Clinical Recommendations for LAI’s and a review of PRHC Retrospective Chart Audit

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Disclosures (Honoraria for CME, Advisory Boards, Investigator Initiated Research and Educational Grants)

- Janssen
- Astra Zeneca
- Eli Lilly
- Pfizer
- BMS
- Lundbeck
- Sunovion
Presentation Objectives

After participating in this program, participants will be able to:

• Appreciate the evidence for the efficacy and use of long-acting injectable (LAI) antipsychotics in the treatment of schizophrenia
• Understand physician and patient perceptions and beliefs regarding LAIs
• Apply recommendations for the use of LAIs at all phases of schizophrenia and strategies to improve patient acceptance of these medications
Prevalence of Schizophrenia

• Between 1 to 2 per 100 people in the general population will have a psychotic disorder sometime in their lives (life time risk)
• Approximately 24 million people suffer from schizophrenia worldwide
• Approximate 240,000 Canadians suffer from schizophrenia
• Every year, 20-25 persons in a population of 100,000 will develop the illness for the first time
Natural History of Schizophrenia

High Risk for Relapse

Relapse Rate (%)

n=104

Year(s) Since First Episode

1 16.2%
2 53.7%
3 63.1%
4 74.7%
5 81.9%

Patients still at risk at end of year:

1 80
2 39
3 22
4 9
5 4

Increasing Time to Remission with Successive Psychotic Episodes

(n=10)

Evidence of Disease Progression with Successive Psychotic Relapse

Abnormal morphology ratings in all regions for the entire study group were significantly intercorrelated (p<0.05).

*p=0.07 compared to first episode patients.

Neuroimaging studies have produced a wealth of data supporting the presence of objective structural and functional abnormalities in the brains of patients with schizophrenia\(^1,2\)

Data have shown that the brain abnormalities observed in patients with first-episode schizophrenia progress with illness\(^1,3,4\)

Progressive brain tissue losses are greatest during early stages of the illness, and may occur as a consequence of impaired neuroplasticity or structural or functional connectivity in the brain\(^5\)

Progressive Brain Change in Patients with Schizophrenia (1)

- The probability of chronicity (in terms of psychotic symptoms) and time to remission increases with every relapse\(^1,2\)
- A subset of patients with schizophrenia experiences progressive gray and white matter brain changes (primarily in the frontal lobes)\(^3\)
  - Study of 542 patients showed longer periods of remission were associated with less expansion of CSF, a marker for brain tissue loss
- Relapse duration was related to significant decreases in both general (e.g., total cerebral volume) and regional (e.g., frontal) brain measures. Number of relapses was unrelated to brain measures. Significant effects were also observed for treatment intensity\(^4\)

Studies show that loss of brain tissue is less likely to occur while patients are in remission; however, the time taken to remission increases with every relapse\(^1-3\)

CSF, cerebrospinal fluid

1. Wiersma et al. Schizophr Bull. 1998;24:75–85;
Progressive Brain Change in Patients with Schizophrenia (2)

- Brain tissue losses have been shown to be greatest during the early stages of the illness
  - Consequence of impaired neuroplasticity or structural or functional connectivity in the brain

Suggests a need for the ongoing search for treatments that are effective during early phases of disease, and that could enhance connectivity, neuroplasticity and cognition

Early initiation of psychosocial therapies may provide a supporting role

Trajectories of Clinical Outcome Following a First Episode of Psychosis

- **35%** Multiple Episodes - No Symptoms
- **31%** Multiple Episodes - Symptoms
- **16%** Single Episode Only
- **7%** Single Episode - No Recovery

Long-term (> 6 years) follow-up study of clinical outcome in 436 patients with a first episode of schizophrenia*

*Additional data - Died during first episode = 1%, Pattern of illness cannot be determined = 9%*
Gap in Levels of Outcome: A Challenge?

- **Response**: Percentage decrease in symptoms

- **Remission (APA consensus)**: SAPS-SANS global rating 2 or less or PANSS item ratings of 3 or less

- **Recovery**: Independent functioning (work, school, social relationships, independent living); requiring minimal or no support (societal perspective) and, personal sense of well being (personal perspective)


Obstacles to Improving Outcome?

- Low rates of remission and remission not sustained
- Non-adherence to treatment a major factor in not sustaining remission
- Delay in adequate treatment
- Substance abuse
- Limited response to medication for negative symptoms, a major driver of functional outcome

In order to improve functional outcome, it is almost a necessary condition to have a sustained remission.

Sustained remission requires continuous treatment (both pharmacological and psychosocial).

Means to facilitate continuous treatment include use of LAIs.
Facts

- Need for long-term treatment of schizophrenia
- Antipsychotics are more effective than placebo
- Maintenance treatment with antipsychotics necessary to prevent relapses
- Early psychosis patients are more responsive to medication but at high risk of relapse; if treatment can be sustained over the first few years, they have a greater chance of a good long-term outcome


Approximately 45 – 90% of patients with schizophrenia are known to be partially or totally non-adherent to oral antipsychotic medication, with no differences evident between oral FGAs and oral SGAs.

Partial adherence is even more common than non-adherence with oral antipsychotics.
Adherence and LAIs

- Register based case linked study in Finland
  - 2588 patients with schizophrenia discharged after first hospitalization between 2000-2007
  - 1406 patients (54.3%) either did not collect an AP prescription or used their meds for less than 30 days
  - LAIs were associated with a 59% lower risk of discontinuation (2-year follow-up)

# Antipsychotics Available in Canada

<table>
<thead>
<tr>
<th>FGAS</th>
<th>SGAS</th>
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<tbody>
<tr>
<td>Chlorpromazine</td>
<td>Clozapine</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>Risperidone</td>
</tr>
<tr>
<td>Flupenthixol</td>
<td>Olanzapine</td>
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<tr>
<td>Haloperidol</td>
<td>Paliperidone</td>
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<tr>
<td>Loxapine</td>
<td>Quetiapine</td>
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<tr>
<td>Methotrimeprazine</td>
<td>Ziprasidone</td>
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<tr>
<td>Perphenazine</td>
<td>Asenapine</td>
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<tr>
<td>Trifluoperazine</td>
<td>Lurasidone</td>
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<tr>
<td>Zuclopenthixol</td>
<td>Aripiprazole</td>
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</tbody>
</table>

FGA: first-generation antipsychotics; SGA: second-generation antipsychotics

Compendium of Pharmaceuticals and Specialties (CPS) 2013
LAIs Available in Canada

First Generation
- Fluphenazine decanoate
- Flupenthixol decanoate
- Haloperidol decanoate
- Pipotiazine palmitate
- Zuclopenthixol decanoate

Second Generation
- Paliperidone palmitate
- Risperidone microspheres
- Aripiprazole monohydrate
Injectable vs. Oral
Total Antipsychotic Use by Province

Injectable Use As % of Total Province
Oral Use As % of Total Province

Independent study conducted by Janssen Inc, using IMS NPA Market DynamicsTM Moving Annual Total 2011, extracted May 2012 (Personal communication).
PRHC Statistics

410 Clients in Schizophrenia Program

- 75 on Long Acting Therapy
  - 17 on First Generation
  - 58 on Second Generation
- 48 on Clozapine
Maintaining Treatment

The treatment for patients with schizophrenia often involves the long-term administration of antipsychotics.

**Risks**

- Reduction of brain tissue
  - Antipsychotics have a subtle but measurable influence on brain tissue loss over time\(^1\)
  - Poor outcomes and higher cumulative intake of antipsychotics is associated with more pronounced cortical thinning\(^2\)

**Benefits**

- Dysregulation of myelination trajectory may contribute to the aetiology of schizophrenia
  - Antipsychotics increase intracortical myelin in first-episode patients with schizophrenia\(^3\)
  - Second generation antipsychotic drugs may enhance cellular resilience and ameliorate the pathophysiology of schizophrenia\(^4\)

**Long-term use of antipsychotics is associated with the risk of brain tissue reduction**

**Maintaining treatment with antipsychotics is associated with fewer recurrent episodes**

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### Treatment Recommendations from the Guidelines in *Multiple-Episode* Patients: Treatment Duration

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>American Psychiatric Association (APA)¹</td>
<td>• Indefinite maintenance of antipsychotic medication</td>
</tr>
<tr>
<td></td>
<td>• Monitor for signs and symptoms of relapse</td>
</tr>
<tr>
<td>British Association for Psychopharmacology (BAP)²</td>
<td>• Not stated</td>
</tr>
<tr>
<td>National Institute for Health and Care Excellence (NICE)³</td>
<td>• Not stated</td>
</tr>
<tr>
<td>World Federation of Societies of Biological Psychiatry (WFSBP)⁴</td>
<td>• 2–5 years in patients with one relapse</td>
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<td></td>
<td>• &gt;5 years in multiple-episode patients</td>
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<tr>
<td>Canadian Psychiatric Association (CPA)⁵</td>
<td>• A minimum of 5 years of stability, without relapse and with adequate functioning, should be observed before a slow withdrawal of antipsychotic medication over 6 to 24 months is considered</td>
</tr>
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Treatment guidelines do not offer a consensus on duration of treatment for *multi-episode* schizophrenia (or for patients with *first-episode* schizophrenia).

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3. NICE Schizophrenia full guidelines CG82 (update) September 2010, [http://guidance.nice.org.uk/CG82/Guidance](http://guidance.nice.org.uk/CG82/Guidance);
Guideline Recommendations on Use of LAI APs

APA Guidelines State:

• LAI APs should be considered for patients with recurrent relapses related to partial/non-adherence. Oral form of the same medication is the logical choice for initial treatment"1

NICE Guidelines State:

• ‘Maintenance treatment with LAI APs should be available for patients with a history of frequent relapse and adherence problems (including covert non-adherence) on oral APs, or who have a preference for the LAI regimen’2

LAI, long-acting injectable; AP, antipsychotic; APA, American Psychiatric Association; NICE, National Institute for Health and Care Excellence

Clinicians should consider offering depot/long-acting injectable antipsychotic medication to people with schizophrenia:

- Who would prefer such treatment after an acute episode
- Where avoiding covert non-adherence (either intentional or unintentional) to antipsychotic medication is a clinical priority within the treatment plan

Patient preference is now explicitly stated when considering which individuals with schizophrenia should be offered a depot/LAI medication
Algorithm for the Use of Antipsychotics in Early Episode Treatment

1st Line
2nd Generation Antipsychotic
- PO or LAI

In case of partial/no response

2nd Line
2nd Generation Antipsychotic
- LAI if not previously used

In case of partial/no response

3rd Line
Clozapine

SGA LAI
If response to PO (Up to 4 weeks)

SGA LAI
If response to PO (Up to 4 weeks)

Canadian Recommendations for Use of LAIs

1. For All Phases of Illness
   • The existence and potential use of LAIs for antipsychotic therapy should be discussed with patients and families at all phases of illness, including “critical period” of first two to five years

2. Informed Patient Decision
   • Provide information regarding LAIs in a collaborative environment
   • Review information about LAIs on a regular basis

Canadian Recommendations for Use of LAIs

3. Clinical Stability and Patient’s Change in Opinions and Attitudes

- Continue discussion regarding:
  - Attitude towards treatment
  - Adherence to treatment
  - LAIs as an option

4. Physician’s Knowledge and Attitude

- Be well informed and trained in the use of LAIs
- Do not assume patient’s rejection of LAI or fear of needles
- Treatment team to be aware of their own biases
5. Non-Adherence

- In case of overt or impending non-adherence to medication, serious consideration should be given to using LAIs as one of the choices for addressing non-adherence.

6. Involuntary Treatment During Acute Phase of Psychosis

- During acute phase of psychosis and after frequent relapses, the use of LAIs may become necessary.
- Under such circumstances, it is recommended:
  - To discuss using LAIs as an option.
  - That clinical realities, at times, demand involuntary hospitalization and LAI treatment.
7. Engagement with Psychosocial Interventions and Rehabilitation

- Active efforts at engagement in treatment of patient and family must continue throughout care

8. Oral Supplementation and Stabilization

- LAIs for initial stabilization if acceptable (after test-dose)
- Acutely ill/uncooperative and not capable of consenting
Canadian Recommendations for Use of LAIs

9. Monitoring

- Follow up and assessment at regular intervals
- Evaluate side effects:
  - Movement disorder (extrapyramidal side effects, tardive dyskinesia, akathisia)
  - Metabolic (BP, weight, glucose, lipids)
  - Signs of hyperprolactinemia
- Ongoing discussions with patient and family

10. Special Situations

- Clinicians should be prepared to proactively address situations that may arise such as pregnancy, travel, moving, medication coverage, age (transfer to geriatric services from adult or to adult from child psychiatry) etc., which may lead to a change or interruption in therapy

Do LAIs have greater efficacy than oral antipsychotics?

Review and Meta-analysis of RCTs
Evidence

- Davis et al (1994)
  - Meta-analysis suggested significant superiority for LAIs compared to orals
- Cochrane Reviews (1999-2007)
  - Earlier reviews showed no convincing difference
- Leucht et al (2011)
  - Recent review showed significant advantage for LAIs

David A, Adams CE, Quraishi SN. Depot flupenthixol decanoate for schizophrenia or other similar psychotic disorders. Cochrane Database Syst Rev. 1999;2:CD001470.
### Recent Meta-Analysis

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<tbody>
<tr>
<td>10 RCTs; n=1700</td>
<td>21 RCTS; n=5176</td>
</tr>
<tr>
<td>&gt;1 yr; OP only</td>
<td>&gt; 6 months; IP &amp; OP</td>
</tr>
<tr>
<td>Narrower criteria</td>
<td>Broader criteria</td>
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Relapse (Primary Outcome)

- Leucht et al (2011)
  - 21.6% LAIs vs 33.3% oral AP (P=0.0009)

- Kishimoto et al (2013)
  - 25.8% LAIs vs 31.4% oral AP (P=0.41)
  - Results similar to Leucht et al when narrower criteria used
  - Fluphenazine LAI 30.6 vs 41.9 oral AP (P=0.02) - N.S. for other LAIs (haloperidol, olanzapine, risperidone, zuclopenthixol) compared to oral APs
Secondary Outcomes

- Re-hospitalization
- Drop out/discontinuation
  - All cause
  - Adverse events
- Non-adherence
- All of the above findings N.S.

Risk of Re-hospitalization After a First Hospitalization (Comparing Antipsychotics)

Objective: To evaluate resource use associated with relapse prevention in patients treated with RISPERDAL® CONSTA® compared to oral atypicals

Study Design:
- Retrospective chart review
- Pre- and post-RISPERDAL® CONSTA®
  - Number of Emergency Room (ER) visits
  - Hospitalizations for acute psychosis
  - Length of stay in the ER and the Mental Health Unit

Eligible patients were treated with an oral antipsychotic
- Minimum treatment duration of one year on previous oral antipsychotic and RISPERDAL® CONSTA®

Reduction in Total Annual ER Visits and Hospital Admissions

**Oral Atypical Treatment**

- **RISPERDAL®**
- **CONSTA®**

* *p<0.0001*

**Source:** Koczerginski & Arshoff, 2011
Reduction in Total Annual Days in ER and Hospital Admissions

- ER visits: 1.2 days (p<0.0001)
- Hospitalizations: 34.7 days

Source: Koczerginski & Arshoff 2011
Healthcare Savings Associated with Switch to RISPERDAL® CONSTA®

- Annual healthcare savings of ~$17,000 per patient or ~$433,000 per 25 patients

ER Hospital Admissions
- ER cost estimated at $800 per day
- Mental Health Ward cost estimated at $700 per day

ER  Hospital Admissions  Injection Clinic  Medication  Total Cost per Patient
$960  $24,290  $0  $6,105  $8,577  $25,932
$80  $1,820  $575  $682  Savings of ~$17,000 per patient

Source: Koczerginski & Arshoff 2011
This was a retrospective cohort study looking at hospitalization rates a year before and a year after initiation of long acting injectables: Consta and Sustenna.

The patients served as their own controls; the two cohorts were defined by the initiation of LAI among schizophrenia patients previously on oral antipsychotic agents. These patients were all outpatients. Patients with schizophrenia who initiated the use of LAI were identified at the PRHC between 28 September 2005 and 26 March 2013. The date at which LAI was initiated was defined as the index event. Each patient essentially served as their own control for the comparison of outcomes between the baseline and follow-up time periods. The patient’s charts were examined for the year before they were switched to LAI and followed for another year.

The impact of initiating LAI on hospitalization events such as days in ER, length of stay (LOS), days to readmission between follow-up and baseline periods was evaluated.
• In our study at the Peterborough Regional Health Centre, it was hypothesized that initiation of LAI reduces ER and ward admissions, total length of stay in the hospital, and time to readmission.

• A reduction in the above events would make the costs of investing in LAI therapy for more patients an advisable clinical decision for the patient’s increase in quality of life and for the resources and direct hospital costs that are saved.
ER and Ward Admissions

![Bar Chart: ER and Ward Admissions for Patients 1-22](chart.png)
Length of Stay

- **Long Acting Injectables**
- **Oral Therapy**

Chart showing the length of stay for patients 1-22, comparing Long Acting Injectables and Oral Therapy.
Total of 781 days of stay on oral therapy versus 25 days of stay on LAI.
The cost in total for all 22 patients before initiation of LAI (just looking at hospital costs and no oral medication was) $669,600 due to 781 days of admission in the ward and 56 ER visits in total.

The cost of LAI for a year for all 22 patients was $172,128 and the total cost of ward and ER admissions was $23,200 (25 days in ward and 4 ER visits), totaling to $195,328. Thus the net savings before LAI and after LAI is roughly $474,272.

This cost excludes the cost of oral antipsychotic medications, which would result in a higher number for the net savings.
Statistically significant difference in number of admissions, total length of stay, and a substantial reduction in cost.

Data is comparable to that of previous studies who reported a 41% reduction in all cause hospitalizations and a 56% reduction in hospitalizations for schizophrenia among patients with schizophrenia after initiating risperidone LAI therapy compared to before treatment began (Crivera et al., 2011)

Several studies have showed such results, providing convincing data for starting LAI therapy early on despite initial costs.
2nd Phase Initiated. Overview

- Retrospective Chart Review
- 22 additional patients
- Treated with oral therapy and then switched to LAI (18 Sustenna, 4 Consta)
- Reviewed admissions and LOS for 12 months for patients on Oral Therapy and subsequently for 12 months following switch to Long Acting Therapy.
- 7 of 22 on CTO
Total of 567 days of stay on oral therapy versus 38 days of stay on LAI. (15 fold difference)
# of Patients with minimum 1 Admission to Mental Health Unit

Atleast 1 Admission

- Oral Therapy: 14
- LAI: 2

N=22

Atleast 1 Admission
Cost Savings

(Using daily bed cost of $800.00 (low estimate) and avg monthly LAI cost per patient of $500.00 (high estimate))

Net savings before LAI and after LAI is roughly $291,200.00

Note: This excludes the cost of oral antipsychotic medications, which would result in a higher number for the net savings.
How are the original 22 patients from 2013 study doing currently?

22 Patients

- 16 have had zero admissions or CRU visits
- 2 with ACTT
- 2 Quit Clinic (lost follow up)
- 1 Deceased
- 1 has had 3 visits to CRU and 2 admissions of 14 days
• Discussion