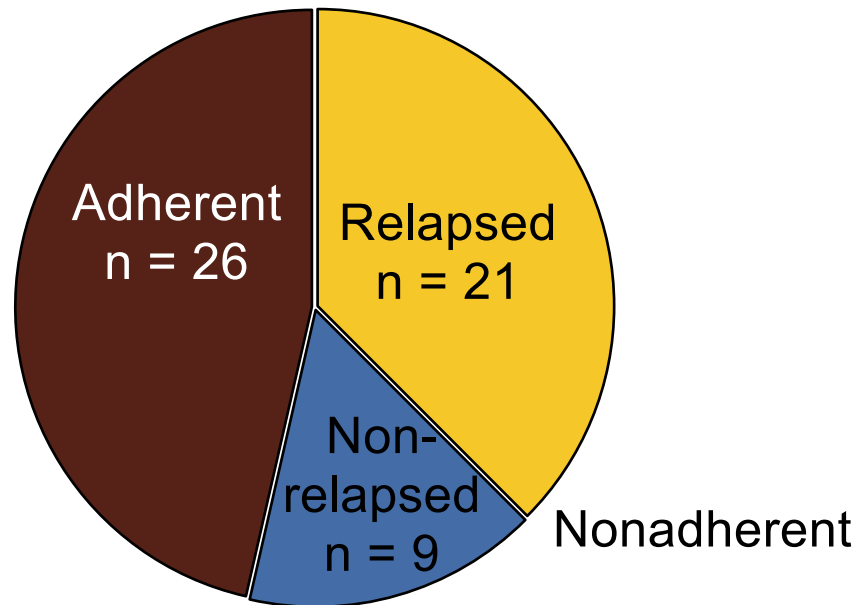
Goals of Long-Term Management in Schizophrenia



- Relapse prevention
- Improvements in long-term functional outcomes
- Minimization of residual psychopathology and cognitive deficits
- Prevention or reduction of suicidality and violence
- Treatment adherence

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%)

Factors that Contribute to Nonadherence



Patient-related Factors

- Persecutory delusions
- Lack of insight
- History of substance abuse
- Previous nonadherence

Medication-related Factors

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

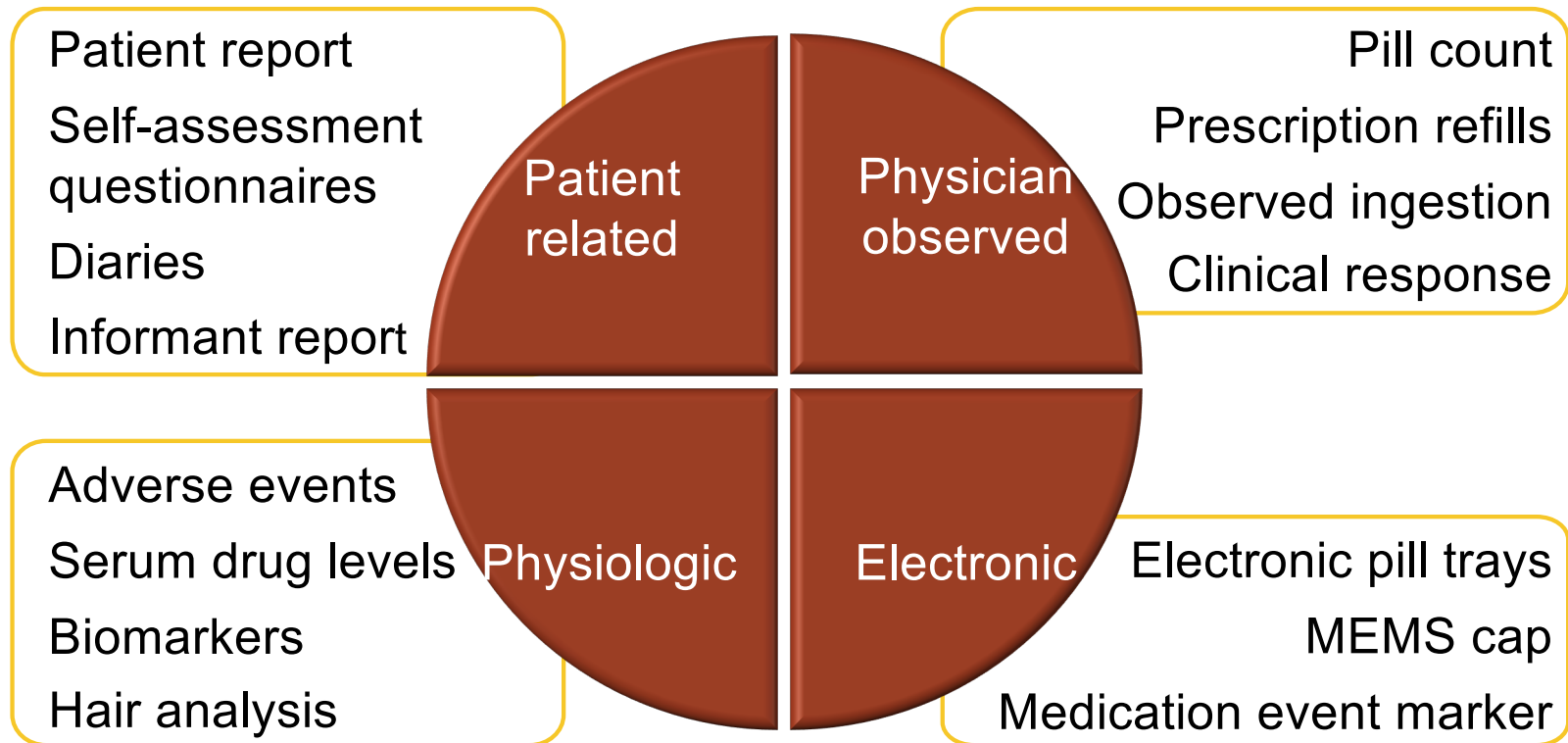
Environmental Factors

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

Clinician-related Factors

- Poor therapeutic alliance
- Attitude of staff

Methods for Monitoring Medication Adherence



MEMS = medication event monitoring system.
Kane JM, et al. *World Psychiatry*. 2013;12(3):216-226.

Pros and Cons of Long-Acting Antipsychotics



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

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/daily

[Package Inserts]. Drugs@FDA Website.

Atypical Antipsychotics LAIs for Schizophrenia

Drug	Formulation (Approval)	FDA Approved Dose Range
Risperidone (Risperdal [®] , Consta [®])	Long-Acting IM (2003)	25, 37.5, or 50 mg IM every 2 weeks
Olanzapine (Zyprexa Relprevv [®])*	Long-Acting IM (2009*)	150-300 mg IM every 2 weeks
Aripiprazole (Abilify Maintena [®])	Long Acting IM (2013)	160-400mg per month
Aripiprazole Lauroxil (Aristada [®])	Long Acting IM (2015)	441, 662 and 882mg per 4-6 weeks, 1064 q8weeks
Aripiprazole loading (Aristada Initio [®])	Long-Acting IM (2018)	675 mg (only as single dose)
Paliperidone (Invega [®] , Sustenna [®])	Long-Acting IM (2009)	117 to 234 mg per month
Paliperidone (Invega Trinza [®])	Long-Acting IM (2015)	273-819 every 12 weeks
Risperidone SubQ (Perseris [®])	Long-Acting SQ (2018)	90 or 120mg q 4weeks

*Includes Risk Evaluation and Mitigation Strategy (REMS) with approval [Package Inserts]. Drugs@FDA Website.

Aripiprazole Lauroxil Loading Dose



- Aripiprazole lauroxil requires 21 day overlap with oral aripiprazole
- New formulation allows the nanocrystals to activate nearly immediately and last about a week
- To achieve adequate early blood levels package insert directs to use one 30mg tablet of aripiprazole
- A second injection of usual aripiprazole lauroxil should be given (hours to days)

[Package Inserts]. Drugs@FDA Website.

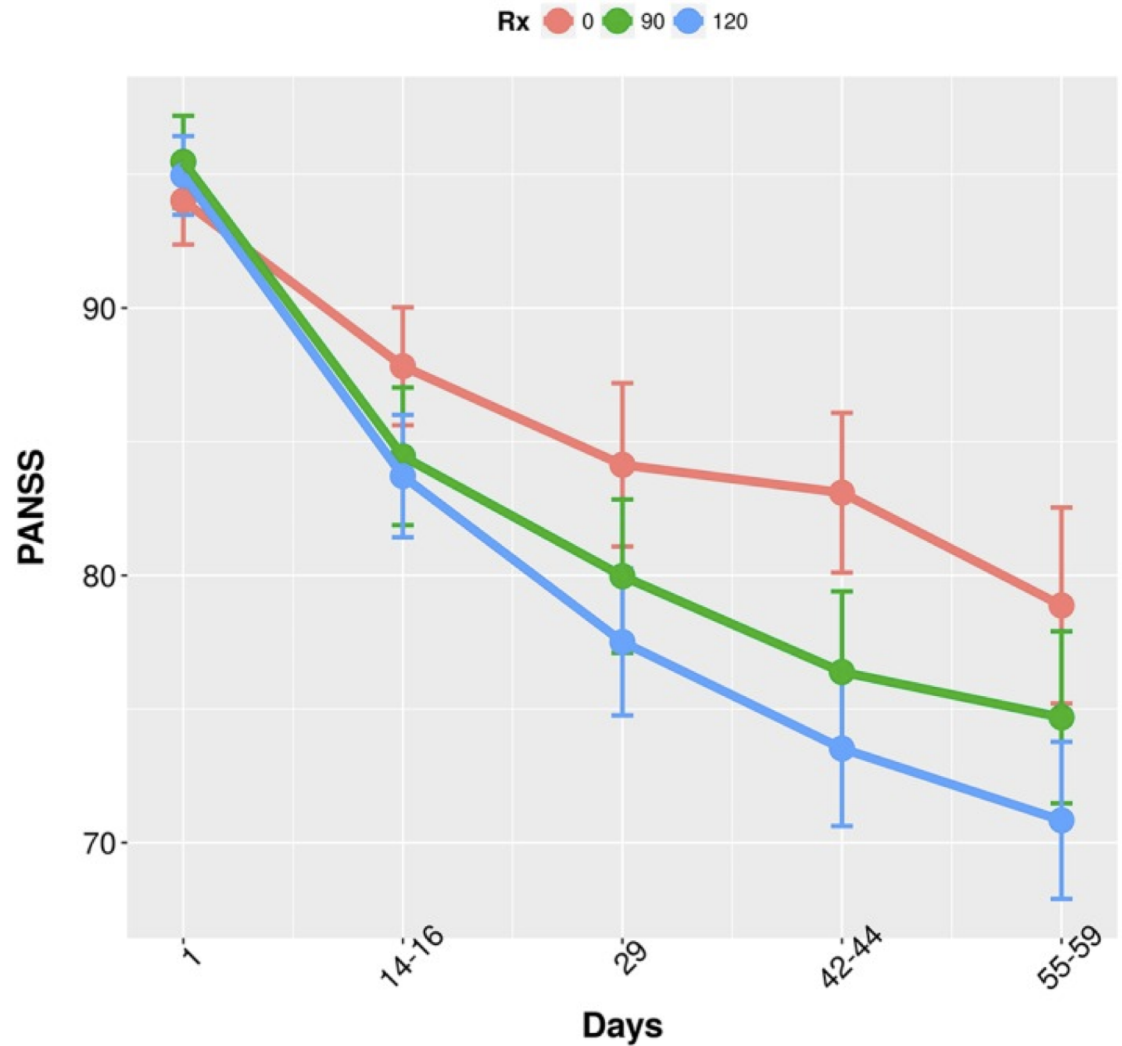
Risperidone Long-Acting SubQ



- First long-acting subcutaneous antipsychotic
- Two dose options 90mg (3mg) or 120mg (4mg)
- CYP2D6 inhibitors (e.g. fluoxetine use 90mg)
- CYP2D6 inducers (e.g. carbamazepine use 120mg)
- No overlap necessary
- Proper mixing technique
- Must be given by a health care professional

[Package Inserts]. [Drugs@FDA Website](#).

Risperidone LAI SubQ Reduces PANSS Scores Over Time Across Dose Groups

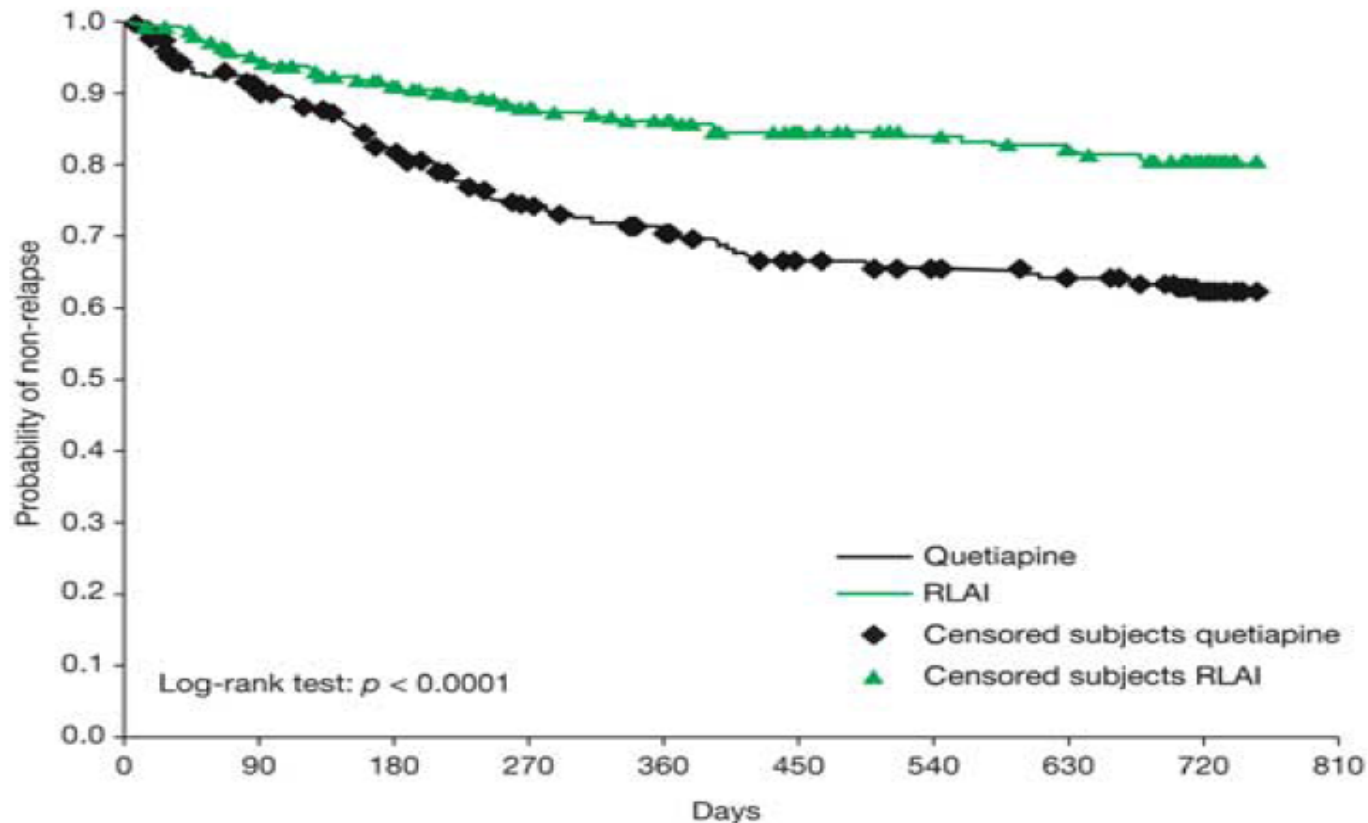


PANSS, Positive and Negative Syndrome Scale
Ivaturi V, et al. *Br J Clin Pharmacol.* 2017;83(7):1476–1498.

Are Long-Acting Antipsychotics Superior to Oral Antipsychotics?



Relapse Prevention with Risperidone Long-acting Injectable (RLAI) vs Oral Quetiapine

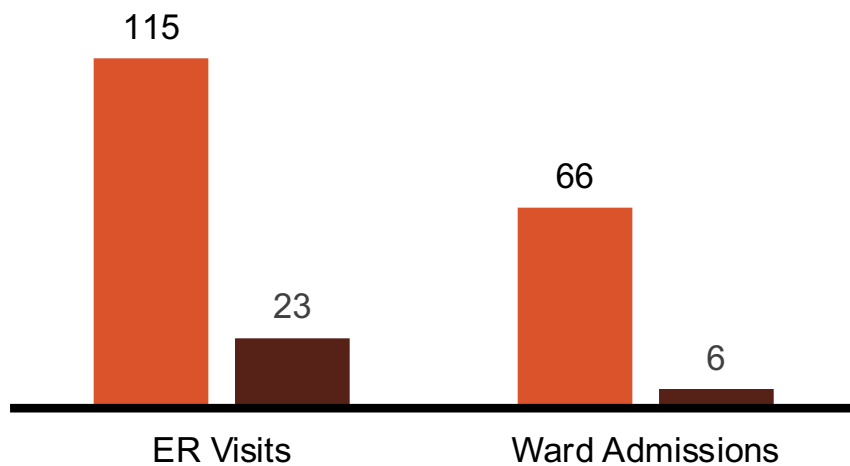


Gaebel W, et al. *Eur Neuropsychopharmacol.* 2010;20(5):310-316.

LAI's Reduce Hospital and ER Visits and Overall Length of Stay Compared to Orals

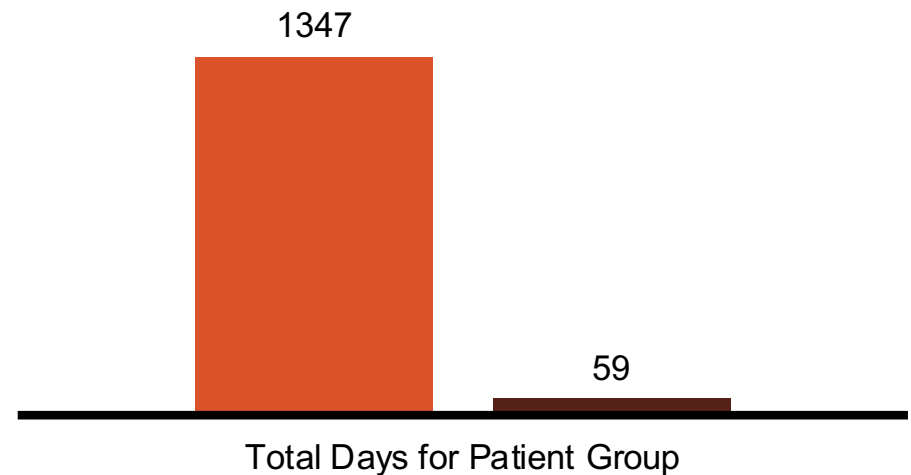
Hospitalizations (N = 44)

- 12 Months Pre-LAI (Oral)
- 12 Months Post-LAI



Length of Stay (N = 44)

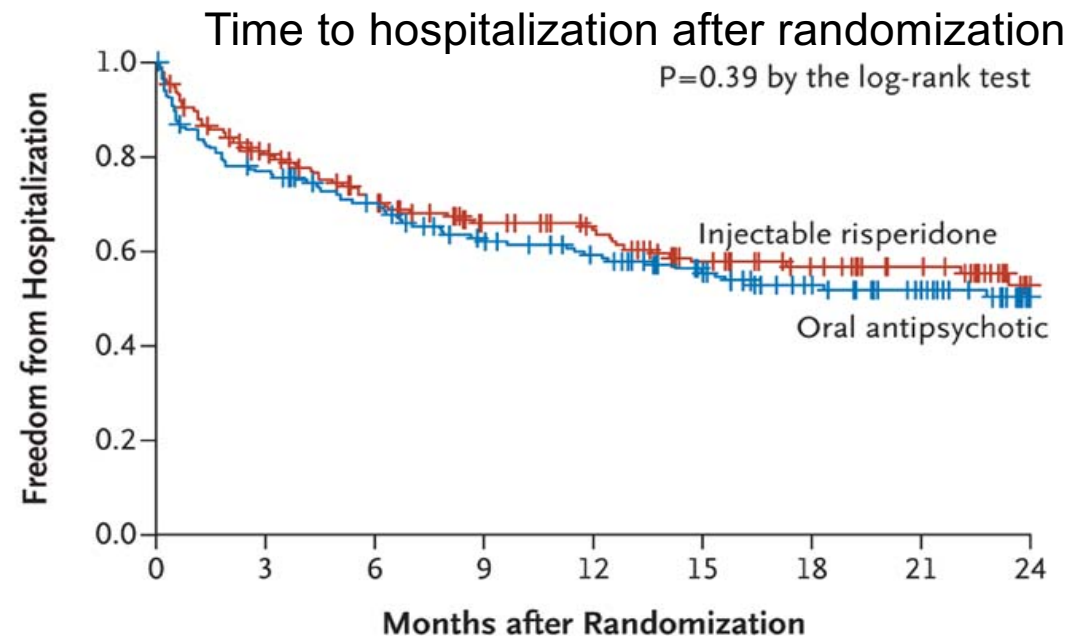
- 12 Months Pre-LAI (Oral)
- 12 Months Post-LAI



Chawla K, et al. *Int J Emerg Ment Health*. 2017;19(4):377.

Long-Acting Risperidone and Oral Antipsychotics in Unstable Schizophrenia

- Long-acting injectable risperidone was not superior to a psychiatrist's choice of oral treatment in unstable patients



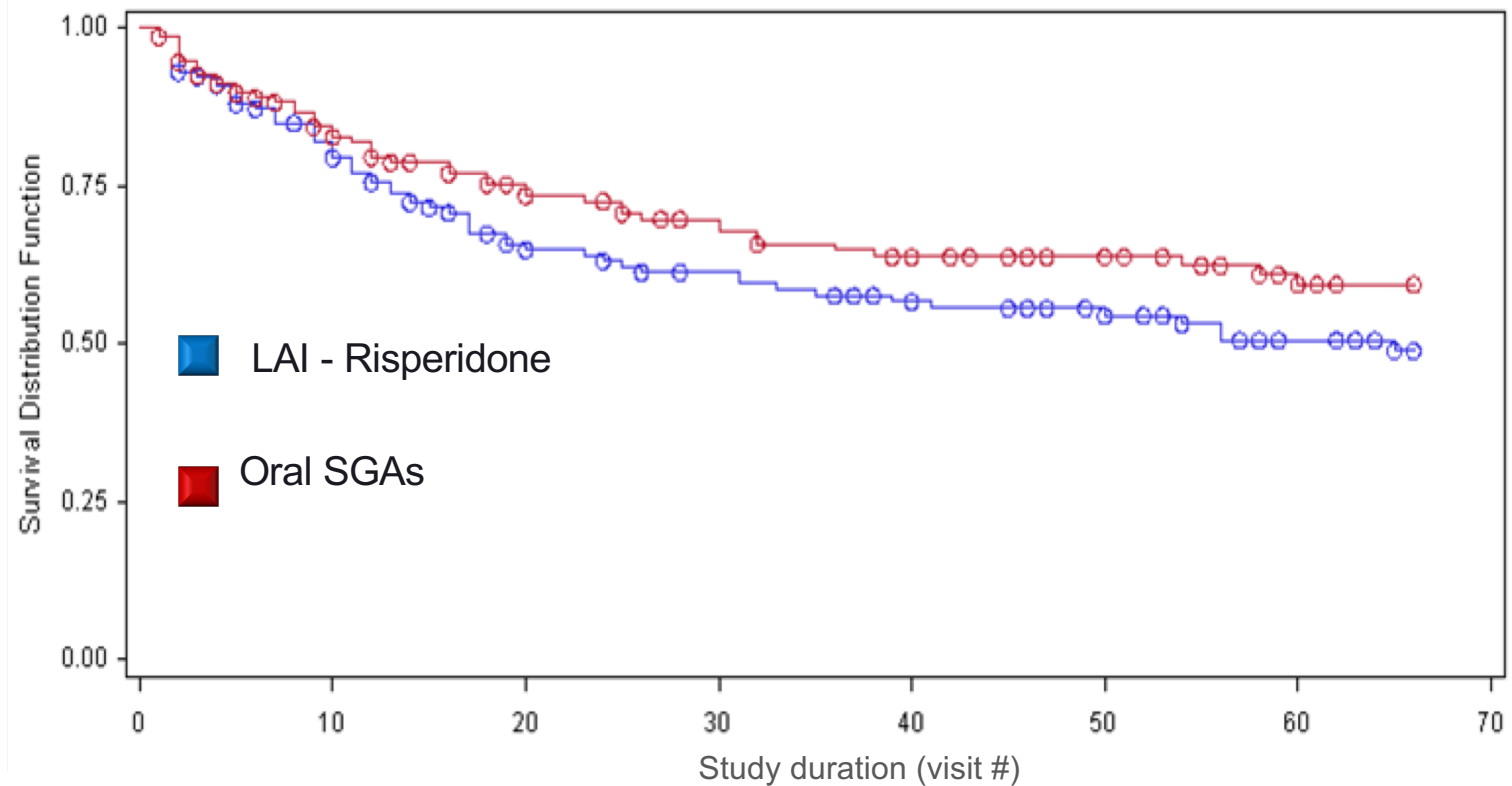
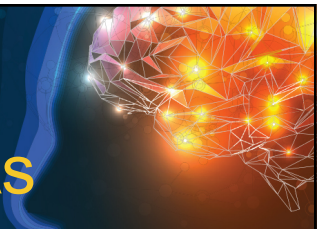
No. at Risk

Oral antipsychotic	182	136	116	96	84	71	58	49	28
Injectable risperidone	187	136	110	92	82	65	53	45	37

Rosenheck RA, et al. *N Engl J Med.* 2011;364:842-851.

PROACTIVE Study

LAI Risperidone Confers No Advantage Over Oral SGAs



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

Reasons for Conflicting Evidence

- Gold standard' RCT design does not reflect everyday clinical practice
- It encompasses inherent compliance-enhancing measures which may camouflage potential advantages of LAIs over oral antipsychotics
- Examples include: frequent visits; enhanced contact with members of treatment team; measures to assure retention in study; double-dummy design may overshadow potential disadvantage of injections; informed consent leads to selection bias
 - Highly compliant patients are preselected

Studies in Selected Populations

First Episode



Is There a Case for Earlier Use of LAI Antipsychotics?

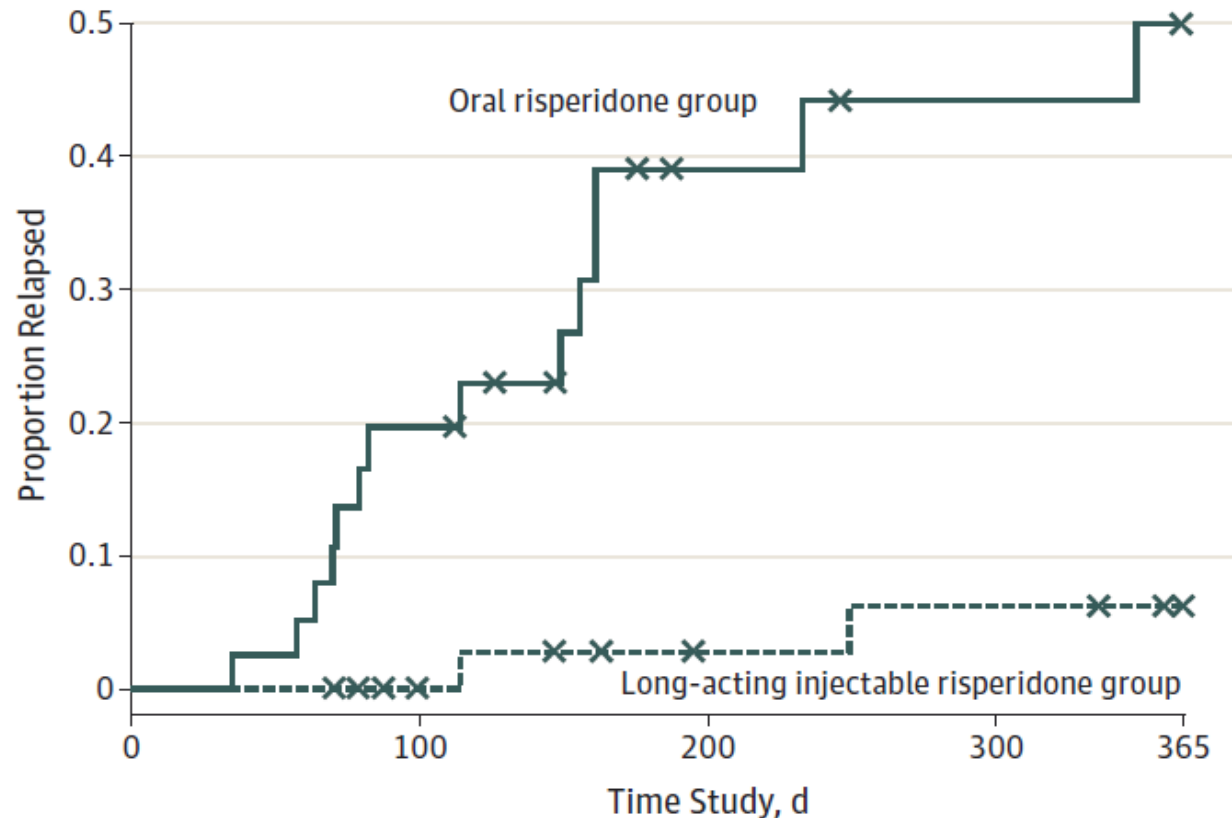
- Potentially decrease the percentage of time spent experiencing psychotic symptoms
 - In the first 2 years, experiencing symptoms is the strongest predictor of long-term symptoms and disability¹
- Potentially decrease the number of psychotic episodes
 - Patients experience a decrease in treatment response with subsequent exacerbations²
 - Neuropathic brain changes often progress with subsequent clinical episodes³
- LAI antipsychotics allow for swift identification of overt non-adherence and eliminate covert non-adherence⁴

¹ Harrison G, et al., *Br J Psychiatry*. 2001;178:506-517; ² Lieberman JA, et al. *Neuropsychopharmacology*. 1996;14:13S-21S; ³ Lieberman JA, et al. *Psychiatr Serv*. 2008;59:487-496; ⁴ Fenton WS, et al. *Schizophr Bull*. 1997;23:637-651.

Long-Acting Risperidone and Oral Antipsychotics in Unstable Schizophrenia

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

Excellent adherence: RIS = 33%



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

PROSIPAL Trial

Prevention of Relapse with Oral Antipsychotics
Vs. Injectable Paliperidone Palmitate



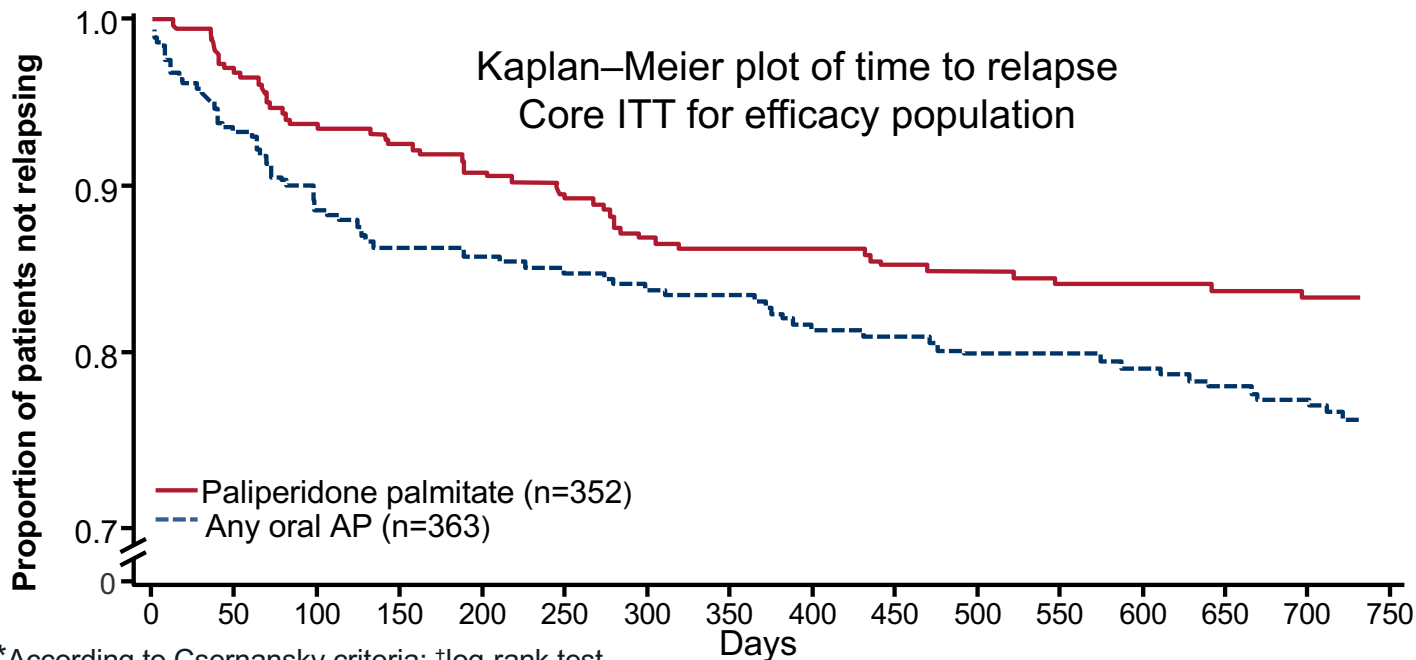
- Multicenter, RCT, active control, open-label but rater-blinded study
- Acute episode of schizophrenia
- Age 18-65 (mean age 32)
- Illness duration 1-5 yrs with >2 relapses in preceding 24 mos
- Performed in 141 centers in 26 countries
- 2 week oral lead in and 24 month treatment phase
- Randomized to a group of oral SGAs or PP

PP = paliperidone palmitate

Schreiner A, et al. *Scizophr Res.* 2015;169(1-3):393-399.

PROSIPAL: Time to Relapse

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



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 oral AP group ($p = 0.0323$).

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

*According to Csernansky criteria; [†]log-rank test

AP = antipsychotic; HR = hazard ratio; ITT = intent-to-treat; PP = paliperidone palmitate.
Schreiner A, et al. *Scizophr Res*. 2015;169(1-3):393-399.

Who Would You Give a Long-Acting Antipsychotic to?



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Communication Strategies When Using LAIs



Patients Are Willing to Accept LAI Antipsychotic Therapy When Properly Informed

- In a survey of psychiatrists:
 - Patient refusal was cited as a primary reason for not prescribing LAI antipsychotics¹
- In a survey of patients without LAI antipsychotic experience:
 - 79% cited having never been informed about the option by their psychiatrist²
 - 75% of psychiatrists felt that they informed the patient, but only 33% of patients felt informed²
- In a survey of patients with ≥ 3 months of LAI antipsychotic experience:
 - Injectable antipsychotics were the preferred formulation³
 - 70% of patients felt better supported in their illness by virtue of regular contact with the doctor or nurse who administered their injection³

1. Heres S, et al. *J Clin Psychiatry*. 2006;67(12):1948-1953. 2. Jaeger M, Rossler W. *Psychiatry Res*. 2010;175(1-2):58-62. 3. Caroli F, et al. *Patient Prefer Adherence*. 2011;5:165-171.

Counseling/Psychotherapy Strategies

- Emphasis on personal choice and responsibility
- Non-judgmental, empathic, active, therapeutic stance
- Focus on eliciting the patients concerns
- Readiness for change is on a continuum
- Therapeutic strategies include:
 - Motivational interviewing
 - Providing education about illness and treatment
 - Paced intervention

Specific Communication Strategies for Presenting LAIs as a Treatment Option

- Be knowledgeable and enthusiastic about the treatment option
- Highlight the individual goals for the patient and link them to continued treatment
 - Live independently
 - Have a job working/go to school
 - Take less medication, have less side effects
 - Develop and maintain relationships
- Encourage the patient to ask all questions and discuss all concerns
- Involve family members or other important people in the patient's life
- Differentiate LAIs from short-acting emergency intramuscular treatment
- Use “once monthly” rather than “depot” or “long-acting injectable”

Specific Communication Strategies for Presenting LAIs as a Treatment Option (cont.)



- Put things into perspective (“those voices, those paranoid thoughts are likely to come back. It may be a matter of time, especially when one misses doses, which is the rule rather than the exception”)
- Deconstruct resistance by understanding the superficial and deeper objections
- Highlight personal gain to the patient (“not having to worry about where your pills are or whether you took them or not that day” “helping you not getting sick again and working towards your own goals”)
- Share other patients’ experience (“Sometimes, patients think that this is easier ...” - “patients who have tried this often prefer it over taking daily medications”)

Last Thoughts

- Schizophrenia is a chronic, often relapsing disorder
- Adherence plays a role in relapse
- LAI antipsychotics could be a potential solution
- Trials that utilize real world design and specific populations may be more informative
- LAIs may be a means not an end in themselves
- Patients need to be informed of their options and whenever possible be involved in their treatment
- A renewed interest in novel delivery systems may lead to further advancements in this area

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely



- Implement the use of long-acting injectables in appropriate patients to ensure delivery of prescribed medications and prevention of relapse
- Incorporate the use of shared decision-making strategies to personalize treatment selection and overall management in patients with schizophrenia

Questions & Answers

Don't forget to complete your evaluation in order to collect your credit.

