How Can We Facilitate Earlier Use of LAIs? The Role of the Clinician, Patient, and Family

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Outline

• Physician barriers to use of LAIs.

• Patient and family barriers to use of LAIs.

• Reasons why LAIs may be beneficial early in the course of treatment.

• Role of motivational interviewing and a ‘shared-decision-making’ approach.

• Overcoming barriers to continued use of LAIs.

• Ongoing work to assess LAIs in early phase schizophrenia.
PREScriber ISSUES

Knowledge
Beliefs
Attitude
Training
Experience
Support
Barriers to Change for Physicians

Figure. Barriers to Physician Adherence to Practice Guidelines in Relation to Behavior Change

JAMA 1999; 282:1458-1465
Psychiatrists (N=246) Cite Multiple Reasons for Not Prescribing Atypical LAI Antipsychotics

EPS=extrapyramidal symptom; LAI=long-acting injectable.

Patient/Family Barriers to LAI Use
HELLO?
ANYBODY?
MENTAL
HEALTH
SYSTEM
Lack of Understanding of the Problems with Nonadherence/Repeated Relapses

• 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

Psychological Impact

• Despair
• Demoralization
• Loss of confidence in self
• Depression & suicide
• Disrupted personality development
• Anxiety, social phobia, PTSD
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
What is my risk of relapse if I miss my medications?

<table>
<thead>
<tr>
<th>Cumulative Relapse: %</th>
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<tbody>
<tr>
<td>3%</td>
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<tr>
<td>77%</td>
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<tr>
<td>90%</td>
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</table>

1 year on AP: 3%
4 Studies
126

1 year off AP: 77%
6 Studies
N=209

2 years off AP: 90%

Prevention of Relapse: LAIs vs Placebo in Multiepisode Pts

![Graph showing number needed to treat for different LAIs and dosages.](Image)

Impact on intracortical myelination trajectory of long acting injection versus oral risperidone in first-episode schizophrenia

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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 (RisO) in first-episode SZ subjects.

Design: Two groups of SZ subjects (RLAI, N = 9; and RisO, 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 RisO 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 increases (chi-square < .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 ($t = 2.48, \text{df} = 21, p = .022$). 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 ($\chi^2 = 8.7, \text{df} = 1, p = .003$). Results are based on covariance analyses adjusted for race.
Subject ratings of LAI injection site pain rated on a visual analogue scale

Long-Acting Injectable (LAI) Antipsychotics: Balancing Pros and Cons for Patients

- More appointments
- Perceived stigma
- Conversion from oral to LAI
- Fear of pain
- Inflexible dosing / stopping
- Lack of experience
- Negative clinician appraisal

- Continuous antipsychotic coverage
- ↓ relapse & hospitalization
- No need to remember
- Less conflict over suspected non-adherence
- Less of peak level related side effects

Dimensions of Change

Against Change:
- Less receptive to future attempts
- Decides it's not a problem
- Decreased desire to change
- No awareness or interest

Toward Change:
- Increased desire to change
- Problem recognition
- Increased awareness
- Makes verbal arguments in support of change

Increases offending behavior
Makes verbal commitments against change

Changes behavior
Why Not?

• Injections are a hassle → just once a month, won’t have to remember to take meds every day
• Someone always nags me about taking my pills → won’t happen again
• Injections hurt → very little pain
• More side effects → less because medicine releases a little at a time
• Control over me → control over your illness
• What if I want to stop → you can stop anytime, and if you do, there is less chance of a withdrawal reaction
• Means I’m sicker → it actually means you are more likely to stay well
• Start with one injection and let’s see how it goes
• Why not give it a try!? You might just like it!
What Is Motivational Interviewing?

• A style of dialogue between two parties, which is intended to motivate one party into making positive changes by compassionately challenging the status quo and helping them explore alternatives.
Motivational Interviewing Basic Principles: Shared Decision-Making

- **Collaboration**
  - Patient is their own expert
  - Caregiver builds partnership

- **Evocation**
  - Patient has the resources to change
  - Caregiver elicits the change

- **Autonomy**
  - Patient has the right to self-direction
  - Caregiver affirms this, but also provides input

Modified based on material from: Maria Arpa, Founder of The Centre for Peaceful Solutions
Therapeutic Relationship

Okay, I've got “ought” and “must” and “should” and “or else” down. Any other motivational words you’d suggest?

A-C-E

Autonomy  V  Authority
Collaboration  E  Coercion
Evocation  S  Education

Card: Autonomy  Collaboration  Evocation

Card: Authority  Coercion  Education
<table>
<thead>
<tr>
<th>Stages of Change**</th>
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<tbody>
<tr>
<td>Precontemplation</td>
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<td>Contemplation</td>
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<tr>
<td>Preparation</td>
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<tr>
<td>Action</td>
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<tr>
<td>Maintenance/Relapse</td>
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Motivational Interviewing

Core Skills

- Open Questions
- Affirmations
- Reflections
- Summaries
Shared Decision Making Approach
Goal Elicitation and Goal Setting

“The new screen saver was created by a motivation expert. It’s a slide show of former employees who were fired for poor performance.”
GAIN Model

• G= Goal Setting
  – Discover what the pts life goals are
  – Talk about current treatment (good/bad)
  – Listen actively, reflecting pts experiences
  – Develop small, concrete, attainable steps to achieve 1 or 2 goal(s)
  – Explore delays to goals caused by relapses
  – Compromise where you can

GAIN Model

• A = Action Planning
  – Explore +/- of once-monthly treatment
  – Listen actively to pts fears
  – Describe link b/t use of LAI and achieving goals
  – Elicit support of family/caregivers

GAIN Model

• I = Initiate Treatment
  – Step by step explanation of treatment process including trial of oral medications first to assess tolerability (if relevant)
  – Listen for negative perceptions of injections and normalize these (eg. Flu shot, vaccinations, insulin)
  – Elicit feedback from the patient on how treatment is going

GAIN Model

• N = Nurturing Change
  – Explore any side effects or negative experiences and assure pt you will address the concerns immediately (removal of – reinforcers)
  – Celebrate positive experiences, reduced symptoms/relapses (+ reinforcement)
  – Identify other aspects of the total treatment plan that may help the pt achieve goals (supported employment/education, job training, therapy, etc)
  – Reassess goals/repeat

Patients May Be Willing to Accept LAI Antipsychotic Therapy When Properly Informed

• In a survey of patients without LAI antipsychotic experience:
  – 79% cited having never been informed about the option by their psychiatrist.\(^1\)
  – 75% of psychiatrists felt that they informed the patient, but only 33% of patients felt informed.\(^1\)

• In a survey of patients with \(>3\) months of LAI antipsychotic experience:
  – Injectable antipsychotics were the preferred formulation.\(^2\)
  – 70% of patients felt better supported in their illness by virtue of regular contact with the doctor or nurse who administered their injection.\(^2\)

• In a small qualitative survey (\(N=11\)) of FEP pts in an EI program in England:
  – Patients would consider LAI if recommended by their psychiatrist.\(^3\)
  – All pts not on LAI stated they were not informed about LAIs as option.\(^3\)
  – They cited injection site pain, fear of needles, stigma as reasons not to try it.\(^3\)

LAI=long-acting injectable antipsychotic

Practical Issues in Starting an LAI

• Establish oral tolerability.
• Titrate on/off one antipsychotic and onto another.
• Begin LAI per package insert.
  -Single vs loading and repeat dose.
  -Continue oral antipsychotics per manufacturer recommendations.
• Adjust dose for efficacy/side effects.
• Consult package insert for handling of missed doses.
Possible Methods for Switching APs

A. Abrupt Switch

B. Cross-Titration

C. Plateau Cross-Titration

**RED closed line:** Initial antipsychotic dose

**GREEN closed line:** New antipsychotic dose

Dotted Line: Antipsychotic plasma concentration

*Stepwise start with partial D2 agonist with lower starting dose recommended

Adapted from: Correll CU. J Clin Psychiatry 2006;67(1):160-1
Dealing with Treatment Emergent Side Effects (& Other Challenges)

Akathisia – consider acute use of beta blockade (propranolol or equivalent) or benzodiazepine. Consider temporary dose reduction.

Sleep disturbance – consider behavioral methods: encourage good sleep hygiene (exercise, reduce caffeine, eat well, OOB if not sleeping, no naps, progressive relaxation, no TV in bed, etc). If not effective, consider melatonin, trazodone, diphenhydramine, benzodiazepines. Consider sleep referral if pt is obese, snores, has EDS. Consider modafinil for oversedation.

Extrapyramidal symptoms – consider dose reduction or addition of anticholinergic, antihistamine, or benzodiazepine.

Weight gain (>7% body wt) - encourage diet and exercise. Have pt meet with dietician. Consider metformin/topiramate treatment, statin for hyperlipidemia or change in antipsychotic.

Transportation – offer bus/subway tickets, cab rides if needed.

Family resistance – offer to meet with family. Share data on treatment of first episode psychosis, risk of relapse. Remind patient and family how well the patient is doing now. Why put their recovery at risk?
Time Course of First Onset of Adverse Events for Patients Receiving LAI Aripiprazole

Participants With AEs, %

Prior to First Dose (n=842) ≤4 Weeks (n=842) 4-8 Weeks (n=809) 8-12 Weeks (n=719) 3-6 Months (n=622) 6-9 Months (n=355) 9-12 Months (n=213) >12 Months (n=90)

Nausea
Weight increased
Akathisia
Headache
Anxiety
Insomnia

AE=adverse event.

Options for Patients Who Relapse on LAI

Based upon your best clinical judgment, you might:

• Give the LAI trial more time.
• Add adjuvant medications of your choice.
  – Oral antipsychotic, other antipsychotics, other classes of psychotropic medications
• Modify the frequency you see the participant or the level of care.
• Add psychosocial interventions.
• Add substance abuse treatments if appropriate.
• If you decide it is clinically appropriate, you can stop LAI.
  – For example, if you want to prescribe clozapine mono-therapy
Ongoing/Future Work
PREvention of RELAPSE in Early Phase Schizophrenia: the PRELAPSE Study

Central Team: John Kane, Delbert Robinson, Nina Schooler, Eric Achtyes, Joanne Severe, Patricia Marcy, Vivianne Dillon, Cristina Gomes, Priya Matneja
Real-World Studies Favor Use of LAI Antipsychotics

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

LAI=long-acting injectable antipsychotic; RCT=randomized controlled trial; RR=risk ratio.

Kirson N et alPoster presented at: 52nd Annual Meeting of New Research Approaches for Mental Health Interventions; May 29-June 1, 2012; Phoenix, AZ.
Matching Trial Design to the Question

• Primary Question in PRELAPSE
  – Does opportunity for treatment with an SGA LAI delay time to first hospitalization in patients with first episode (0-1 yr antipsychotic treatment) and recent onset (1-5 yrs) schizophrenia?

• Compare patients who receive LAI aripiprazole to those in a Clinicians’ Choice arm
  – Prescriber decides on best choice for pt (could be oral or LAI)
Study Design: Large Simple Trial

• Large
  – 40 sites (10 sites will include MRI assessments)
  – 500 subjects (250 FEP, 250 Recent Onset)

• Simple
  – Broad inclusion criteria
  – Limited assessment
    • Primary outcome measure is obtainable from records

• Trial
  – Site level randomization

• 24-Month Follow-up
  – Hospitalization is an infrequent event
Subjects

• Inclusion criteria
  – Schizophrenia diagnosis*
    • First Episode (FE) cohort: >1 year of prescribed treatment with antipsychotic medication and 1 episode of psychosis
    • Recent Onset (RO) cohort: 1-5 years of antipsychotic treatment and/or >1 episode of psychosis
  – M and F; Age 18 – 35
  – Able to provide informed consent

*DSM 5 SCID diagnosis, confirmed by centralized raters
Subjects

• Exclusion criteria
  – Primary DSM-5 diagnosis other than schizophrenia
  – Women who are pregnant or lactating
  – Unstable medical condition that makes trial participation unwise – clinical judgment
  – History of clozapine treatment
Safety and Outcomes

• Safety Assessments
  – Laboratory tests and Vital Signs
    • Baseline and every six months
  – Medication visit record – whenever one occurs
  – Adverse events
    • Baseline and every six months
Safety and Outcomes cont.

• Outcome assessments
  – HEC – Hospitalization and Emergency Room record
    • Every 2 months – by phone and record review
  – SURF – Services Utilization and Resources Form
    • Every four months by phone
  – RBANS – Repeatable Battery to Assess Neuropsychological Status
    • Baseline, one and two years
Progress to Date

• 235 enrolled in Clinicians’ Choice arm.
• 183 enrolled in the LAI arm.
QUESTIONS?