The Non-Adherence Challenge: Strategies for Achieving Best Clinical Outcomes

The Care Transitions Network

National Council for Behavioral Health
Montefiore Medical Center
Northwell Health
New York State Office of Mental Health
Netsmart Technologies
This webinar series focuses on the use of long acting formulations of antipsychotics

• Today’s webinar will focus upon
  • Medication non-adherence among the general population
  • Medication non-adherence among a high risk group, people with schizophrenia
  • How Long Acting Formulations by eliminating non-adherence can improve clinical decision making

• Future webinars will discuss educating prescribers and patients about LAIs and practical issues prescribing LAIs
The cost of non-adherence in the treatment of chronic disorders

- In developed countries, about 50% of patients with chronic diseases adhere to long-term therapy\(^1\)

- 33–69% of all medication-related hospital admissions in the US are due to poor medication adherence\(^2\)

- One-third of all prescriptions are never filled\(^3\)

- >50% of filled prescriptions are associated with incorrect administration (not taken as prescribed)\(^3\)

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U.S. Patients Do Not Take Medications as Prescribed

- 12% of Rx prescribed
- 12% of Rx filled
- 29% of Rx taken
- 47% of Rx continued

* 22% of U.S. patients take less of the medication than is prescribed

Given that long term medication adherence is a problem within the general population, what does adherence typically look like for people with psychosis?
### Antipsychotic non-adherence in adult outpatients with schizophrenia – point prevalence

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Non-adherence</th>
<th>Measure</th>
</tr>
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<tbody>
<tr>
<td>Baloush 2011</td>
<td>29.8%</td>
<td>Patients/relatives</td>
</tr>
<tr>
<td>Huang 2009</td>
<td>50.0%</td>
<td>Patient report</td>
</tr>
<tr>
<td>Jónsdóttir 2013</td>
<td>44.8%</td>
<td>Patient report</td>
</tr>
<tr>
<td>Klingberg 2008</td>
<td>24.1%</td>
<td>Clinician ratings</td>
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<tr>
<td>McCabe 2012</td>
<td>27.6%</td>
<td>Clinician ratings</td>
</tr>
<tr>
<td>Meier 2010</td>
<td>23.6%</td>
<td>Clinician ratings</td>
</tr>
<tr>
<td>Rabinovitch 2009</td>
<td>45.1%</td>
<td>Clinician ratings</td>
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</table>
Analysis of 34,128 VA patients with schizophrenia receiving regular outpatient mental healthcare. Poor antipsychotic adherence defined as annual MPR <0.80. 18% had poor antipsychotic adherence in all 4 years.

MPR = medication possession ratio.
Why is non-adherence a concern in schizophrenia?

• Avoid relapse
• Avoid hospitalization
• Avoid missing school/work
• Avoid missing friends
Social impact

• Disruption to interpersonal relationships
• Disruption to education or employment
• Isolation from families and friends
• Impact on the family
• Increase in unemployment
• Involvement in risky behaviors
• Risks associated with homelessness
• Risk of victimization
• Increased risk of legal problems
Costs of non-adherence
3-year prospective observational US study

Adherence based on patient-reported adherence and MPR (% days with prescription for any antipsychotic)

Figure from Haddad P, et al. Patient Relat Outcome Meas; 2014;5:43-62
Besides improving clinical outcomes, enhanced adherence early in the course of schizophrenia may modify disease progression.
Impact on intracortical myelination trajectory of long acting injection versus oral risperidone in first-episode schizophrenia

George Bartzokis a,b,c, Po H. Lu d, Erika P. Raven a,c, Chetan P. Amar a,c, Nicole R. Detore a, Alexander J. Couvrette a,c, Jim Mintz c, Joseph Ventura a, Laurie R. Casaus a, John S. Luo a, Kenneth L. Subotnik a, Keith H. Nuechterlein e,f

a Department of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and Human Behavior, The David Geffen School of Medicine at UCLA, Los Angeles, California, United States
b Laboratory of Neuroimaging, Department of Neurology, Division of Brain Mapping, The David Geffen School of Medicine at UCLA, Los Angeles, California, United States
c Greater Los Angeles VA Healthcare System, West Los Angeles, California, United States
d Department of Neurology, The David Geffen School of Medicine at UCLA, Los Angeles, California, United States
e Department of Epidemiology and Biostatistics, University of Texas Health Science Center at San Antonio, San Antonio, Texas, United States
f Department of Psychology, UCLA, Los Angeles, California, United States

ABSTRACT

Context: Imaging and post-mortem studies suggest that frontal lobe intracortical myelination is dysregulated in schizophrenia (SZ). Prior MRI studies suggested that early in the treatment of SZ, antipsychotic medications initially increase frontal lobe intracortical myelin (ICM) volume, which subsequently declines prematurely in chronic stages of the disease, insofar as the trajectory of ICM decline in chronic SZ is due to medication non-adherence or pharmacokinetics, it may be modifiable by long acting injection (LAI) formulations.

Objectives: Assess the effect of risperidone formulation on the ICM trajectory during a six-month randomized trial of LAI (RLAI) versus oral (RSo) in first-episode SZ subjects.

Design: Two groups of SZ subjects (RLAI, N = 9; and RSo, N = 13) matched on pre-randomization oral medication exposure were prospectively examined at baseline and 6 months later, along with 12 healthy controls (HCs). Frontal lobe ICM volume was assessed using inversion recovery (IR) and proton density (PD) MRI images. Medication adherence was tracked.

Main outcome measure: ICM volume change scores were adjusted for the change in the HCs.

Results: ICM volume increased significantly (p = .005) in RLAI and non-significantly (p = .39) in the RSo groups compared with that of the healthy controls. A differential between-group treatment effect was at a trend level (p = .093). SZ subjects receiving RLAI had better medication adherence and more ICM increase (chi-square p < .05).

Conclusions: The results suggest that RLAI may promote ICM development in first-episode SZ patients. Better adherence and/or pharmacokinetics provided by LAI may modify the ICM trajectory. In vivo MRI myelination measures can help clarify pharmacotherapeutic mechanisms of action.
Fig. 2. Individual residual z-scores (based on healthy controls) of frontal lobe intracortical myelin (ICM) in first-episode schizophrenia subjects randomized to treatment with risperidone long-acting injection (RLAI) versus oral risperidone (RisO). Both SZ groups have a positive mean z-score change and combined, they had a higher ICM than the HCs ($t = 2.48$, $df = 21$, $p = .022$). Within-group $t$-test: ** $p = .005$ between group test: RLAI versus RisO * $p = .093$. Seven of thirteen RisO subjects had z-scores below the lowest value of the RLAI subjects as depicted by the dotted horizontal line ($\chi^2 = 8.7, df = 1, p = .003$). Results are based on covariance analyses adjusted for race.

Who might benefit by adherence enhancing interventions?

- The data suggest that half of all patients would benefit
  - A very large need
- In the absence of infinite resources, who to prioritize?
CTN suggestions for initial prioritization

• People with schizophrenia and related disorders
  • High rates of non-adherence
  • Clear adverse consequences of non-adherence
  • Antipsychotics have long acting formulations that are not available with almost all other classes of medications
If resources are limited, which patients with schizophrenia should receive adherence enhancement interventions?

• Patients with known problems with adherence
• Patients at high risk
  • Patients with poor response to treatment or requiring recent inpatient treatment as non-adherence is often a factor in these outcomes
• Comorbid substance misuse
• Lack of insight
LAI’s and your practice
Detection of antipsychotic non-adherence is difficult in routine practice.

Criterion standard (n=19) is MEMS MPR ≤.80 over 12 wks, compared with patient self-report, physician impressions, and unannounced in home pill counts. Patient and physician reports correlated with BPRS.

BPRS=Brief Psychiatric Rating Scale; MPR=medication possession ratio.

How could using LAIs change my clinical practices?

• The mechanics of prescribing change of course but that is only a relatively minor change.

• The most important changes derive from knowing absolutely whether your patients are or are not taking the medications you prescribe.
Central clinical management issues

• Most patients with a chronic medical condition do not take their prescribed medication
• Many people who take a prescribed medication do not take it at the dose or frequency prescribed
• There is often a time lag between the start of medication non-adherence and symptom relapse
• Maintenance medication decreases the risk of relapse but does not eliminate the occurrence of relapse
Clinical implications

LAI s eliminate covert non-adherence
If you know your patient is not taking medication, you can work with them and their family on monitoring plans and additional educational efforts about maintenance treatment
Treating an acute episode

• If a patient does not respond to an adequate trial of a LAI, you know that you should definitely change to another antipsychotic

• For non-response to oral medication, you often do not know if it is because of non-adherence or actual non-response to the antipsychotic
  • Mistaking non-adherence for non-response can lead to frequent medication switches, adding unnecessary additional medications or escalating the prescribed dose
Treating a relapse

• Patients can relapse with any treatment, including LAIs.
  • If a patient relapses while taking LAIs you immediately know that it was due to a failure of the medication and not a failure of the patient to take the medication
  • This eliminates the need to “grill” the patient about adherence as you need to do with oral medications
Evaluating the need for clozapine

• You want to offer clozapine to all patients who need it but
• You also do not want to give clozapine to patients who would do well with other antipsychotics
• LAIs facilitate determining which patients do not respond to antipsychotics other than clozapine and for whom the benefit/risk ratio for clozapine is favorable.
LAIs and Real World Outcomes
# Strengths and Weaknesses of Different Study Types Involving LAIs: Impact on Outcomes

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Strengths</th>
<th>Weaknesses</th>
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<tbody>
<tr>
<td>Randomized controlled trials</td>
<td>• Design reduces expectancy and rater biases</td>
<td>• Not the best way to study interventions with potential adherence benefits&lt;br&gt;• Patients not representative of clinical practice – more adherent, less severe disease&lt;br&gt;• Double-blind studies may increase selection bias</td>
</tr>
<tr>
<td>Mirror-image studies</td>
<td>• More reflective of clinical practice</td>
<td>• Expectation bias is inherent in mirror-image studies and may impact the main outcome&lt;br&gt;• Patients switch from oral antipsychotics to LAIs but not vice versa&lt;br&gt;• Time/cohort effects (eg, change in hospitalization policies)</td>
</tr>
<tr>
<td>Cohort studies</td>
<td>• Patient selection bias is reduced compared with other study types</td>
<td>• Selection of medication in open studies may introduce bias by improving adherence&lt;br&gt;• LAI patients are categorically different and more seriously ill than oral antipsychotic patients&lt;br&gt;• Confounding factors must be adjusted</td>
</tr>
</tbody>
</table>

Real-world Studies Favor Use of LAI Antipsychotics

As study design shifts toward real-world populations, LAI formulations display significant advantages.

Favors oral

Favors LAI

- Relapse
- Hospitalization
- All-cause discontinuation
- Overall

**Adjusted Risk Ratio**

- RR=0.622
- RR=0.877
- RR=0.558

**RCTs**=randomized controlled trials; **RR**=risk ratio

Mirror-image Studies May Reflect the Real-world Impact of LAIs

<table>
<thead>
<tr>
<th>Meta-analysis of all available mirror-image studies</th>
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<tbody>
<tr>
<td><strong>Date range</strong></td>
</tr>
<tr>
<td><strong>Number of studies</strong></td>
</tr>
<tr>
<td><strong>Number of patients</strong></td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
</tr>
<tr>
<td><strong>Setting</strong></td>
</tr>
<tr>
<td><strong>Primary endpoints</strong></td>
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<tr>
<td><strong>Other endpoints</strong></td>
</tr>
</tbody>
</table>

LAI s Reduce Risk of Hospitalization Compared with Oral Antipsychotics

<table>
<thead>
<tr>
<th>Study</th>
<th>RR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Girardi et al. 2010</td>
<td>0.024</td>
<td>0.009</td>
</tr>
<tr>
<td>Beauclair et al. 2005</td>
<td>0.092</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arató &amp; Erdös 1979</td>
<td>0.204</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Devito et al. 1978</td>
<td>0.281</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Denham &amp; Adamson 1971</td>
<td>0.333</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Morritt 1974</td>
<td>0.343</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lam et al. 2009</td>
<td>0.369</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lindholm 1975</td>
<td>0.391</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peng et al. 2011</td>
<td>0.452</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gottfries &amp; Green 1974</td>
<td>0.529</td>
<td>0.005</td>
</tr>
<tr>
<td>Rosa et al. 2012</td>
<td>0.529</td>
<td>0.094</td>
</tr>
<tr>
<td>Chang et al. 2012</td>
<td>0.557</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Johnson &amp; Freeman 1972</td>
<td>0.570</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Crivera et al. 2011</td>
<td>0.597</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ren et al. 2011</td>
<td>0.663</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Svestka et al. 1984</td>
<td>1.286</td>
<td>0.569</td>
</tr>
</tbody>
</table>

Total (16 studies) (n=4.066)

Favors LAI

Favors oral APs

LAI s showed strong superiority over oral APs in preventing hospitalization

APs=antipsychotics; CI=confidence interval; RR=relative risk.

A Nationwide Cohort Study of Oral and Depot Antipsychotics After First Hospitalisation for Schizophrenia

Jari Tiihonen, M.D., Ph.D.
Jari Haukka, Ph.D.
Mark Taylor, F.R.C.Psych.
Peter M. Haddad, M.D., F.R.C.Psych.
Maxine X. Patel, M.D., M.R.C.Psych.
Pasi Korhonen, Ph.D.

Objective: Data on the effectiveness of antipsychotics in the early phase of schizophrenia are limited. The authors examined the risk of rehospitalization and drug discontinuation in a nationwide cohort of 2,588 consecutive patients hospitalised for the first time with a diagnosis of schizophrenia between 2000 and 2007 in Finland.

Method: The authors linked national databases of hospitalization, mortality, and antipsychotic prescriptions and computed hazard ratios, adjusting for the effects of sociodemographic and clinical variables, the temporal sequence of the antipsychotics used, and the choice of the initial antipsychotic for each patient.

Results: Of 2,588 patients, 1,507 (58.2%) collected a prescription for an antipsychotic during the first 30 days after hospital discharge, and 1,182 (45.7%, 95% confidence interval [CI]=43.7–47.6) continued their initial treatment for 30 days or longer. In a pairwise comparison between depot injections and their equivalent oral formulations, the risk of rehospitalization for patients receiving depot medications was about one-third of that for patients receiving oral medications (adjusted hazard ratio=0.36, 95% CI=0.17–0.75). Compared with oral risperidone, clozapine (adjusted hazard ratio=0.48, 95% CI=0.31–0.76) and olanzapine (adjusted hazard ratio=0.54, 95% CI=0.40–0.73) were each associated with a significantly lower rehospitalization risk. Use of any antipsychotic compared with no antipsychotic was associated with lower mortality (adjusted hazard ratio=0.45, 95% CI=0.31–0.67).

Conclusions: In Finland, only a minority of patients adhere to their initial antipsychotic during the first 60 days after discharge from their first hospitalization for schizophrenia. Use of depot antipsychotics was associated with a significantly lower risk of rehospitalization than use of oral formulations of the same compounds. Among oral antipsychotics, clozapine and olanzapine were associated with more favorable outcomes. Use of any antipsychotic was associated with lower mortality.
LAI Antipsychotics Significantly Improve Treatment Outcomes in Patients with Schizophrenia

Risk of discontinuation or rehospitalization after a first hospitalization for schizophrenia, by antipsychotic treatment (N=2588)

- Any depot injection compared with equivalent oral formulation
- Haloperidol depot injection compared with oral haloperidol
- Perphenazine depot injection compared with oral perphenazine
- Risperidone depot injection compared with oral risperidone
- Zuclopenthixol depot injection compared with oral zuclopenthixol


CI=confidence interval.
Summary

- Sustained medication adherence is a challenge for most patients in all of medicine.
- Patients with schizophrenia may particularly benefit by adherence enhancement interventions.
- LAIs do not eliminate non-adherence as patients can refuse them just as they can refuse oral medications.
- However, knowing absolutely if your patients are or are not taking medications as prescribed:
  - can greatly simplify making treatment decisions.
  - eliminate the need with oral agents to do lengthy adherence assessments.
    - There are much more productive/interesting things than adherence to spend time discussing with your patients!
- Studies using “real world” designs suggest that LAI prescription is associated with better clinical outcomes.
Thank you!

www.CareTransitionsNetwork.org
CareTransitions@TheNationalCouncil.org

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