A Review of Risperidone Long Acting Injection in Schizophrenia Spectrum Illnesses: Evaluating Outcomes Compared to First Generation Depot Treatments.

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Introduction

Schizophrenia is a chronic, progressively debilitating illness with no cure; the mainstay of therapy is antipsychotic medication.

Many studies have demonstrated that poor adherence to medications is a primary contributor to relapse in schizophrenia. For patients who have shown poor adherence or tolerability to oral antipsychotic medications, depot antipsychotics are often initiated.

First generation antipsychotic depot injections (FGAI) or typicals include: flupenthixol decanoate, zuclopenthixol decanoate, fluphenazine decanoate, haloperidol decanoate, and pipotiazine palmitate. FGAI treat the positive symptoms of schizophrenia (hallucinations, delusions and disorganized speech or behaviour), but have no benefits in improving negative symptoms (alogia, anhedonia, affective flattening, and avolition) or cognition. Often the main drawback of these agents is the risk of extra pyramidal symptoms (EPS) and tardive dyskinesia (TD).

Of the second generation or atypical antipsychotics, risperidone long acting injection (RLAI) is the only one available in depot form. Atypical antipsychotics treat the positive symptoms and are reported to have fewer motor side effects than typical agents. In addition, they may also reduce negative symptoms and improve affect and cognition.

Objectives

Primary objectives

- Determine the time to discontinuation and the time to hospitalization for patients receiving risperidone long acting injection (RLAI) as compared to first generation depot antipsychotic injections (FGAI)

Secondary objectives

- Determine the use of concomitant medications (additional antipsychotics, anticholinergics, mood stabilizers, antidepressants, and benzodiazepines)
- Determine the incidence of side effects, including TD and EPS
- Duration of hospitalization
- Conduct a direct drug cost comparison of RLAI and FGAI acquisition

Methods

Design

- Single center → Victoria Mental Health Centre, Partnership Medication Clinic
- Retrospective chart review of all active outpatients → sample size calculation not performed, is a hypothesis generating preliminary study

Inclusion Criteria

- Individuals with a DSM IV diagnosis of Schizophrenia, Schizophreniform disorder or Schizoaffective disorder
- ≥ 18 years of age
- Have received at least 3 injections of depot antipsychotic

Exclusion Criteria

- Prior clozapine trial (considered treatment resistant)
- Active alcohol or substance abuse
- Current pregnancy or lactation

Statistical Analysis

- Pearson chi square and Fisher's exact tests performed for categorical variables
- Student's *t*-test performed for parametric variables
- KS-test performed for non-parametric variables
- Cox proportional hazards modeling performed to determine if any baseline characteristics were predictors of the primary outcomes

Results

Figure 1: Kaplan Meier survival curve of time to treatment discontinuation

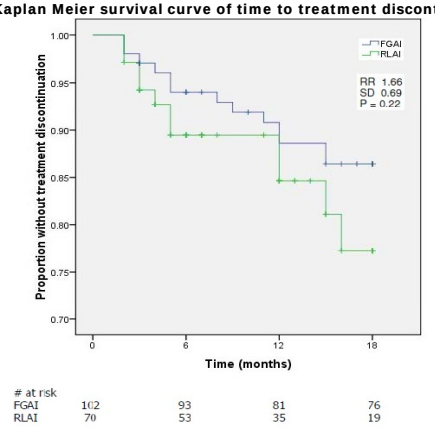


Figure 2: Kaplan Meier survival curve of time to hospitalization

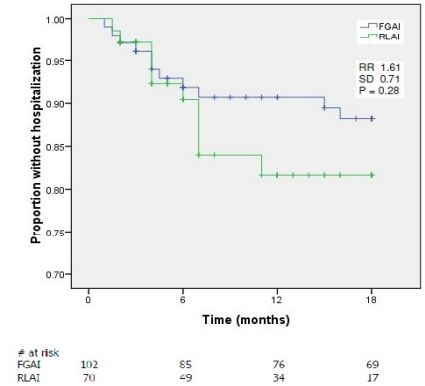
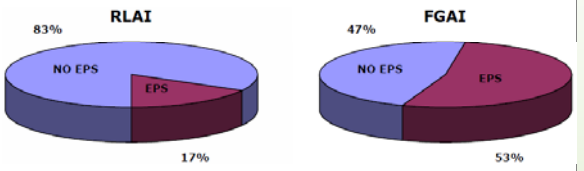


Table 1: Summary of Primary & Secondary Outcomes

	RLAI (N=70)	FGAI (N=102)	P value
Hospitalization			
Proportion Hospitalized	14.3% (10)	12.7% (13)	0.09
Average Time to Hospitalization	5.4 months (SD 2.8)	5.8 months (SD 5.1)	0.80
Average Duration of Hospitalization	35 days (SD 24)	29 days (SD 17)	0.49
Discontinuation			
Proportion Discontinued	15.7% (11)	12.7%(13)	0.30
Average Time to Discontinuation	7.2 months (SD 5.4)	7.9 months (SD 4.8)	0.99
Abnormal Movement Assessments			
Proportion with TD	1.4% (1)	4.9% (5)	0.4
Proportion with EPS	17% (12)	53% (54)	<0.001
Concomitant Medications			
Additional Antipsychotic	30% (21)	41% (42)	0.14
Anticholinergic	6% (4)	35% (36)	<0.001
Mood Stabilizer	18.6% (13)	10.8% (11)	0.15
Antidepressant	14.3% (10)	25.5% (26)	0.08
Benzodiazepine	10% (7)	9% (9)	0.79
Side Effects			
Proportion Reporting Side Effects	10% (7)	17% (17)	0.21
Cost Analysis			
Average Monthly Cost of Depot	$442	$23	<0.001

Results

Figure 3: Incidence of Extra Pyramidal Symptoms (EPS)



P < 0.001

Discussion

- No statistically significant differences were seen for the primary outcomes of time to discontinuation or hospitalization (P value > 0.05)
- The significant finding was the proportion with EPS in the FGAI group → there was 3X the incidence of EPS with FGAI as compared to RLAI
- RLAI is 19X more expensive than FGAI (based on cost of medication) → a more comprehensive cost analysis is necessary to fully evaluate differences between treatments in overall economic burden
- Cox proportional hazards modeling resulted in no significant predictors of discontinuation or hospitalization
  - Predictors analyzed were: depot antipsychotic, age, gender, time since diagnosis and weight
- A subgroup analysis of those on mono depot therapy was conducted as ~35% of patients were taking additional oral antipsychotics → similar results to the total study population were found
- Groups had similar characteristics for age (41 years) and gender (63% male), however time since diagnosis was 3.75 years longer in FGAI → these FGAI patients may be more stable and have fewer relapses
- Limitations of the study:
  - Retrospective review → limited by available data
  - Limited to current patients of the PMC → patients on depots who had an event and are no longer on depot injections were not included
  - There are a limited number of patients who have been exposed to RLAI for a significant duration (drug is relatively new to the market), thus many may not have had significant exposure to allow for relapse or discontinuation
  - The event rates for discontinuation and hospitalization were small, and the sample size available was limited, therefore power may be insufficient to detect significant differences

Conclusions

There is insufficient evidence to demonstrate differences in discontinuation or hospitalization with RLAI as compared to FGAI. RLAI resulted in decreased incidence of EPS, but the direct cost of drug acquisition was higher than FGAI.

The results of this review are hypothesis generating; a larger study is needed to determine if outcomes are improved with RLAI as compared to FGAI.

References available on request