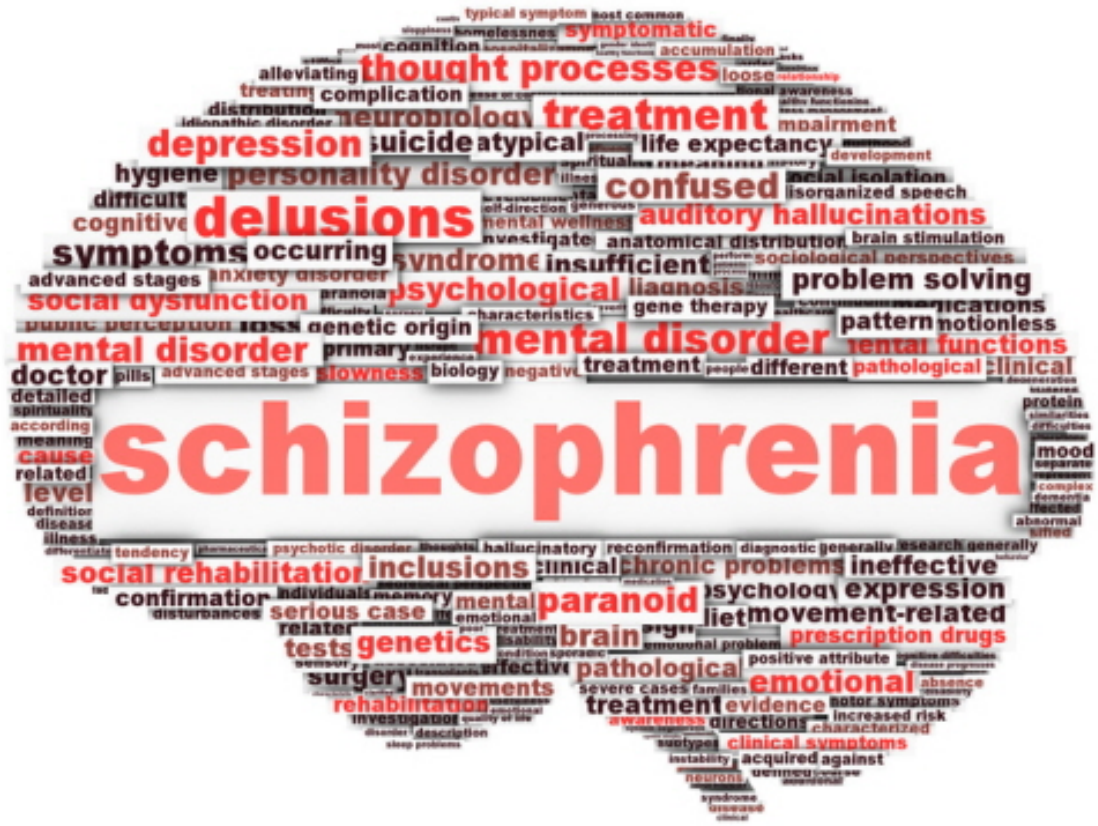
The Use of Long-Acting Injectable Antipsychotics for First Episode Schizophrenia



http://www.smrionline.com/schizophrenia.html

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Learning Objectives

1. Discuss the occurrence and implications of schizophrenia especially first episode schizophrenia
2. Understand the potential role of antipsychotics and long-acting injectable formulations
3. Evaluate the literature for the use of long-acting injectable antipsychotics for patients with first episode schizophrenia
4. Formulate evidence-based conclusions regarding the use of long-acting injectable antipsychotics for this patient population

First Episode Schizophrenia

I. **Definitions**[1,2,3]
   a. Schizophrenia (See Appendix A)
      i. A severe mental disorder in which people experiences altered perceptions of reality that includes a combination of symptoms:
         1. Hallucinations: can be involved with any senses but auditory hallucinations are most common
         2. Delusions: false beliefs that are not based in reality
         3. Disorganized thinking: impaired effective communication, unrelated answers to questions, putting meaningless words together
         4. Abnormal motor behavior: resistance to instructions, inappropriate/bizarre posture, complete lack of response, useless/excessive movement
         5. Negative symptoms: lack of emotion and facial expressions, not making eye contact, monotone speech, decreased talking, neglect of personal hygiene, loss of interest
   b. First Episode Schizophrenia (See Appendix A)[1,4]
      i. First manifestation of the disorder after meeting all of the defining diagnostic criteria for schizophrenia
      ii. Primary clinical and psychosocial deterioration occurs within the first 5 years following the onset of illness
      iii. Prodromal phase occurs preceding first episode schizophrenia: tension, nervousness, eating less, worsening concentration, trouble sleeping, depression, mild psychotic symptoms[5]

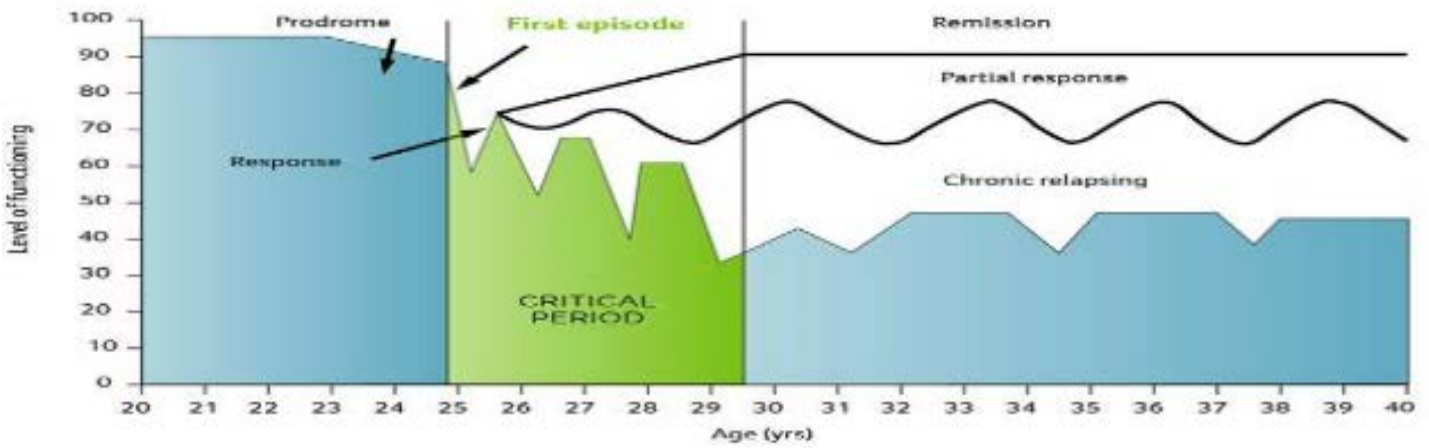

Figure 1: Time Course of Schizophrenia[6]

II. **Epidemiology of Schizophrenia**[1,7]
   a. Lifetime prevalence is approximately 0.3-0.7%
      i. 4 cases/1000 of adult population >18 years (50 million people worldwide)
   b. Male > Female (1.4:1)
   c. Psychotic features typically emerge between the late teens and the mid-30s
   d. Peak age at onset for the first episode is in the early- to mid-20s for males and late-20s for females
   e. Only 20% of patients have favorable prognosis

III. **Consequences of Schizophrenia**[1,3]
   a. Poor medication compliance (i.e. due to impaired insight)
   b. Physical comorbidities (i.e. metabolic diseases)
   c. Poor hygiene/self-care
   d. Increased risk of suicide or risky behavior
   e. Impaired interpersonal relationships

IV. **Etiologic Theories of Schizophrenia**[1,3]

a. Genetics: Occurs in 10% of people who have first-degree relative with this disorder; 50% with identical twins
b. Environment: Exposure to viruses or malnutrition before birth (in first and second trimesters)
c. Brain chemistry: dopamine and glutamate
d. Substance use: Especially during teen years and young adulthood

V. **Treatment of First Episode Schizophrenia**[4,8,9,10]

a. Pharmacologic
    i. Antipsychotics: first generation (FGA) and second generation (SGA)
        1. **American Psychiatric Association (APA):** SGA as first-line option for first episode schizophrenia and long-acting injectable antipsychotics (LAI) is reserved for noncompliant patients with chronic schizophrenia[8]
        2. **Texas Medication Algorithm Project (TMAP):** SGA as first-line option for first episode schizophrenia and LAI antipsychotics can be considered if patient is non-adherent at any stage of the illness[9]
        3. **The Schizophrenia Patient Outcomes Research Team (PORT) psychopharmacological treatment recommendations:** Antipsychotic medications, other than clozapine and olanzapine, are recommended as first-line treatment for first episode schizophrenia[11]
            a. LAI antipsychotics should be offered as an alternative to oral agents for the maintenance treatment of schizophrenia when LAI agents are preferred to oral forms[11]
        4. **World Federation of Societies of Biological Psychiatry (WFSBP):** First-line use of both FGA and SGA medications at the lower end of the standard dose range are recommended[12]
            a. Haloperidol, olanzapine, risperidone, and quetiapine have the most evidence for efficacy in treatment of first episode schizophrenia[12]
            b. Treatment duration of 1-2 years is recommended; however, limited evidence supports the impact on relapse rates[5]
            c. LAIs should be a treatment option when patient expresses a preference for such option to ensure compliance[5]
        5. First episode schizophrenia require lower doses of antipsychotics and exhibit greater sensitivity to side effects[4,9,11,12]
        6. Early antipsychotic treatment or shorter duration of untreated psychosis was associated with better outcomes in first episode schizophrenia[12]
b. Non-pharmacologic[10]
    i. Therapeutic alliance between patients, family, healthcare professions
    ii. Family interventions
    iii. Supported employment
    iv. Assertive community treatment
    v. Social skills training
    vi. Cognitive behavioral therapy
c. Goals of treatment[10]
    i. Prevent relapse and clinical deterioration
        1. Minimum of 3 months sustained remission of symptoms over the first 2 years of treatment predicts good functional recovery[10]
        2. 81.9% have first relapse in initial 5 years; 78% will have second relapse; 86.2% will have a third relapse[10]
        3. Relapses are associated with longer time to achieve remission, worsen treatment response, increased in chronic symptoms, gradual psychosocial deterioration[10]
    ii. Restore socio-occupational functioning to premorbid level

iii. Enhance patient's adaptation to life in the community
iv. Facilitate reduction in symptoms, consolidate remission, and promote process of recovery

VI. **Reasons for discontinuation of medications[4,13]**
- a. Severity of disease/impaired insight
- b. Comorbid substance abuse
- c. Medication side effects
- d. Negative patient attitudes

VII. **Clinical implications of medication discontinuation[14]**
- a. Increased rates of psychiatric hospitalization, use of emergency psychiatric services
- b. Arrests, violence, victimizations, poorer mental functioning and life satisfaction
- c. Greater substance abuse problems
- d. Greater risk of suicide
- e. **In first episode schizophrenia[13]:**
  - i. Increased risk of relapse and greater likelihood of emergence of treatment resistant symptoms
  - ii. Almost a 5-fold increase in relapse rates after medication discontinuation
  - iii. Malla et al found 82% of patients achieved remission over 2 years[15]
    1. Greater adherence was a significant predictor of remission status

VIII. **Incidence of discontinuation of medications in first episode schizophrenia[13]**
- a. Overall all-cause discontinuation rate was **40.8%** with mean duration of treatment of **34.8 weeks**

Use of Long-acting Injectable Antipsychotics (LAI) in Schizophrenia

I. **Long-acting Injectable Antipsychotics (LAI)[16]**
- a. LAIs were developed in response to high rates of poor adherence to oral formulations[17]
- b. Risperidone long-acting injectable has been shown to have equal or less side effects compared to oral risperidone[17,18]
  - i. Higher adherence rates, clinical improvement, reduction in EPS and prolactin levels, reduction of relapses and hospitalizations[17]

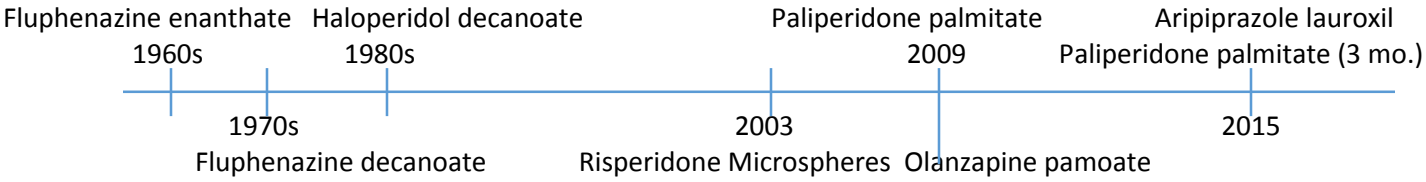

Figure 2: Timeline of availability of LAI antipsychotics

- c. <u>Advantages of LAIs</u>[10,19]
  - i. Non-adherence can be accurately measured by receiving injections at clinic visits
  - ii. Eliminates the need for daily medication use
  - iii. Drug concentrations can be maintained in a stable state; less fluctuations in troughs and peaks
  - iv. Decrease risk of accidental or deliberate overdose
  - v. Reduce hospitalizations and rate of relapse
- d. <u>Limitations of LAIs</u>[20]
  - i. Delayed disappearance of medication-related side effects
  - ii. Limited number of medications available in LAI form
  - iii. Not easy to adjust small doses
  - iv. Stigmatism towards injectable medications and patients feeling of being controlled

v. Negative attitudes of clinicians based on presumptions that patients would not accept treatment with LAIs
vi. May cause pain and discomfort at the injection site

e. Differing attitudes towards the use of LAIs[21]:
   i. **Patients' attitudes:**
      1. Fear of being limited in their autonomy
      2. Fear of needles
      3. 1/3 of patients were insufficiently informed about different formulations
      4. 67% of patients did not receive information about LAIs from their psychiatrists
   ii. **Psychiatrists' attitudes:**
      1. Support the advantages of LAIs but did not consider to be more advantageous than oral forms
      2. 2/3 of psychiatrists feel that patients are insufficiently informed
      3. Mainly recommend changing to LAIs when patients are non-adherent or when patients requests LAIs
      4. Changing to LAIs is almost never recommended after a first psychotic episode
      5. Anticipate a negative attitude of patients toward LAIs
   iii. **Relatives' attitudes:**
      1. 50% of relatives thinks that patients were not taking their medications voluntarily
      2. Supported potential advantages of LAIs more strongly than patients did

Table 1: Comparison of properties of available long-acting injectable (LAI) antispychotics[20,22]

Generic (Brand)	Oral dose vs. LAI dose	Usual Adult dose	Dosing interval (wks)	Terminal half-life (days)
Aripiprazole (Abilify Maintena)	Establish tolerability – **Overlap oral x14 days** after 1st injection **10-20 mg PO = 400 mg IM Q4W** Decrease to 300 mg prn tolerability	300-400mg Q4W	4	29.9 → 46.5 (300 → 400mg)
Aripiprazole lauroxil (Aristada)	Establish tolerability – 10 mg/day PO = 441 mg IM Q4W 15 mg/day PO = 662 mg IM Q4W ≥20 mg/day PO = 882 mg IM Q4-6W **Overlap oral x21 days** after 1st injection	441-882mg Q4W; 882mg Q6W	4-6	29.2-34.9
Fluphenazine decanoate (Prolixin Decanoate)	1 mg PO = 1.2-1.25 mg IM Q1-3W	12.5-100mg Q2W	1-3	14-21
Haloperidol decanoate (Haldol Decanoate)	Stabilize on oral 20x oral 1st month 15x oral 2nd month 10x oral ≥3rd month	20-450mg Q4W	3-4	21
Olanzapine pamoate (Zyprexa Relprevv)	10 mg/day PO = 210 mg IM Q2W OR 405 mg IM Q4W x8	150-405mg Q2-4W	2-4	30

	wks; then 150 mg IM Q2W OR 300 mg IM Q4W 15 mg/day PO = 300 mg IM Q2W x8 wks; then 210 mg IM Q2W OR 405 mg IM Q4W 20 mg/day PO = 300 mg IM Q2W	300mg IM Q2W		
Paliperidone palmitate (Invega Sustenna)	Day 1: 234mg; Day 8: 156mg Monthly injection: 3 mg/day PO = 39-78 mg IM 6 mg/day PO = 117 mg IM 9 mg/day PO = 156 mg IM 12 mg/day PO = 234 mg IM	117-234 mg Q4W	4	25-49
Paliperidone Palmitate (Invega Trinza)	After ≥4 months; Can convert monthly to 3 month (**1 month dose x3.5 = 3 month dose**) Conversion from Sustenna to Trinza: 78 mg IM = 273mg IM 117 mg IM = 410mg IM 156 mg IM = 546mg IM 234 mg IM = 819 mg IM	410-819mg Q3M	12	84-95
Risperidone microspheres (Risperdal Consta)	Establish tolerability **Overlap with oral x21 days after 1st injection** Administer every 2 weeks: ≤3 mg/day PO = 25mg IM >3-5 mg/day PO = 37.5 mg IM >5 mg/day PO = 50 mg IM	12.5-75 mg Q2W	2	3-6

II. **Meta-analyses on the use of LAIs in schizophrenia**

a. Efficacy and safety of second-generation LAI (SGLAI) in schizophrenia[23]:

i. Included 13 randomized, controlled trials (RCTs) between 2003 and 2011 comparing either SGLAI to placebo or oral antipsychotics
   1. SGLAI vs. placebo: n = 2627, mean age = 39.2 years, 62.5% men
   2. SGLAI vs. oral antipsychotics: n = 3686, mean age = 41.3 years, 62.9% men

ii. Primary efficacy measure (PANSS change over time):
   1. SGLAI better than placebo ($p < 0.001$)
   2. SGLAI not significantly different from oral antipsychotics ($p = 0.326$)
   3. SGLAI superior to combined control groups (placebo + oral antipsychotics); $p < 0.001$

iii. Secondary efficacy measures (number of responders → increase of ≥20% in PANSS total score from baseline to endpoint):
   1. Higher in SGLAI vs placebo (47% SGLAI vs. 24% placebo; RR = 1.841, $p < 0.001$)
   2. SGLAI not superior to oral antipsychotics (RR = 0.962, $p = 0.094$)

iv. No significant differences between SGLAI and placebo or oral antipsychotics in **number of deaths, overall adverse events, insomnia, or pain in injection site**

1. SGLAI has greater risk of EPS than in placebo or oral antipsychotics groups
2. SGLAI more likely to use anti-EPS medications
3. SGLAI doubled the risk of weight gain compared with placebo; no difference compared with oral antipsychotics

b. LAIs vs. oral antipsychotics for relapse prevention[24]:
   i. Included 20 RCTs that compared LAI to oral antipsychotics for relapse prevention or maintenance treatment in schizophrenia
   ii. Primary outcome: relapse at the latest point of follow-up
      1. Fluphenazine LAI showed significant superiority over oral antipsychotics (RR = 0.79, p = 0.02)
      2. Other LAIs were not significantly superior
      3. Pooled result: risk for LAIs were similar to oral antipsychotics (RR = 0.93, p = 0.35)
   iii. Secondary outcomes:
      1. Relapse at 3,6,12,18,24 months: pooled LAIs did not separate from oral antipsychotics
         a. Fluphenazine LAI showed trend superiority at 18-months (RR = 0.66, p = 0.05) and significant superiority at 24-months (RR = 0.56, p = 0.002)
      2. All-cause discontinuation: LAIs did not separate from oral antipsychotics (RR = 1.00, p = 0.99)
      3. Discontinuation due to adverse events: LAIs did not separate from oral antipsychotics (RR = 1.10, p 0.65)
      4. Drug inefficacy: Pooled LAIs did not separate from oral antipsychotics
         a. Fluphenazine LAI was superior to oral antipsychotics (RR = 0.78, p = 0.002)
      5. Hospitalization: Pooled LAIs showed a trend toward superiority over oral antipsychotics (RR = 0.89, p = 0.09)
         a. Fluphenazine LAI was superior to oral antipsychotics in preventing hospitalization (RR =0.82, p = 0.04)
      6. Non-adherence: Pooled LAIs did not separate from oral antipsychotics (RR = 0.77, p = 0.22)
   iv. FGA-LAIs seemed superior over oral antipsychotics may be due to publication bias with older studies and differences in definition of relapse
   v. Oral antipsychotics may have higher adherence in RCTs compared to real-world adherence rates
   vi. Large naturalistic, cohort studies are needed to evaluate real-world effectiveness of LAIs compared to oral antipsychotics which resemble common clinical practice and adherence

Remission in patients with first-episode schizophrenia receiving assured antipsychotic medication: a study with risperidone long-acting injection[25]

Emsley R, Oosthuizen P, Koen L, Niehaus DJ, Medori R, Rabinowitz J. International Clinical Psychopharmacology. 2008; 23: 325-331.

Design	2 year, prospective, single-site, open-label study
Objective	To investigate the remission rates, predictors, and correlates in patients treated with risperidone long acting injectable (RLAI) in first episode schizophrenia
Patient Population	• Adults (age 16-45 years) meeting DSM-IV criteria for schizophrenia for ≤ 12 months, with first psychotic episode • N = 50
Intervention	• After a washout period of 4-7 days, patients were administered oral risperidone 1-3 mg daily • After 7 days of oral risperidone, initated RLAI 25mg every 2 weeks (can be increased to 50 mg based on treatment response) • Oral risperidone was continued for 21 days after first RLAI injection • Assessment: Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression-Severity Scale (CGI-S) • Remission: Maintain ≥ 6 months a mild (3) or lower level on PANSS items
Endpoints	• Remission and non-remission groups compared on clinical, functional, and quality of life (QOL)
Statistical Analysis	• Kaplan-Meier survival analysis • Fisher's exact test or χ^2 test for categorical variables • Wilcoxon two sample test for continuous and ordinal variables • Cox regression analysis to examine variables for predicotrs of time to remission
Results	• 42 (84%) patients achieved at least 50% reduction on PANSS total scores • 32 (64%) patients achieved remission at some point in the study → 31 (97%) of these patients maintained remission throughout the study • PANSS total score, change from baseline: **-41.0 (remission) vs. -26.37 (non-remission); p<0.0001** • CGI-S change from baseline: **-3.61 (remission) vs. -1.74 (non-remission); p<0.0001** • Chance of remission was increased (p<0.10) by being a woman, higher BMI, higher level of depression, higher CGI-S rating, early symptom improvement (change in PANSS total score) o Significant change in PANSS total score by week 2 was associated with likelihood of remission (hazard ratio = 0.95; p=0.002)
Authors Conclusions	• The results from this study provide further evidence that a substantial proportion of patients with first-episode schizophrenia are able to achieve remission (62%). Patients achieving remission also do better in other outcome measures such as excitement/hostility, depression/anxiety, and insight. The functional and QOL outcomes did not show significant improvement.
Comments and Conclusions	Strengths: • Adequate duration of study period – 24 months • Patient population has limit prior exposure to antipsychotics • Assured adherence to medication Limitations: • Open-label design, single-center, small sample size, no randomization • Study did not publish permitted PRN medications (e.g. lorazepam, oral risperidone) • Study did not account for potential adverse events during the study Conclusions: • RLAI seems to be effective for patients with first episode schizophrenia, especially when treated early in the course of illness • Need better designed studies to further evaluate the efficacy, safety, tolerability of RLAI as well as investigate the rate of relapse and hospitalization in first episode schizophrenia

Treatment adherence with early prescription of long-acting injectable antipsychotics in recent-onset schizophrenia[26]

Viala A. Cornic F, Vacheron MN. *Schizophrenia Research and Treatment*. 2012; 1-5

Design	18-month, epidemiological, observational, noninterventional study in usual-care settings
Objective	Evaluate the impact on relapse, rehospitalization rate, and treatment adherence
Patient population	• 18 years of age or older • Diagnosis of schizophrenia (DSM-IV criteria) • N = 25
Intervention	• All patients were treated with risperidone 4-8mg orally before changing to RLAI • First injection prior to discharge and oral bridge was continued for 3-4 weeks • Assessment: Patients were assessed at baseline and after 6, 12,and 18 months for adherence, efficacy, RLAI dosage, number and duration of hospitalization, social functionality, and reintegration (CGI and GAF scales)
Endpoints	• Better compliance with RLAI integrated in a psychosocial treatment program • The number and duration of hospitalizations
Statistical Analysis	• Descriptive stats were generated for quantitative data for all patients • Wilcoxon signed rank test or paired Student's t-test (quantitative data) • McNemar's test for qualitative data • Bowker's test for symmetry was used for dosage changes
Results	• After RLAI initiation, 19 patients could live in their own apartment, 1 in shelter, 11 can restart work or find a job, 3 can restart school • All improved QOL over time → more possibilities to meet friends and family, to live more stable and independent life • CGI-S decreased from **5.44 on day 0 to 3.14 on month 18**; p<0.0001 • GAF increased from **36.2 on day 0 to 75.7 at month 18**; p<0.0001 • 4 patients (16%) relapsed → fewer patients were hospitalized after RLAI therapy compared to whole cohort (n = 120) o **37% for whole cohort vs. 16% for first episode**
Authors Conclusions	Patients gained improvements in CGI and GAF scores, reduced rates and durations of hospitalizations. Clinical benefits may be linked with psychosocial programs associated with RLAI from the beginning of the treatment. Treating as early as possible can reduce relapse, number and duration of hospitalizations, cognitive symptoms, illness worsening, and suicide attempts.
Comments and Conclusions	Strengths: • Evaluated relapse rate and hospitalization rates • Adequate duration of the study Limitations: • No randomization, no comparator group, small sample size • Did not fully explain how quality of life was measured → only subjective observations • Did not report adverse events and tolerability issues Conclusion: • The use of RLAI early in the treatment of first episode schizophrenia seems to help reduce the number of and shorter hospitalizations, and improvement in CGI-S and GAF scores. • Will need better designed trials to confirm these findings

Effectiveness of long-acting injectable risperidone versus oral antipsychotics in the treatment of recent-onset schizophrenia: a case-control study[27]

Barrio P, Batalla A, Castellvi P, et al. International Clinical Psychopharmacology 2013;28:164-170.

Design	2 year, retrospective, observational, matched, case-controlled study
Objective	Compare the number of remission rate, number of hospital readmissions and personal and social functioning after 2 years between patients with recent-onset schizophrenia (<2 years)
Patient Population	• Patients with schizophrenia in Psychiatric Unit between 2004-2008 • Started on treatment within 2 years of illness • Were followed up for at least 2 years after treatment
Intervention	• Cases: treatment with risperidone long-acting injectable (RLAI) • Matched control: treatment with oral antipsychotic after their first episode • Matching criteria: consecutively selected from Psychiatry Unit, matched by age and sex, followed for at least 2 years. • Assessment: Social demographic and clinical variables at the time of diagnosis were collected from patients chart. Patient were assessed after 2 years of follow up and the efficacy of the antipsychotic treatment were collected
Endpoints	Primary endpoints: • Positive and Negative Syndrome Scale (PANSS score) • Personal and Social Performance Scale (PSP score) • Hospital readmission and illness remission according to symptom based criteria
Statistical Analysis	• Descriptive study were computed for sociodemographic data and for clinical, social adjustment and treatment variable, reporting 95% confidence interval • Used absolute and relative frequencies for categorical variables and mean and SD for quantitative variables. • Differences were compared with Chi-square between categorical variable • Student t parametrical test was used for continuous variables • Difference between baseline and endpoint PANSS scores were tested by repeated measures analysis of variance. • A separate generalized estimating equations (GEE) model was used to assess the effect of treatment on each dependent variables • Statistical significance was set at $P \leq$ to 0.05

Barrio, et al. 2013 continued

Results

Outcome variables at baseline				
PANSS dimensions	RLAI group- Mean (SD)	OA group- Mean (SD)	Odds Ratio (95% CI)	p-value
Positive	23.2 (11.4)	25.1 (4.6)	1.03 (0.96-1.10)	0.439
Negative	18.7 (7.8)	21.2 (7.1)	1.05 (0.97-1.13)	0.231
General psychopathology	37.9 (15.5)	42.2 (7.6)	1.03 (0.98-1.08)	0.214
Total	79.9 (28.6)	88.5 (16.1)	1.02 (0.99-1.04)	**0.186**
Outcome variables at 2 years of follow-up				
	RLAI group	OA group		
Readmission	N (%)	N (%)	Odds Ratio (95% CI)	p-value
No	21 (80.8)	15 (57.5)	0.32 (0.07-1.43)	0.136
Yes	5 (19.2)	11 (42.3)		
PANSS dimensions	Mean (SD)	Mean (SD)	Odds Ratio (95% CI)	p-value
Positive	10.0 (2.5)	14.2 (8.7)	-3.92 (-7.49 to -0.36)	0.031
Negative	14.3 (6.1)	19.4 (6.4)	-4.33 (-7.36 to -1.31)	0.005
General psychopathology	23.4 (6.3)	32.7 (8.1)	-8.68 (-12.55 to -4.81)	<0.001
Total	47.7 (12.0)	66.2 (18.5)	-16.89 (-25.67 to -8.12)	**<0.001**
PSP score	72.4 (14.8)	59.7 (13.5)	12.77 (5.22-20.32)	**0.001**
Symptom-based remission criteria				
Yes	17 (63.0)	10 (37.0)	3.02 (0.93-9.84)	0.066
No	9 (36.0)	16 (64.0)		

Multiple logistic regression:

- In both group, there was significant decrease in the PANSS total score as well as in all the subscales
- After adjusting for educational level and PANSS score at baseline as possible confounding factors, the RLAI group showed greater reduction in the PANSS total scale as well as in the negative and general psychopathology subscale compared with the oral antipsychotic group
- After 2 years of treatment, PSP scores, adjusted for educational level, were higher in the RLAI group, suggesting better psychosocial functioning
- Although not statistically significant, there were fewer readmissions in the RLAI group, with more than twice the number of patients in the oral antipsychotic group requiring hospital readmission during the study period

Authors Conclusions

LAIAs may offer some significant improvement over oral treatments as a means to optimize outcomes not only for overt non-adherent patients but for a wider range of patients.

Comments and Conclusions

Strengths:

- Assessment of outcomes after 2 years

Limitations:

- Retrospective observational study, non randomized trial
- Small sample size and case-control design
- Missing baseline characteristics and possible confounding factors

Conclusions:

- No significant evidence of hospital readmission and illness remission between two groups
- PANSS total score decreased after two year but to a greater extent in the RLAI group.

Clinical outcomes of long-acting risperidone in recent versus long-term diagnosed Belgian schizophrenic patients: results from electronic Schizophrenia Treatment Adherence Registry (e-STAR) and Trial for the Initiation and Maintenance of Remission in Schizophrenia with risperidone (TIMORES) [28]

Dubois V, Peusken J, Geerts P. Early Intervention in Psychiatry 2014;8:39-49.

Design	Data from two non-interventional observational studies (TIMORES and e-STAR) over at least 12 month
Objective	To examine potential differences in psychiatric clinical outcomes and hospitalization rate before and after the initiation of long-acting risperidone (RLAI) among recently and long-term diagnosed schizophrenia patients were studied
Patient Population	• Schizophrenic patients who student treatment with RLAI • Patient with contraindication to RLAI, participation in another drug related study or treatment-resistant schizophrenia, as well as females who are pregnant or breast feeding, were excluded • e-Star: multinational electronic study registry, containing pooled data from different European countries but the presented data are exclusively from finished Belgian study arm • TIMORES: exclusively Belgian study in patients having experience less than or equal to 4 episode
Intervention	• e-Star: data for each patient were recorded at baseline, retrospectively for 12 month prior to baseline, and prospectively up to 24 months • TIMORES: patients were tested at baseline and prospectively followed up for 12 months • Titration: RLAI was administered per intramuscular injection every 14 days during 12 (TIMORES) or 24 (e-STAR) months. In order to cover the lag time of risperidone release of the long-acting formulation, oral risperidone was continued during the first 3 weeks of treatment
Endpoints	• Treatment and hospitalization information were collected retrospectively for the 12 month period immediately preceding the start of the RLAI treatment and prospectively for 12 months after baseline. • The clinical effectiveness was evaluated prospectively as changes from baseline in CGI-S, GAF scores, as well as clinical deterioration
Analysis	4 analyses to cover all possible viewpoints • TIMORES vs e-STAR "Total" (endpoint: 1 year) • TIMORES vs e-STAR "Late" (endpoint: 1 year) • e-STAR "Early" vs e-STAR "Late" (endpoint: 1 year) • e-STAR "Early" vs e-STAR "Late" (endpoint: 2 year) "Early" those diagnosed 3 years ago or less, "Late" those diagnosed more than 3 years ago
Result	Patient characteristics • e-STAR (n=408) and TIMORES (n=105), e-STAR "early" (n=155), "late" (n=253) • Mean age in baseline was significantly lower in e-STAR (63.5 yo) than TIMORES (75.2 yo) • Discontinuation rate at 12 month in the TIMORES and e-START was relatively low with 23% and 16% respectively Clinical Outcomes • The severity of schizophrenia (CGI-S) over time showed a decrease in all patient groups • There was also a significant ($p<0.001$) improvement in GAF score from baseline to 12 and 24 month follow up in all patient groups. • Decrease in percentage of patients responding to criteria of clinical deterioration in all patient group at 12 and 24 month follow up, with recent patient group (TIMORES -53.5 and e-STAR "early" -49.2 and -49.6) score less deterioration than the long-term patient groups (e-STAR Total and e-STAR "late" -35.3 and -38.8) • Remission rate at 12 month and employment status for the recent and long-term patient groups were also observed to be different. • The difference in duration of hospitalization days was statically significant different ($p<0.01$ between e-STAR "early" and "late" patient group at both 12 and 24 month.

Dubois, et al. 2014 continued	
Authors Conclusions	The analyses support the significance of pharmacological interventions such as long-acting risperidone, in addressing discontinuity issue, especially in recently diagnosed patients
Comments & Conclusions	Strengths: • Study population followed up for extended duration (1-2 years) with multiple outcomes measures Limitations: • Generalizability to US population based on Belgian study • Post hoc analysis of observational study (not randomized) • There may be selection bias • Non-consistent baseline characteristics between the two studies (e-STAR vs TIMORES) Conclusions: • In general, there was significant clinical improvement and enhance patient functioning at both 12 and 24 week after the initiation of RLAI, with greatest improvement among recently diagnosed schizophrenic patient (less than or equal to 3 years since diagnosis of <4 episodes)

Conclusions/Recommendations

- **Conclusions:**
  - It is very important to provide adequate treatment with antipsychotics within the first five years after diagnosis of first episode schizophrenia to help prevent relapse and promote recovery of functioning.
  - Medication non-adherence is one of the most common reasons for relapse in patients with first episode schizophrenia.
  - Overall, studies with long acting risperidone injection shows efficacy and positive trend towards reducing relapse rate and hospitalization in treatment of first episode schizophrenia.
  - In general, LAIs has similar side effect profile compared to their oral counterparts due to the prevention of troughs and peaks following each administration.
  - However, these studies are all open-label, observational studies with limited sample size and thus are not considered strong evidence.
    - Only risperidone long-acting injectable was well studied in first episode schizophrenia.
  - There is still a need for long term randomized control studies to determine the efficacy, tolerability, relapse prevention and overall outcomes in patients with schizophrenia in the early phases of their treatment.
  - It's also important to ensure clinical studies mirror real world practice in using long acting injectable antipsychotics in patients with first episode schizophrenia.
- **Recommendations:**
  - Preventing or slowing relapse is extremely important in the first 5 years of schizophrenia, identify patients with high risk of non-adherence and consider using long acting injectable antipsychotics as a form of treatment with proper education and non-pharmacological interventions.
  - LAIs are not recommended in patients who are hypersensitive to the oral forms and had experienced significant side effects (e.g. EPS and weight gain)

Appendix

Appendix A: Diagnostic and Statistical Manual (DSM) – 5 Diagnostic Criteria[1]

Schizophrenia Diagnostic Criteria

A. Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these symptoms must be 1, 2, or 3:
    1. Delusions
    2. Hallucinations
    3. Disorganized speech (e.g. frequent derailment or incoherence)
    4. Grossly disorganized or catatonic behavior
    5. Negative symptoms (i.e. diminished emotional expression or avolition)

B. For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relationships, or self-care, is markedly below the level achieved prior to the onset.

C. Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e. active phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed in in Criterion A present in an attenuated form (e.g. odd beliefs, unusual perceptual experiences).

D. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either 1. No major depressive or manic episodes have occurred concurrently with active-phase symptoms, or 2. If mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.

E. The disturbance is not attributable to the physiological effects of a substance or another medical condition.

F. If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least 1 month (or less if treated successfully).

First Episode Schizophrenia: only to be used after a 1-year duration of the disorder

A. **First episode, currently in acute episode:** First manifestation of the disorder meeting the defining diagnostic symptom and time criteria. An *acute episode* is a time period in which the symptom criteria are fulfilled.

A. **First episode, currently in partial remission:** *Partial remission* is a period of time during which an improvement after a previous episode is maintained and in which the defining criteria of the disorder are only partially fulfilled.

B. **First episode, currently in full remission:** *Full remission* is a period of time after a previous episode during which no disorder-specific symptoms are present.

Appendix B: Assessment Rating Scales[29,30,31]	
Rating Scale	**Description**
Positive and Negative Symptom Scale (PANSS)	• Clinician rated assessment to measure symptoms of psychosis 1. 30-item, 7-point (1-7) rating scale divided into positive, negative, and general psychopathology sub-scales, with higher scoring being more severe 2. Scores: 0-58 (mildly ill); 59-75 (moderately ill); 76-116 (markedly ill); >116 (severely ill) 3. Response: generally **20-30%** reduction in symptoms
Clinical Global Impression – Severity Scale (CGI-S)	• Clinician or self-rated scale 1. Rates the overall severity of any mental disorder 2. Three-item scale that asks the clinician to rate the patient: ➢ Scored 1-7, with higher scoring being more severe. Score of 0 = not assessed ➢ 1 = normal, not at all ill, 2 = borderline mentally ill, 3 = mildly ill, 4 = moderately ill, 5 = markedly ill, 6 = severely ill, 7 = among the most extremely ill
Global Assessment of Functioning (GAF)	• Clinician rated scale used to measure level of function o Rates an individual's overall functioning level in terms of psychological, social, and occupational/school functioning. o The scale ranges from 0 (inadequate information) to 100 (superior functioning) o Each category will have a range of up to 10 points o The number that is most descriptive of the overall functioning of the individual is chosen
Personal and Social Performance Scale (PSP)	• Assesses patient's functioning in four main areas: 1. Socially useful activities; 2. Personal and social relationships; 3. Self-care; and 4. Disturbing and aggressive behaviors o 100-point, single item scale subdivided into 10 equal intervals o 91-100 points: adequate functioning; 90-70 points: mild difficulties; 70-31 points: manifests disabilities of various degrees; <30 points: poor functioning, intensive support or supervision is needed

Appendix C: Summary of Studies				
Study	**Patient Population**	**Treatment**	**Assessments**	**Outcomes**
Emsley *et al.,* 2008[25]	• 50 patients with ≤12 weeks drug treatment • 46% antipsychotic naïve	• Open label LAI risperidone x24 months • Compared with oral antipsychotic	• PANSS, EPS, BMI	• LAI group: fewer d/c, lower PANSS scores, higher remission rate, lower relapse rate • EPS lower with LAI, BMI higher
Viala *et al.,* 2012[26]	• 25 schizophrenia patients hospitalized for the first time	• Open label study of switch from oral to risperidone LAI	• CGI, GAF at 6,12,18 months; Hospitalization	• Sig improvement from baseline CGI-S and GAF • 16% relapsed • Fewer and shorter hospitalizations
Barrio *et al.,* 2013[27]	• 26 patients with recent onset treated with LAI vs. 26 recent onset with oral	• Case control study of LAI vs. oral for 2 years	• PANSS, PAS, remission, hospitalization	• LAI showed sig improvement in PANSS, PAS • Higher remission, lower hospitalization
Dubois *et al.,* 2014[28]	• 155 patients with schizophrenia (≤3years) vs. 253 (>3 years)	• Observational study of LAI for 12 or 24 months	• CGI-S, GAF, hospital, remission	• Sig improvements in CGI-S, GAF, remission, and # of hospital days for early patients
Kim *et al.,* 2008[32]	• 50 patients with first episode schizophrenia	• Open label treatment with LAI or oral x2 years	• PANSS, CGI, GAF, relapse, remission, adherence	• Sig improvements in all parameters with LAI
Weiden *et al.,* 2012[33]	• Continuation of 2009 study for 104 weeks	• Randomized to LAI or oral for 104 weeks	• Adherence, attitudes	• No difference in adherence between oral and LAI
Weiden *et al.,* 2009[34]	• 37 patients with ≤16 weeks lifetime exposure to antipsychotics	• Randomized to LAI or oral x12 weeks	• Adherence, attitudes	• No difference in adherence, acceptance of LAI associated with better adherence
Parellada *et al.,* 2005[35]	• 382 patients with ≤3 years diagnosis; mean 1.5 years	• Open label trial of LAI x6 months	• PANSS, CGI-A, GAF, QoL	• Sig improvement from baseline PANSS, CGI-S, QoL
Olivares *et al.,* 2009[36]	• Patients with recent (≤2 years) or long term (>2 years)	• Observational study of LAI x24 months	• CGI-S, GAF, hospital	• Greater improvements w/recent group for CGI-S, hospital rate and days
Sliwa *et al.,* 2012[37]	• Compared recent dx (n=216, ≤5 year) vs. chronic illness (n=429, >5 years)	• Open label LAI x1 year	• Tolerability	• Improved tolerability with LAI compared with baseline
Tiihonen *et al.,* 2011[38]	• 2588 hospitalized for the first time in schizophrenia	• Registry based study of LAI vs oral x2 years	• Hospital, D/C rate	• Hospitalization was 1/3 with LAI vs oral med

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