SCHIZOPHRENIA & SCHIZOAFFECTIVE DISORDER
Utilizing Tools to Optimize Outcomes Across the Spectrum of Acute to Maintenance Treatment

Friday, April 17, 2015

Activity Chair
Leslie L. Citrome, MD, MPH
Defining Moments: Early Schizophrenia and Schizoaffective Disorder

Jonathan M. Meyer, MD
Assistant Clinical Professor of Psychiatry
University of California
Psychopharmacology Consultant
California Department of State Hospitals
San Diego, CA
Agenda

- Defining and subtyping using DSM-5
  - What has changed?
- Directing therapy and early treatment following 1st episode
  - Long-term impact
- Use of oral and depot antipsychotics
DSM-5 Criteria Changes
Schizophrenia: Major Changes

- Simplified ‘A’ criterion
- Removal of subtypes
  - Lack of predictive value for course, treatment
  - Largely dropped in the literature
- New course specifiers
  - Catatonia recognized as a specifier across multiple disorders

Schizoaffective Disorder: ‘B’ Criterion - Clarifying Wording

• **DSM-IV:**
  – B. Delusions and hallucinations for 2 or more weeks in the absence of prominent mood symptoms

• **DSM-5:**
  – B. Delusions or hallucinations for 2 or more weeks in the absence of a major mood episode (depressive or manic) during the lifetime duration of the illness
Schizoaffective Disorder: ‘C’ Criterion - Clarifying Wording

- DSM-IV:
  - C. Symptoms that meet criteria for a major mood episode are present for a substantial portion of the total duration of the active and residual portion of the illness

- DSM-5:
  - C. Symptoms that meet criteria for a major mood episode are present for the majority of the total duration of the active and residual portion of the illness

Schizoaffective Disorder: Subtypes and Specifiers

• Subtypes
  – Bipolar
  – Depressive

• Specifier
  – With catatonia

• Course Specifiers
  – Same as schizophrenia

Depression in Schizophrenia: The ABC Longitudinal Study

- 232 1st-episode schizophrenia patients in Germany enrolled (1987-1989) and followed up to 12 years
  - 107 had follow-up data after mean 136 months
  - Percentage of patients with persistent moderate or severe depressive symptoms
    - Acute phase: 81.0%
    - Chronic phase: 42.9%

Depression in Schizophrenia: Review of Clinical Trials Data

- Only 11 studies met inclusion criteria
- All were small and randomized <30 to each group
- The literature was of poor quality and only a small number of trials (5) made useful contributions
- For the 5 studies with interpretable outcomes, the NNT is 4 (95% CI 3 - 8) to achieve clinical response
  - Change in depression rating scales was suggestive of benefit but not statistically significant
- Conclusion: Antidepressants may benefit depressed patients with schizophrenia, but the randomized trial data do not support this, mostly due to lack of good quality data

Directed Therapy: The First Episode Patient
What We Want to Avert

The Young Patient with Schizophrenia: Plan for Early Intervention (EI) Services

**PSYCHOLOGICAL INTERVENTION**
- Cognitive remediation
- CBT
- Adherence therapy

**PHARMACOLOGIC INTERVENTION**
- Appropriate AP choice
- Improve symptoms
- Minimize AEs

**SOCIAL INTERVENTION**
- Indiv & Family Education
- Voc & Social Skills training
- Community support

**MINIMIZE**
- Wt gain, CV risk
- Sexual dysfunction
- Movement disorders

**IMPROVE**
- Self-esteem and self-efficacy
- Cognition
- Positive symptoms
- Negative symptoms
- Knowledge and skills

**INCREASE**
- Friendships and family contact
- Self-inclusion and community involvement
- Employment opportunities

**GOAL**
High QoL and remission

AEs = adverse effects; AP = antipsychotic; CBT = cognitive behavioral therapy; QoL = quality of life.
Polypharmacy and Mortality in First Episode (FE) Schizophrenia

Finnish data from 2588 patients hospitalized for the 1st time with a schizophrenia diagnosis 2000-2007

• Demographics
  – Mean age 37.8 (± 13.7) years
  – 62.0% male
  – Follow-up 4.2 (± 2.2) years
    ▪ 160 deaths occurred during the follow-up period

In FE Schizophrenia: Benzodiazepines Increase Suicide, Antidepressants Reduce Suicide

Outcomes

• Use of ≥2 antipsychotics did not increase mortality during the follow-up period
• Benzodiazepine use doubled mortality rate (HR 1.91, 95% CI 1.13 - 3.22)
  – Suicide deaths up almost 4-fold (HR 3.83, 95% CI 1.45 - 10.12)
• Antidepressant use did not increase mortality
  – Suicide deaths decreased 7-fold (HR 0.15, 95% CI 0.03 - 0.77)

Nonadherence Risk in First Episode (FE) Patients

• Data on 100 consecutive admissions to a specialized EI service in Canada followed for 6 months
  – 54.9% were adherent (76% to 100% of doses taken)
• Nonadherent patients were:
  – Less likely to have good social support ($P=.02$), as rated by a case manager
  – More likely to be single ($P=.019$)
  – More likely to have refused medication at the first offer of treatment ($P=.001$)
• Using logistic regression, level of social support (OR = 3.56, $P=.03$) and early medication acceptance (OR = 11.09, $P<.001$) were significant as predictors of adherence
## Relapse Risk: Oral versus Depot Antipsychotics After First Schizophrenia Hospitalization

<table>
<thead>
<tr>
<th>Comparison</th>
<th>All-cause Comparison</th>
<th></th>
<th>Rehospitalization</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Adjusted Hazard Ratio</td>
<td>95% CI</td>
<td>P</td>
</tr>
<tr>
<td>Any depot injection versus equivalent oral formulation</td>
<td>0.41</td>
<td>0.27-0.61</td>
<td>&lt;.0001</td>
<td>0.36</td>
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<tr>
<td>Haloperidol depot injection versus oral haloperidol</td>
<td>0.27</td>
<td>0.08-0.88</td>
<td>.03</td>
<td>0.12</td>
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<tr>
<td>Perphenazine depot injection versus oral perphenazine</td>
<td>0.32</td>
<td>0.19-0.53</td>
<td>&lt;.0001</td>
<td>0.53</td>
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<td>Risperdone depot injection versus oral risperdone</td>
<td>0.44</td>
<td>0.31-0.62</td>
<td>&lt;.0001</td>
<td>0.57</td>
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<td>Zuclopenthixol depot injection versus oral zuclopenthixol</td>
<td>0.75</td>
<td>0.29-1.89</td>
<td>.54</td>
<td>0.49</td>
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</table>

# Atypical Depot Indications

*Monotherapy or adjunctive to mood stabilizer*

**Monotherapy or adjunctive to mood stabilizer and/or antidepressant**

<table>
<thead>
<tr>
<th>Drug</th>
<th>SCZ</th>
<th>SAD</th>
<th>Bipolar I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperdone microspheres</td>
<td>XX</td>
<td></td>
<td>XX*</td>
</tr>
<tr>
<td>Paliperidone palmitate</td>
<td>XX</td>
<td>XX**</td>
<td></td>
</tr>
<tr>
<td>Olanzapine pamoate</td>
<td>XX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aripiprazole monohydrate</td>
<td>XX</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*SAD: Schizoaffective disorder, SCZ: Schizophrenia*

Early Comprehensive Intervention Often Reduces Total Costs of Care

- Australia (EPPIC), 1 Denmark (OPUS), 2 UK (Lambeth Early Onset), 3 Italy (Programmema2000) 4
  - Most studies show reduced total care costs over extended period in early intervention versus usual care patients
  - Nearly every study shows reduced inpatient costs that more than cover initial high outpatient costs

Conclusions

• The DSM-5 criteria provide modest improvements for diagnosing schizoaffective disorder
• Primary issue is a large fraction of schizophrenia spectrum patients have persistent depressive symptoms
• In first-episode patients there is compelling data that antidepressant use reduces suicide mortality by 7-fold
• Poor adherence equates to high-relapse risk
  – Depot agents reduce relapse risk, especially in first episode patients
Improving the Bottom Line in Treatment of Schizophrenia and Schizoaffective Disorder - Adherence Defines Outcomes

Leslie L. Citrome, MD, MPH
Clinical Professor of Psychiatry and Behavioral Sciences
New York Medical College
Valhalla, NY
Scope of the Problem

- Medication adherence is poor across psychiatric and other medical disorders\textsuperscript{1,2}
- Medication adherence is particularly poor in persistent disorders\textsuperscript{1}
  - Treatments are designed to prevent symptom onset or recurrence
  - Consequences of stopping treatment are delayed
- \textasciitilde 75\% of patients with schizophrenia become nonadherent within 2 years of hospital discharge\textsuperscript{3}

Partial Adherence in Schizophrenia Begins Early and Prevalence Increases Over Time

Clinical Consequences of Nonadherence are Severe

- ~50% of patients who discontinue/do not take antipsychotics will relapse within 3 to 10 months\(^1,2\)
- Relapse rates are much higher in nonadherent patients\(^3\)
  - 69% of patients with poor adherence relapsed compared with 18% of patients with good adherence (NNT=2)

Unrecognized Nonadherence as a Cause of Failed Psychopharmacology

- We assume lack of adequate response as “treatment-resistance” and lack of efficacy for the antipsychotic for that patient
  - This is a possible explanation for high dosing of antipsychotics, polypharmacy with other antipsychotics, and combination treatment with anticonvulsants
    - This is a no-win cycle: adherence is even more of a challenge with complex regimens

## Risk Factors for Nonadherence

<table>
<thead>
<tr>
<th>Patient Related Risk Factors for Nonadherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor insight</td>
</tr>
<tr>
<td>Negative attitude toward medication</td>
</tr>
<tr>
<td>Prior nonadherence</td>
</tr>
<tr>
<td>Substance abuse</td>
</tr>
<tr>
<td>Cognitive impairment</td>
</tr>
<tr>
<td>Negative symptoms</td>
</tr>
</tbody>
</table>
## Risk Factors for Nonadherence

<table>
<thead>
<tr>
<th>Treatment-related Risk Factors&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Environment/Relationship-related Risk Factors&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Societal-related Risk Factors&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Side effects</td>
<td>• Lack of family/social support</td>
<td>• Stigma attached to illness</td>
</tr>
<tr>
<td>• Lack of efficacy/continued symptoms</td>
<td>• Problems with therapeutic alliance</td>
<td>• Stigma caused by medication side effects</td>
</tr>
<tr>
<td></td>
<td>• Practical problems (financial, transportation, etc.)</td>
<td></td>
</tr>
</tbody>
</table>

Medication-related Side Effects and Nonadherence

- Potential drivers
  - Level of distress rather than severity
  - Attribution to the medication
  - Vary from patient to patient
- Most commonly associated with nonadherence
  - Weight gain
  - Sedation
  - Akathisia
  - Sexual dysfunction
  - Parkinsonian symptoms
  - Cognitive problems

Reverberations From Side Effects: How Patient and Clinician Responses May Differ


- Subjective Distress
- Objective Severity
- Adherence Impact
- Safety and Risk

Side effect appears

Influencing patient response

Influencing clinician response
Potential Advantages of Long-acting Injectable Antipsychotics

- Reduces dosage deviations\(^1\)
- Eliminates guessing about adherence status\(^2,3\)
- Shows start date of nonadherence\(^2,3\)
- Helps disentangle reasons for poor response to medication\(^3\)
- Eliminates need for the patient to remember to take a daily pill\(^1\)
- Enables prescribers to avoid first-pass metabolism, therefore a better relationship between dose and blood level exists\(^1\)
- Results in predictable and stable plasma levels\(^1\)
- Eliminates abrupt loss of efficacy if dose missed\(^1,3\)
- Many patients prefer them, especially if already receiving them\(^4\)

Potential Obstacles to Long-acting Injectable Antipsychotics

- Lack of infrastructure in outpatient settings
- Need to refrigerate, store, reconstitute, etc.
- Overburdened public agencies
- Frequency of injections and consequent inconvenience for staff and patients
- Need to take concomitant medications orally
- Anti-shot sentiment

Long-acting Injectable Antipsychotics Are Currently Underutilized

- Most clinicians report using long-acting injectable atypical antipsychotics in <10% of patients\(^1\)
- Psychiatrists have not offered an LAI antipsychotic to nearly two-thirds of their patients\(^2\)
- Only 12.4% of patients who were not taking oral therapies as prescribed were switched to an LAI antipsychotic formulation during a 3-year prospective study\(^3\)

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 al. J Clin Psychiatry 2013;74(6):568-75. Figure adapted from Kirson N et al. Poster presented at: 52nd Annual Meeting of New Research Approaches for Mental Health Interventions; May 29-June 1, 2012; Phoenix, AZ.
SGA LAIs After Risperidone

- Olanzapine pamoate
- Paliperidone palmitate
- Aripiprazole monohydrate
OLAI, olanzapine pamoate long-acting injection.


- OLAI is a crystalline salt of olanzapine and pamoic acid
- Efficacy was established in 2 double-blind, randomized clinical trials of OLAI for the treatment of acute schizophrenia and for the maintenance of response
- Therapeutic OLAI dosages are 150 mg every 2 weeks, 210 mg every 2 weeks, 300 mg every 2 weeks or every 4 weeks, and 405 mg every 4 weeks
- OLAI has essentially the same general tolerability as that of oral olanzapine; however, with the depot there is the additional risk of a post-injection delirium sedation syndrome occurring at a rate of 0.07% of injections, requiring a risk management plan that includes observing the patient for 3 hours after each injection
Paliperidone Palmitate Long-Acting Injection

- Paliperidone palmitate is an aqueous suspension using a proprietary technique dubbed by its developer as “NanoCrystal” technology.
- Acute efficacy was evidenced by 4 short-term (one 9-week and three 13-week) double-blind, randomized, placebo-controlled, fixed-dose studies of acutely relapsed adult inpatients with schizophrenia.
- In 3 longer-term studies, treatment with paliperidone palmitate at doses between 39 mg and 156 mg significantly delayed the time to recurrence of symptoms of schizophrenia after 24 weeks of maintained symptom stability.
- Also studied in persons with recent contact with the criminal justice system.
- Recently approved for schizoaffective disorder.

Aripiprazole Monohydrate Long-Acting Injection

- Approved as gluteal muscle injection (21G) for treatment of schizophrenia (every 4 week injections)
  - Deltoid administration under development
- Significantly delays time to relapse as evidenced in a 52-week, double-blind, randomized-withdrawal clinical trial and in a 38-week, double-blind, active-controlled, non-inferiority study
- Acute efficacy in schizophrenia demonstrated in a 12-week study
- Available in single use vial kits of 400 mg and 300 mg, and in a pre-filled dual-chamber syringe
- Starting dose 400 mg, can reduce to 300 mg
- Oral supplementation for 14 days required
- Safety concerns: same as oral formulation

# LAI SGAs for Schizophrenia: What’s Different?

<table>
<thead>
<tr>
<th>Feature</th>
<th>Risperidone LAI</th>
<th>Olanzapine LAI</th>
<th>Paliperidone LAI</th>
<th>Aripiprazole LAI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year approved</strong></td>
<td>2003</td>
<td>2009</td>
<td>2009</td>
<td>2013</td>
</tr>
<tr>
<td><strong>Other indications?</strong></td>
<td>Bipolar disorder</td>
<td>No</td>
<td>Schizoaffective disorder</td>
<td>No</td>
</tr>
<tr>
<td><strong>Injection sites</strong></td>
<td>Deltoid or gluteal</td>
<td>Gluteal</td>
<td>Deltoid or gluteal</td>
<td>Gluteal (approval for deltoid pending)</td>
</tr>
<tr>
<td><strong>Needle gauge</strong></td>
<td>20G or 21G</td>
<td>19G</td>
<td>22G or 23G</td>
<td>21G</td>
</tr>
<tr>
<td><strong>Injection volume</strong></td>
<td>~2 mL</td>
<td>1.0 to 2.7 mL</td>
<td>0.25 to 1.5 mL</td>
<td>2 mL (400 mg)</td>
</tr>
<tr>
<td><strong>Injection frequency</strong></td>
<td>Every 2 weeks</td>
<td>Every 2 or 4 weeks</td>
<td>Every 4 weeks</td>
<td>Every 4 weeks</td>
</tr>
<tr>
<td><strong>Starting dose</strong></td>
<td>25 mg</td>
<td>Varies from 210 mg q2wk or 405 mg q4wk to 300 mg q2wk</td>
<td>234 mg Day 1 + 156 mg Day 8 in deltoid</td>
<td>400 mg</td>
</tr>
<tr>
<td><strong>Maintenance dose</strong></td>
<td>25 mg (max 50 mg)</td>
<td>Varies from 150 mg q2wk or 300 mg q4wk to 300 mg q2wk</td>
<td>117 mg (range 39 to 234 mg)</td>
<td>300 or 400 mg (adjust for CYP2D6 or CYP3A4 issues)</td>
</tr>
<tr>
<td><strong>Oral supplementation?</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Reconstitution needed?</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes (however, dual-chamber syringe now available)</td>
</tr>
<tr>
<td><strong>Refrigeration needed?</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Requires observation?</strong></td>
<td>No</td>
<td>3 hours</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

SGA: Second Generation Antipsychotic
LAI SGAs for Schizophrenia: Prevention of Relapse NNTs

- Paliperidone Palmitate
  - Flexibly dosed: 39-156 mg/4-weeks
    - Number Needed to Treat (NNT): 5

- Olanzapine Pamoate
  - 150 mg/2-weeks
    - NNT: 7
  - 300 mg/2-weeks
    - NNT: 4
  - 405 mg/4-weeks
    - NNT: 5

- Aripiprazole Monohydrate
  - 400 mg/4-weeks
    - NNT: 4

Investigational LAIs in Phase III of Clinical Development

• Aripiprazole Lauroxil
  - Differs from aripiprazole monohydrate in that a pro-drug is injected using a pre-filled syringe and aripiprazole is subsequently released from the muscle through an enzymatic process

• Paliperidone Palmitate q3Months
  - Injections q3months does not mean patients can’t be seen more often, but decreases the frequency of potential struggles over medication administration

# How to Choose a Long-acting Injection

## 1. Is the patient demonstrating adequate efficacy and tolerability on oral fluphenazine, haloperidol, risperidone, paliperidone, olanzapine, or aripiprazole?

- Switch to the corresponding depot formulation
- For patients receiving oral risperidone, can consider using paliperidone palmitate for convenience
  - No requirement for oral supplementation upon initiation, less frequent injections, supplied in prefilled syringes, smaller needle bore, lower injection volume, no refrigeration required
- For patients receiving oral fluphenazine or haloperidol, need to weigh the potential disadvantages of using concomitant oral anticholinergics for the management of motoric adverse effects
  - These agents add complexity to the regimen (an oral tablet/capsule)
  - Anticholinergic agents can interfere with memory and other cognitive functions

## 2. Is the patient being treated acutely?

- Consider depot antipsychotics that do not require oral supplementation and where the clinical trials have demonstrated acute efficacy, either paliperidone palmitate or olanzapine pamoate
### How to Choose a Long-acting Injection

<table>
<thead>
<tr>
<th>3. Are weight gain and metabolic adverse effects a concern for this individual patient?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Consider aripiprazole monohydrate, paliperidone palmitate, or risperidone microspheres among the SGAs, in that order</td>
</tr>
<tr>
<td>• Can consider the first-generation long-acting injectable antipsychotics as well</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. Is prolactin elevation a clinical concern for this individual patient?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Consider aripiprazole monohydrate</td>
</tr>
<tr>
<td>• Avoid paliperidone palmitate, risperidone microspheres, or the first-generation long-acting injectable antipsychotics</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. Is cost the primary concern?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• The first-generation depot antipsychotics may be the only option available</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. Are any of the following people or entities NOT enrolled in the Olanzapine Pamoate Patient Care Program: patient, prescriber, healthcare facility, pharmacy?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Olanzapine pamoate cannot be used</td>
</tr>
</tbody>
</table>
Conclusions

- Partial or non-adherence is common
- Partial or non-adherence increases the risk of relapse
- Strategies to improve adherence include
  - Admitting that partial or non-adherence is a possibility
  - Identifying risk factors specific to the individual
  - Tailoring interventions to adherence attitudes and behavior
- Pharmacologic strategies to improve adherence include
  - Considering patient history, efficacy, and side effect profile when choosing treatment
  - Considering utilizing long-acting injectable antipsychotics in patients with recurring relapses related to nonadherence
Improving Care Coordination

Ralph Aquila, MD
Medical Director – Fountain House, Inc.
Assistant Professor of Psychiatry
Icahn School of Medicine at Mount Sinai
New York, NY
Schizophrenia is Treatable

- Outpatient treatment and rehabilitation programs for people with schizophrenia can reduce psychiatric re-hospitalization rates, improve quality of life, prevent homelessness, and increase the likelihood of gainful employment\(^1\)

- Half of the people who receive treatment for schizophrenia either recover completely or are able to live independently with only modest psychosocial support\(^2\)

Practice Guidelines?  
Acute Psychosis  

Long-term  
Reintegration?
Relapse: Psychosocial

- Lack of support
  - Family and/or caregiver
  - Stressful environment

- Complex mental health system
  - Only 50% of patients keep their first outpatient appointment

Cognitive Dysfunction in Schizophrenia

- Cognitive dysfunction is strongly related to social/occupational functioning
- Improvement in cognitive function may also improve other symptom clusters
- Typical antipsychotic agents are not effective in treating cognitive dysfunction
- Psychosocial interventions such as CBT, cognitive remediation, clubhouse, ACT teams, and various hybrids help with keeping people in treatment

CBT: cognitive behavior therapy, ACT: assertive community treatment

Medications and Life Goals

• Many patients have terrible living conditions
• Relapse prevention doesn’t equal “recovery”
• Start by asking about life goals
Medications and Life Goals

- Patients have trouble seeing long-term benefits of antipsychotics.
- We need to help the person associate the taking of their medication with the meeting of life goals.
- Long-acting medication may help.
- Ongoing contact with involved families is essential.
- Families can be part of the solution, not the problem.
Why Rehabilitation

- Persons with serious & persistent mental illness can improve their lives
- Every person has strengths
- Time as an ally
- Work as the catalyst
- Empowerment
The When of Rehabilitation

• Psychosocial rehabilitation?
• “Maintenance” before 1980
• Psychiatrists not included
• 1990 ACT model includes work
• Consumers speak up
• Clubhouse & psychiatry

ACT: Assertive community treatment
Rehabilitation Alliance

- Collaboration with patient & system, patient (person) becomes co-team leader
- Treat symptoms with specific goals in mind
- Focus on strengths & opportunities instead of only psychotic symptoms
Clubhouse

- Intentional community/relationships
- Membership
- Made to feel needed
- Member needs to give back
- Cost-effective
- Generalist model
- Replicated worldwide
Other Rehabilitation Modalities

- Cognitive Behavioral Therapy
- Cognitive Remediation
- The Village
- ACT/IPS
- Hybrids

ACT: Assertive community treatment
IPS: Individual placement and support
Optimizing Outcomes: The Process of Recovery

Moving toward one’s individual potential and a better quality of life

Emerging Evidence About Improving Function, Recovery, and Patient Care

John M. Kane, MD
Chairman, Department of Psychiatry
Zucker Hillside Hospital
Senior VP for Behavioral Health Services
The North Shore–Long Island Jewish Health System
Professor and Chairman
Department of Psychiatry
Hofstra North Shore LIJ
School of Medicine
Glen Oaks, NY
Reported Mean Duration of Untreated Psychosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ho 2003</td>
<td>10</td>
</tr>
<tr>
<td>Wiersma 2000</td>
<td>20</td>
</tr>
<tr>
<td>Amminger 2002**</td>
<td>30</td>
</tr>
<tr>
<td>Malla 2002</td>
<td>40</td>
</tr>
<tr>
<td>Linszen</td>
<td>50</td>
</tr>
<tr>
<td>Verdoux 2001</td>
<td>60</td>
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<tr>
<td>Black 2001</td>
<td>70</td>
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<tr>
<td>Szymanski 1996</td>
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</tr>
<tr>
<td>Loebel 1992*</td>
<td>180</td>
</tr>
</tbody>
</table>

1 year

Implications of Delayed Treatment

- Greater decrease in functioning
- Loss of educational opportunities
- Impaired psychosocial and vocational development
- Personal suffering/family burdens
- Potential poorer response once treatment is provided
- Greater costs
Key Concepts for Optimal First-episode Medication Treatment

• Response rates for positive symptoms are very high.
  – No antipsychotic has demonstrated superior efficacy for the treatment of the initial psychotic episode. Tolerability is key.
• Effective antipsychotic doses are usually lower than those needed for multi-episode patients.
• Despite low antipsychotic doses, rates of adverse effects are high.
• Relapse is frequent and the most important factor driving relapse is medication nonadherence.
• There is often an overwhelming drive by patients and their families to stop treatment.
Recovery After Initial Schizophrenia Episode – Early Treatment Program

RAISE
A Research Project of the NIMH
Early Treatment Program
Quality of Life Scale Fitted Model
Group by time interaction ($P=.046$)

<table>
<thead>
<tr>
<th>Months</th>
<th>Community Care- Fitted</th>
<th>NAVIGATE - Fitted</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>12</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>18</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td>24</td>
<td>70</td>
<td>70</td>
</tr>
</tbody>
</table>

Cohen’s $d = 0.257$

Quality of Life Scale: Effects of Shorter vs Longer Duration of Untreated Psychosis (DUP; $P<.03$)

![Graph showing the relationship between months and QOLS total score for different care options and DUP categories.](image)

- **Community Care (Low DUP)**: ES=0.94
- **Community Care (High DUP)**: ES=0.51
- **Navigate (Low DUP)**: ES=0.51
- **Navigate (High DUP)**: ES=0.57

High DUP: DUP > 74 weeks

# How Long Should We Wait Before Considering an Antipsychotic Ineffective?


<table>
<thead>
<tr>
<th>Inadequate response to:</th>
<th>Minimum number of weeks to wait</th>
<th>Average (SD)</th>
<th>Maximum number of weeks to wait</th>
<th>Average (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Antipsychotic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Little or no response</td>
<td></td>
<td>2.6 (1.3)</td>
<td></td>
<td>5.5 (2.6)</td>
</tr>
<tr>
<td>Partial response</td>
<td></td>
<td>4.4 (1.7)</td>
<td></td>
<td>9.9 (5.1)</td>
</tr>
</tbody>
</table>
Time Course of Antipsychotic Effect: Psychotic Symptoms After Subtraction of Placebo Effect

Meta-analysis of 42 studies with 7450 patients

Early Treatment Responders Demonstrated Better Symptom Improvement than Early Non-Responders

- Early responders showed significantly more improvement on PANSS total score than early non-responders at all time points from Week 1 to Week 24
- Response was defined as ≥ 20% improvement in PANSS Total Score at 2 weeks
- Patients who don't achieve a minimal response after 2 weeks, go on to somewhat improve
  - Never end up doing as good as those who did experience at least minimal early response at 2 weeks

Results – Primary Outcome

Mean Change From Baseline in PANSS Total Score (*RIS Only Patients*)

- Early responders to RIS (n=144)
- Early nonresponders to RIS (n=192)

*P* < 0.001 at every post baseline time point

The Risk for Psychotic Relapse is High

<table>
<thead>
<tr>
<th>Year*</th>
<th>Relapse rate (%)</th>
<th>95% limit (%)</th>
<th>Number of patients still at risk at end of year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>1</td>
<td>16.2</td>
<td>8.9</td>
<td>23.4</td>
</tr>
<tr>
<td>2</td>
<td>53.7</td>
<td>43.4</td>
<td>64.0</td>
</tr>
<tr>
<td>3</td>
<td>63.1</td>
<td>52.7</td>
<td>73.4</td>
</tr>
<tr>
<td>4</td>
<td>74.7</td>
<td>64.2</td>
<td>85.2</td>
</tr>
<tr>
<td>5</td>
<td>81.9</td>
<td>70.6</td>
<td>93.2</td>
</tr>
</tbody>
</table>

n=104 first-episode schizophrenia patients
*Year(s) since previous episode

Stopping Medication is the Most Powerful Predictor of Relapse

Survival analysis: risk of a first or second relapse when not taking medication ~5 times greater than when taking it.

<table>
<thead>
<tr>
<th>Year</th>
<th>Cumulative Recovery Rate (%)</th>
<th>Lower 95% Limit</th>
<th>Upper 95% Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>9.7</td>
<td>3.7</td>
<td>15.8</td>
</tr>
<tr>
<td>4</td>
<td>12.3</td>
<td>5.4</td>
<td>19.1</td>
</tr>
<tr>
<td>5</td>
<td>13.7</td>
<td>6.4</td>
<td>20.9</td>
</tr>
</tbody>
</table>

Conclusions:
Based on the best available data, approximately, 1 in 7 individuals with schizophrenia met our criteria for recovery. Despite major changes in treatment options in recent decades, the proportion of recovered cases has not increased.
Is There a Case for Earlier Use of LAI Antipsychotics?

- The percentage of time spent experiencing psychotic symptoms in the first 2 years is the strongest predictor of long-term symptoms and disability.\(^1\)
- With subsequent exacerbations, patients may experience a decrease in their treatment response.\(^2\)
- Neuropathological brain changes often progress with subsequent clinical episodes.\(^3\)
- LAI antipsychotics allow for swift identification of covert nonadherence and elimination of covert nonadherence.\(^4\)

LAI = Long-acting injectable

Impact on Intracortical Myelination Trajectory of Long Acting Injection Versus Oral Risperidone in First-episode Schizophrenia

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 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.

Management of Treatment Resistant Patients

1. Reassess diagnosis, rule out medical or substance related condition
2. Identify comorbidities and optimize their management
3. Review nature and effectiveness of current and past treatments
4. Assess for side effects potentially contributing to refractoriness
5. Rule out potentially interfering drug-drug interactions
6. Check and address reasons for nonadherence
7. Optimize non-pharmacologic treatments
8. Continue treatment and wait for a potentially delayed response
9. Increase dose to symptom response / therapeutic level
10. Reduce antipsychotic dose to minimize side effects
11. Switch to agent of the same pharmacologic class
12. Switch to agent of a different pharmacologic class
13. Augment with agent of the same pharmacologic class
14. Augment with agent of a different pharmacologic class

Kane JM, Kishimoto T, Correll CU. UpToDate - in press.
Meta-analysis of 19 RCTs of Antipsychotic Combinations: Inefficacy as Defined by Study

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>AP + AP n/N</th>
<th>AP n/N</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anil Yagcioglu 2005</td>
<td>14/16</td>
<td>10/14</td>
<td>6.38 1.23 [0.84, 1.79]</td>
<td>6.18</td>
<td></td>
</tr>
<tr>
<td>Barrett 1957</td>
<td>3/10</td>
<td>5/10</td>
<td>2.67 0.60 [0.19, 1.86]</td>
<td>3.45</td>
<td></td>
</tr>
<tr>
<td>Barrett 1957a</td>
<td>3/10</td>
<td>7/10</td>
<td>2.27 0.43 [0.15, 1.20]</td>
<td>2.82</td>
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</tr>
<tr>
<td>Chien 1973</td>
<td>2/15</td>
<td>8/15</td>
<td>1.18 0.53 [0.11, 2.50]</td>
<td>1.06</td>
<td></td>
</tr>
<tr>
<td>Chien 1973a</td>
<td>2/15</td>
<td>4/16</td>
<td>1.18 0.53 [0.11, 2.50]</td>
<td>1.06</td>
<td></td>
</tr>
<tr>
<td>Honer 2006</td>
<td>33/34</td>
<td>31/35</td>
<td>8.51 1.10 [0.96, 1.25]</td>
<td>7.83</td>
<td></td>
</tr>
<tr>
<td>Liu 1996</td>
<td>10/31</td>
<td>19/29</td>
<td>4.67 0.49 [0.28, 0.87]</td>
<td>7.83</td>
<td></td>
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<tr>
<td>Liu 1996a</td>
<td>10/31</td>
<td>22/32</td>
<td>4.77 0.47 [0.27, 0.82]</td>
<td>7.83</td>
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<tr>
<td>Peng 2001</td>
<td>26/32</td>
<td>30/34</td>
<td>7.98 0.92 [0.75, 1.13]</td>
<td>7.83</td>
<td></td>
</tr>
<tr>
<td>Peng 2001a</td>
<td>26/32</td>
<td>30/34</td>
<td>7.98 0.92 [0.75, 1.13]</td>
<td>7.83</td>
<td></td>
</tr>
<tr>
<td>Talbot 1964</td>
<td>0/27</td>
<td>0/25</td>
<td>2.99 0.21 [0.09, 0.49]</td>
<td>1.48</td>
<td></td>
</tr>
<tr>
<td>Talbot 1964a</td>
<td>0/27</td>
<td>0/25</td>
<td>2.99 0.21 [0.09, 0.49]</td>
<td>1.48</td>
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<tr>
<td>Wang 1994</td>
<td>5/36</td>
<td>23/35</td>
<td>3.44 1.00 [0.47, 2.14]</td>
<td>3.91</td>
<td></td>
</tr>
<tr>
<td>Wang 1994a</td>
<td>5/36</td>
<td>18/34</td>
<td>4.73 0.83 [0.47, 1.47]</td>
<td>4.73</td>
<td></td>
</tr>
<tr>
<td>Xie 2001</td>
<td>8/20</td>
<td>8/20</td>
<td>4.28 0.94 [0.50, 1.77]</td>
<td>4.28</td>
<td></td>
</tr>
<tr>
<td>Zhang 1989</td>
<td>10/20</td>
<td>12/20</td>
<td>3.73 0.80 [0.60, 1.05]</td>
<td>3.73</td>
<td></td>
</tr>
<tr>
<td>Zhang 1989a</td>
<td>10/20</td>
<td>9/17</td>
<td>4.28 0.94 [0.50, 1.77]</td>
<td>4.28</td>
<td></td>
</tr>
<tr>
<td>Yagi 1976</td>
<td>103/116</td>
<td>93/117</td>
<td>5.11 0.55 [0.32, 0.92]</td>
<td>5.11</td>
<td></td>
</tr>
<tr>
<td>Shiloh 1997</td>
<td>8/16</td>
<td>11/12</td>
<td>6.63 0.72 [0.51, 1.03]</td>
<td>6.63</td>
<td></td>
</tr>
<tr>
<td>Josiassen 2005</td>
<td>13/20</td>
<td>18/20</td>
<td>6.95 0.89 [0.64, 1.22]</td>
<td>6.95</td>
<td></td>
</tr>
<tr>
<td>Freudenreich 2007</td>
<td>9/11</td>
<td>12/13</td>
<td>6.95 0.89 [0.64, 1.22]</td>
<td>6.95</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>604</td>
<td>598</td>
<td>100.00 0.76 [0.63, 0.90]</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 320 (AP + AP), 396 (AP)
Test for heterogeneity: Chi² = 89.85, df = 19 (P < 0.00001), I² = 78.9%
Test for overall effect: Z = 3.05 (P = 0.002)

N=22, n=1202, RR: 0.76, 95% CI: 0.63-0.90, P=.002, NNT: 7, CI: 4-17, P=.0008

Figure used with permission. Correll CU, et al. Schizophr Bull. 2009;35(2):443-457.
# Guidelines Regarding Clozapine

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Basic Use</th>
<th>Specific Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>American Psychiatry Association (APA)</strong></td>
<td>• Persistent psychotic symptoms after 2 AP trials</td>
<td>• Persistent hostility, aggressive behavior</td>
</tr>
<tr>
<td></td>
<td>– “should be given strong consideration”</td>
<td>• Persistent SI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• TD</td>
</tr>
<tr>
<td><strong>Schizophrenia Patient Outcomes Research Team</strong></td>
<td>• Persistent and clinically significant positive Sx after &gt;2 AP trials</td>
<td>• Persistent hostility/ violent behaviors</td>
</tr>
<tr>
<td><strong>(PORT)</strong></td>
<td>(including &gt;1 SGA)</td>
<td>– “should be used”</td>
</tr>
<tr>
<td></td>
<td>– “should be used”</td>
<td>• Marked and persistent SI/ behaviors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– “should be offered”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• NMS, persistent dystonia/severe or very distressing TD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– “should be offered”</td>
</tr>
<tr>
<td><strong>Texas Medication Algorithm Project (TMAP)</strong></td>
<td>• No-response or partial response to 2 AP trials (including ≥1 SGA)</td>
<td>• History of recurrent suicidality, violence or comorbid substance abuse –”consider earlier trial”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Persistent positive Sx &gt;2 years –”warrants”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Persistent positive Sx &gt;5 years –”requires” clozapine trial independent of # of AP trials</td>
</tr>
<tr>
<td><strong>Canadian Psychiatric Association</strong></td>
<td>• No-response to AP trials from 2 classes</td>
<td>• Persistent SI/ behaviors –”should be considered”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Persistent aggressivity –”may be helped by”</td>
</tr>
<tr>
<td><strong>National Institute for Health and Clinical Excellence (NICE)</strong></td>
<td>• Sequential use of ≥2 APs (including ≥1 SGA)</td>
<td></td>
</tr>
</tbody>
</table>

AP=antipsychotic, NMS=neuroleptic malignant syndrome, SI=suicidal ideation, Sx=symptoms, TD=tardive dyskinesia
Clozapine Prescription Rate for Schizophrenia -International Comparison-

Data were obtained from several studies and the settings can vary from study to study.
Kishimoto et al. In preparation

High Probability of Failed Trials: Schizophrenia and Psychosis Trials

Falling Success Rate of Schizophrenia Trials
N. America and Multiregional 1991-2008

- 74% (14 of 19) in 1999–2008

Increasing Placebo Response
Schizophrenia Clinical Trials 1993–2008

Correlates with time study was done


2 Kemp AS, et al. *Schizophr Bull*. 2008;36(3):504-509. Figure used with permission.
Positive and Negative Syndrome Scale total score results (mean change from baseline of two Phase 2 studies for LY2140023 monohydrate in schizophrenia showing incongruent placebo response between the 2 trials

• A comparison of the results of the two Phase 2 studies of LY2140023 monohydrate in schizophrenia (double-blind treatment phases only).
  • In the earlier study, placebo-treated patients as a group worsened over time.
  • In the later study, the placebo group showed symptom improvement similar to active treatment groups.
## Novel Agents: Monoamine Mechanisms

<table>
<thead>
<tr>
<th>Neurotransmitter/Mechanism (main or additional)</th>
<th>Established Agent (emerging agent)</th>
<th>Target Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine D1 Agonism</td>
<td>(Dihydrexidine)</td>
<td>Cognition</td>
</tr>
<tr>
<td>Dopamine D2 Antagonism</td>
<td>FGA, SGA [except for Aripiprazole, (Cariprazine, Brexpiprazole)]</td>
<td>Psychosis, Aggression/Agitation, Tics, OCD</td>
</tr>
<tr>
<td>Dopamine D2 Partial Agonism</td>
<td>Aripiprazole, (Cariprazine, Brexpiprazole)</td>
<td>Psychosis, Aggression/Agitation, Tics, OCD, Depression</td>
</tr>
<tr>
<td>Dopamine D3 Antagonism</td>
<td>(ABT-925)</td>
<td>Psychosis</td>
</tr>
<tr>
<td>Dopamine D3 Partial Antagonism</td>
<td>(Cariprazine)</td>
<td>Psychosis</td>
</tr>
<tr>
<td>5HT 1A Partial Agonism</td>
<td>Aripiprazole, Lurasidone, Ziprasidone (Brexipiprazole; Caripiprazine, SLV-313, SSR-181507, F-15063, S-16924)</td>
<td>Psychosis, Depression, Anxiety</td>
</tr>
</tbody>
</table>

# Novel Agents: Monoamine Mechanisms

<table>
<thead>
<tr>
<th>Neurotransmitter/ Mechanism (main or additional)</th>
<th>Established Agent (emerging agent)</th>
<th>Target Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>5HT 2a Antagonism</td>
<td>SGAs, except Amisulpride (Cariprazine, Pimavanserin)</td>
<td>Psychosis, Anti-extrapyramidal side effects</td>
</tr>
<tr>
<td>5HT 2c Agonism</td>
<td>(Vabicaserin (CP-809 101, WAY-163909))</td>
<td>Psychosis, Anti-weight gain</td>
</tr>
<tr>
<td>5HT 6 Antagonism</td>
<td>Asenapine</td>
<td>Depression</td>
</tr>
<tr>
<td>5HT 7 Antagonism</td>
<td>Lurasidone</td>
<td>Depression</td>
</tr>
<tr>
<td>SSRI</td>
<td>Quetiapine (Brexpiprazole)</td>
<td>Depression, Anxiety</td>
</tr>
<tr>
<td>Alpha 2 Blockade</td>
<td>Clozapine, Quetiapine</td>
<td>Depression</td>
</tr>
<tr>
<td>Metabotropic (m)Glutamate Receptor 2/3 Agonism</td>
<td>(mGLu2/3R agonist: pomaglumetad (LY2140023))</td>
<td>Positive and Negative Symptoms</td>
</tr>
<tr>
<td>Metabotropic (m)Glutamate Receptor PAM</td>
<td>(ADX71149)</td>
<td>Positive and Negative Symptoms</td>
</tr>
</tbody>
</table>

### Novel Agents: Monoamine Mechanisms

<table>
<thead>
<tr>
<th>Neurotransmitter/Mechanism (main or additional)</th>
<th>Established Agent (emerging agent)</th>
<th>Target Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMDA Receptor Agonism</td>
<td>GLYT 1 Inhibitor (Bitopertin)</td>
<td>Negative Symptoms, Cognition</td>
</tr>
<tr>
<td>D-amino acid oxidase inhibition</td>
<td>(RG1678)</td>
<td>Negative Symptoms</td>
</tr>
<tr>
<td>GABA ester of perphenazine</td>
<td>(BL-1020)</td>
<td>Cognition</td>
</tr>
<tr>
<td>M1/M4 (mAChR) Agonism</td>
<td>(Xanomeline)</td>
<td>Cognition</td>
</tr>
<tr>
<td>Alpha 7 nAChR Agonism</td>
<td>(Anabaseine, EVP-6124)</td>
<td>Negative Symptoms</td>
</tr>
<tr>
<td>Alpha 4 beta 2 nAChR Agonism</td>
<td>(Varenenecline)</td>
<td>Negative Symptoms</td>
</tr>
<tr>
<td>Histamine-3 Receptor Antagonism</td>
<td>(MK-0249, pitolisant, bavisant)</td>
<td>Cognition, Negative Symptoms</td>
</tr>
<tr>
<td>PDE 10A Antagonism</td>
<td>(MP-10)</td>
<td>Cognition, Negative Symptoms</td>
</tr>
<tr>
<td>Neurokinine 3 Antagonism</td>
<td>(Osanetant, Talnetant, AZD2624)</td>
<td>Psychosis</td>
</tr>
</tbody>
</table>

Conclusions

• Health care in the future will be heavily influenced by:
  – Genomics
  – Biomics
  – Neuroimaging
  – Technology
  – Stratification strategies
  – Consumerism
  – Cost containment
Conclusions

• Early and effective intervention is key for achieving the best outcomes in schizophrenia.
• Nonadherence remains a major challenge and is a frequent cause of relapse and re-hospitalization.
• Recovery rates remain disappointingly low.
• Different symptom domains require attention.
• A combination of pharmacotherapy and psychosocial treatments are critical to facilitate recovery.
SCHIZOPHRENIA
& SCHIZOAFFECTIVE DISORDER
Utilizing Tools to Optimize Outcomes Across the Spectrum of Acute to Maintenance Treatment

Friday, April 17, 2015

Activity Chair
Leslie L. Citrome, MD, MPH