Saturday, August 9, 2014
Philadelphia, PA

COURSE CHAIR
Henry A. Nasrallah, MD
SCHIZOPHRENIA: Clinical and Neurobiological Advances

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Learning Objectives

• Review the genetic and nongenetic factors in schizophrenia
• Recognize the brain structural and functional MRI changes associated with schizophrenia
• Discuss the neuroinflammation and oxidative stress that occur during psychotic episodes
• Review the development of biomarkers in the schizophrenia syndrome that may be used in the future as lab tests for its various biological subtypes
Neuropsychiatric Features of Schizophrenia
Features of Schizophrenia

Positive Symptoms
- Delusions
- Hallucinations
- Disorganized speech
- Catatonia

Negative Symptoms
- Flat/blunted affect
- Alogia
- Avolition, apathy
- Anhedonia
- Social withdrawal

Cognitive Deficits
- Attention
- Verbal & Working Memory
- Executive functions
- Learning
- Processing speed

Mood Symptoms
- Depression
- Hopelessness
- Suicidality
- Anxiety
- Agitation
- Hostility

Social/Occupational Dysfunction
- Work
- Interpersonal relationships
- Self-care

Comorbid Substance Abuse

Neurocognitive Impairment in Schizophrenia
Cognitive Deficits in First-Episode Schizophrenia

Neuropsychological Performance in Schizophrenia

Z Score

The Relationship Between Schizophrenia and Frontotemporal Dementia

Joseph J. Cooper, MD¹, and Fred Ovsiew, MD²

Abstract

Schizophrenia is a relatively common disorder diagnosed by the presentation of psychotic symptoms in the absence of identifiable neurologic or other organic causes. Frontotemporal dementia (FTD) is a relatively rare progressive neurodegenerative disorder that can present with a multitude of cognitive and behavioral symptoms including psychosis. At times, this phenotypic overlap can mean that schizophrenia and FTD are 2 possibilities in the differential diagnosis of a psychotic presentation. In this article, we systematically review the literature on the relationship between schizophrenia and FTD including case reports that highlight the potential for diagnostic confusion, clinical studies examining the relationship between the disorders, and the molecular evidence of shared pathophysiologic mechanisms. Although a relationship between the disorders is not definitively supported by the current literature, we identify the characteristics of a psychotic presentation that should alert the clinician to the possibility of FTD and describe the areas where further research is needed to clarify the pathophysiologic relationship.

Keywords

schizophrenia, frontotemporal dementia, psychosis, dementia
Recent Advances in the Neurobiology of Schizophrenia
Neurogenetics of Schizophrenia
Lifetime Risk of Developing Schizophrenia

- General population
- Spouses of patient
- First cousins (third degree)
- Uncles, aunts
- Nephews, nieces
- Grandchildren
- Half siblings
- Children
- Siblings
- Siblings with one schizophrenic parent
- Dizygotic twins
- Parents
- Monozygotic twins
- Offspring of dual matings

Pennisi E. Science 2012; 337: 1159-1160
Genes and Brain Development

- There are about 20,000 genes on the 23 chromosome pairs in humans
- 50% of all the human genes (10,000 genes) are dedicated to brain development or are expressed only in the brain
- The rest of the body (about 200 types of tissue) share the other 10,000 genes

Personal communication
Neurogenetics of Schizophrenia

Risk genes
Copy number variations
Mutations
Epigenetics

The Schizophrenia Syndrome

## Risk Genes for Schizophrenia: The Majority Are Related to Glutamate Pathways

### Genes for:

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein/Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysbindin (dystrobrevin binding protein 1 or DTNBP1)</td>
<td>ERBB4</td>
</tr>
<tr>
<td>Neuregulin (NRG1)</td>
<td>FEZ1</td>
</tr>
<tr>
<td>DISC1 (disrupted in schizophrenia 1)</td>
<td>MUTED</td>
</tr>
<tr>
<td>DAOA (d-amino acid oxidase activator; G72/G30)</td>
<td>MRDS1 (OFCC1)</td>
</tr>
<tr>
<td>DAO (d-amino acid oxidase)</td>
<td>BDNF (brain-derived neurotrophic factor)</td>
</tr>
<tr>
<td>RGS4 (regulator of G protein signaling 4)</td>
<td>Nur77</td>
</tr>
<tr>
<td>COMT (Catechol-O-methyl transferase)</td>
<td>MAO-A (monoamine oxidase A)</td>
</tr>
<tr>
<td>CHRNA7 (alpha-7-nicotinic cholinergic receptor)</td>
<td>Spinophilin</td>
</tr>
<tr>
<td>GAD1 (glutamic acid decarboxylase 1)</td>
<td>Calcyon</td>
</tr>
<tr>
<td>GRM3 (mGluR3)</td>
<td>Tyrosine hydroxylase</td>
</tr>
<tr>
<td>PPP3CC</td>
<td>Dopamine-D2 receptor (D2R)</td>
</tr>
<tr>
<td>PRODH2</td>
<td>Dopamine-D3 receptor (D3R)</td>
</tr>
<tr>
<td>AKT1</td>
<td></td>
</tr>
</tbody>
</table>

Nasrallah HA; The Neurology of Schizophrenia, edited by HA Nasrallah and DR Weinberger, Elsevier, 1986
Can EPIGENETICS Help Prevent Schizophrenia?

- **SILENCING** culprit genes
- **or**
- **EXPRESSING** protective genes
When DNA is coiled tightly around the histones, the genes within it tend to be inaccessible and silent.
Nongenetic (Environmental) Factors Associated With the Schizophrenia Syndrome

The Schizophrenia Syndrome

- Childhood trauma
- Paternal age >45 years
- Migration
- Urbanicity
- Pregnancy and delivery complications
- NMDA antibodies
- Winter birth (vitamin D deficiency)

SCHIZOPHRENIA IS ASSOCIATED WITH MANY GENETIC AND ENVIRONMENTAL FACTORS.

THUS, SCHIZOPHRENIA IS A VERY HETEROGENEOUS SYNDROME!
Neuroimaging Findings in the Schizophrenia Syndrome

- **Structural changes MRI**
  - Numerous hypoplastic regions, especially frontal, temporal, and limbic cortices

- **Neurochemical changes on MRS**
  - Abnormalities in NAA using proton spectroscopy and in high-energy phosphates (ADP, ATP) using 31p spectroscopy

- **Aberrations in brain activity on fMRI**
  - Especially low frontal blood flow

- **White matter changes on DTI**
  - Abnormalities in myelin integrity in white matter tracts, leading to widespread disconnection both intra- and interhemispheric. The initial pathology is brain edema (swelling) due to excessive extracellular water in both white and gray matter, detected with free-water imaging. This triggers a neuroinflammatory response.

Impaired Neuroplasticity in the Schizophrenia Syndrome

- Several perturbations of neuroplasticity in schizophrenia
  - Increased apoptosis (cell death)
  - Decreased neurogenesis (in the hippocampus and SVZ)
  - Low neurotropic factors (NGF, BDNF, etc)
- The risk genes of schizophrenia are involved in regulating neuroplasticity.
  - DISC-1
  - Neuregulin/ErbB4
  - Dysbindin
  - AKt
- Impaired neuroplasticity disrupts neuronal development, neurotransmission, and signaling pathways, especially of the key neurotransmitters glutamate and GABA.

Progressive MRI Changes After Multiple Psychotic Relapses in a Man With Schizophrenia Over Several Years

The Deteriorating Course, Brain Tissue Loss, and Treatment Resistance with Repetitive Relapses Following the First Episode in Schizophrenia

Level of Functioning

Premorbid
Prodrome
First episode
Nonadherence following response
Chronic relapsing/Residual symptoms
Progressive brain tissue loss
Treatment Resistance

Age (years)

First Episode  Second Episode  Third Episode  Fourth Episode
Brain Volume Changes in First-episode Schizophrenia: A 1-year Follow-up Study

- First-episode schizophrenia (n=34) and matched healthy controls (n=36)
- MRI obtained at inclusion and after 1 year
- Outcome measured at 2 years
- Total brain volume and cerebral gray volume significantly decreased and lateral ventricle volume significantly increased in patients compared with controls
- Decrease in global gray matter volume significantly correlated with outcome and, independent of that, with higher cumulative dosage of antipsychotic medication

MRI, magnetic resonance imaging

Gray Matter Loss and Marijuana Use

Rate of Gray Matter Loss in Schizophrenia and Control Subjects

Normal Adolescents  Subjects With Schizophrenia

BOYS

GIRLS

Average Annual Loss

0%
1%
2%
3%
4%
5%


Slide courtesy of Martha Shenton, PhD
Original Article

White matter abnormalities in bipolar disorder and schizophrenia detected using diffusion tensor magnetic resonance imaging

Susamann JE, Lymer GKS, McKirdy J, Moorhead TWJ, Muñoz Maniega S, Job D, Hall J, Bastin ME, Johnstone EC, Lawrie SM, McIntosh AM. White matter abnormalities in bipolar disorder and schizophrenia detected using diffusion tensor magnetic resonance imaging.

Bipolar Disord 2009; 11: 11-18. © 2009 The Authors Journal compilation © 2009 Blackwell Munksgaard

Objectives: Strong qualitative and quantitative evidence exists of white matter abnormalities in both schizophrenia and bipolar disorder (BD). Diffusion tensor imaging (DTI) studies suggest altered connectivity in both disorders. We aim to address the diagnostic specificity of white matter abnormalities in these disorders.

Methods: DTI was used to assess white matter integrity in clinically stable patients with familial BD (n = 42) and familial schizophrenia (n = 28), and in controls (n = 38). Differences in fractional anisotropy (FA) were measured using voxel-based morphometry and automated region of interest analysis.

Results: Reduced FA was found in the anterior limb of the internal capsule (ALIC), anterior thalamic radiation (ATR), and in the region of the uncinate fasciculus in patients with BD and those with schizophrenia compared with controls. A direct comparison between patient groups found no significant differences in these regions. None of the findings were associated with psychotropic medication.

Conclusions: Reduced integrity of the ALIC, uncinate fasciculus, and ATR regions is common to both schizophrenia and BD. These results imply an overlap in white matter pathology, possibly relating to risk factors common to both disorders.
Mechanisms of disease

Oligodendrocyte dysfunction in schizophrenia and bipolar disorder

Dmitri Tkachev, Michael L Mimmack, Margaret M Ryan, Matt Wayland, Tom Freeman, Peter B Jones, Michael Starkey, Maree J Webster, Robert H Yolken, Sabine Bahn

Summary
Background Results of array studies have suggested abnormalities in expression of lipid and myelin-related genes in schizophrenia. Here, we investigated oligodendrocyte-specific and myelination-associated gene expression in schizophrenia and bipolar affective disorder.

Methods We used samples from the Stanley brain collection, consisting of 15 schizophrenia, 15 bipolar affective disorder, and 15 control brains. Indexing-based differential display PCR was done to screen for differences in gene expression in schizophrenia patients versus controls. Results were cross-validated with quantitative PCR, which was also used to investigate expression profiles of 16 other oligodendrocyte and myelin genes in schizophrenia and bipolar disorder. These genes were further investigated with an ongoing microarray analysis.

Findings Results of differential display and quantitative PCR analysis showed a reduction of key oligodendrocyte-related and myelin-related genes in schizophrenia and bipolar patients; expression changes for both disorders showed a high degree of overlap. Microarray results of the same genes investigated by quantitative PCR correlated well overall.

Interpretation Schizophrenia and bipolar brains showed downregulation of key oligodendrocyte and myelination genes, including transcription factors that regulate these genes, compared with control brains. These results lend support to and extend observations from other microarray investigations. Our study also showed similar expression changes to the schizophrenia group in bipolar brains, which thus lends support to the notion that the disorders share common causative and pathophysiological pathways.

Lancet 2003; 362: 798–805
White Matter Tractography From 3T Magnet

Oxidative Stress

- Oxidative stress is defined as an imbalance between toxic reactive species or ROS (free radicals) and antioxidant systems.
- It is relevant to the pathophysiology of schizophrenia.
- Free radicals are counteracted by several cytoprotective antioxidant enzymes that limit their damage, such as:
  - Superoxide dismutase
  - Glutathione peroxide

Oxidative Stress (cont’d)

• Oxidative stress markers in schizophrenia studies include: SOD, GPX, MDA, TBARS, CAT, TAOP, TpERoX, 4-HNE, TRY.

• Mitochondria dysfunction has been reported in schizophrenia and may account for the low levels of the powerful antioxidant glutathione

• Atypical antipsychotics have been reported to normalize the abnormal free-radical metabolism, but the first-generation antipsychotics like haloperidol increase oxidative stress.

Neuroinflammation

• There are many lines of evidence for immune dysregulation and neuroinflammation in schizophrenia.
• Microglia activation by various mechanisms directly contribute to neuronal degeneration by producing proinflammatory cytokines and free radicals, inhibition of neurogenesis, and toxicity to white matter.
• Elevated inflammatory cytokines in schizophrenia (TNF-α, 1FN-γ, IL-6). Microglia are the primary reservoirs of proinflammatory cytokines, which act as antigens in the CNS and play a major role in innate immunity.

Some antipsychotic drugs (second generation) reduce inflammation and oxidative stress while others (first generation) increase inflammation and oxidative stress.

Adding anti-inflammatory agents to antipsychotic drugs potentiates response, eg, minocycline, Cox-2 inhibitors, omega-3 fatty acids. ESPECIALLY in first episode!

Meta-analysis Suggests NSAID Augmentation May Improve Symptom Severity in Schizophrenia

<table>
<thead>
<tr>
<th>Study</th>
<th>Hedges g</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
<th>P Value</th>
<th>Hedges g &amp; 95% CI</th>
<th>NSAID, mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Müller et al, 2002</td>
<td>0.54</td>
<td>-0.01</td>
<td>1.10</td>
<td>0.06</td>
<td></td>
<td>Celecoxib, 400</td>
</tr>
<tr>
<td>Rapaport et al, 2005</td>
<td>-0.34</td>
<td>-0.99</td>
<td>0.31</td>
<td>0.31</td>
<td></td>
<td>Celecoxib, 400</td>
</tr>
<tr>
<td>Akhoundzadeh et al, 2007</td>
<td>0.93</td>
<td>0.41</td>
<td>1.46</td>
<td>0.00</td>
<td></td>
<td>Celecoxib, 400</td>
</tr>
<tr>
<td>Müller et al, 2010</td>
<td>0.52</td>
<td>-0.03</td>
<td>1.08</td>
<td>0.06</td>
<td></td>
<td>Celecoxib, 400</td>
</tr>
<tr>
<td>Laan et al, 2010</td>
<td>0.37</td>
<td>-0.10</td>
<td>0.83</td>
<td>0.13</td>
<td></td>
<td>Asprin, 1,000</td>
</tr>
<tr>
<td>Overall</td>
<td>0.43</td>
<td>0.06</td>
<td>0.80</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adjunctive Nonsteroidal Anti-inflammatory Drugs (NSAIDs) in Schizophrenia

Inpatients with acute psychosis
Akhondzadeh et al. (2007)

Chromically ill, but stable
Rapaport et al. (2005)

Also, subjects with higher levels of inflammatory parameters may be more likely to respond to adjunctive NSAIDs.

Long-chain Omega-3 Fatty Acids May Prevent Progression to Psychosis

Genetic Risk Factors

- Oxidative stress
- Altered myelination
- Synaptic dysfunction

Environmental Risk Factors

- Chronic inflammation
- Altered glucose metabolism
- Abnormal plasticity

→ Abnormal maturation of brain circuits

→ Disconnectivity

→ Abnormal neural coordination
WHAT COMPONENTS OF BRAIN TISSUE ARE LOST IN SCHIZOPHRENIA DURING PSYCHOTIC RELAPSES??

THE NEUROPIIL!
Brain Tissue Atrophy in Schizophrenia:
Mostly in the Neuropil

↓ Dendrite length by 50%
↓ In the number and size of dendritic spines
↓ In the size (contraction) of neurite extension
↓ In # of glial cells

Brightfield Photomicrographs Illustrating Golgi-impregnated Basilar Dendrites and Spines on Dorsolateral Prefrontal Cortex Layer 3 Pyramidal Neurons from Normal Control Subject 390 (A) and 2 Subjects with Schizophrenia (Subjects 410 [B] and 466 [C])

<table>
<thead>
<tr>
<th>Decline in Neurotropic Factors in Schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ in neurotrophin 3 (NT-3)</td>
</tr>
<tr>
<td>↓ nerve growth factor (NGF)</td>
</tr>
<tr>
<td>↓ brain-derived growth factor (BDNF)</td>
</tr>
</tbody>
</table>

Biomarkers of Schizophrenia

• Contrary to the belief that there are no lab tests or biomarkers for schizophrenia, there are more than 365 biomarkers for this syndrome, 273 of which are identifiable in plasma.
• 81 are diagnostic, 77 are markers of drug response, and 115 are for both.
• These biomarkers are associated with the “various biological subtypes” of schizophrenia and thus cannot be used to diagnose the syndrome.
• The Stanley Foundation postmortem studies of the brain in schizophrenia have identified more than 2,000 tissue biomarkers.

Examples of Serum Biomarkers of the Schizophrenia Syndrome

- BDNF: brain derived neurotropic factor
- CD5L: CD5-like molecule
- CTGF: connective tissue growth factor
- EGFR: epidermal growth factor receptor
- FSH: follicle-stimulating hormone
- ICAM1: intercellular adhesion molecule1
- IL-6: interleukin 6
- IL-7: interleukin 7 (same for 10, 11, 17)
- KIM-1: kidney injury molecule-1
- MCP-2: monocyte chemotactic protein
- MDC: mature dendritic cell
- MIF: macrophage migration inhibiting factor
- MI-1α: macrophage inflammatory protein 1α
- MMP-2: matrix metalloproteinase 2
- PYY: peptide YY
- TNFR2: tumor necrosis factor receptor 2

Summary

- Schizophrenia is a heterogeneous brain syndrome, not 1 disease
- There are several genetic pathways to schizophrenia such as risk genes, copy number variations and de novo mutations
- Many environmental factors are associated with the risk for schizophrenia, most of them during fetal life, disrupting neurodevelopment
- Several neuroimaging techniques reveal multiple structural and functional abnormalities in schizophrenia
- Neuroinflammation, oxidative and nitrosative stress appear to play a role in brain tissue loss during psychotic episodes
- The apoptosis in schizophrenia is mainly in the neuropil, involving dendritic length and spines, neurite extension and glial cells
Treatment of Schizophrenia: Current Strategies and Future Paradigm Shifts

Peter J. Weiden, MD
Professor of Psychiatry
University of Illinois Medical Center
Chicago, Illinois
Advances in Psychopharmacology of Schizophrenia

- New information on “old” therapies
- Most recently approved oral antipsychotics
- Recently approved long-acting formulations
- Treatment selection
- In the pipeline
Achieving Stability: PORT 2009 Evidence-based Interventions

- Select antipsychotic based on individual factors related to tolerability and past history
- Olanzapine and clozapine not recommended for “first-episode” patients
- Stay within recommended therapeutic dose range

Port Schizophrenia 2009
Antipsychotic Doses

- Older medications still accepted as first-line therapy
- Maintenance doses lower than acute doses
- Newer medications cannot be classified in dose equivalent
- Cannot use same dose-response across newer medications
Relapse Prevention: PORT 2009 Pharmacologic Interventions

• Avoiding medication gaps
  – “those who experience acute and sustained symptom relief should be offered continued antipsychotic treatment [to] maintain symptom relief and to reduce risk of relapse or worsening of positive symptoms”
  – Targeted, intermittent antipsychotic maintenance strategies should not be used routinely…due to increased risk of symptom worsening and relapse

Evolution of Pharmacologic Treatments of Schizophrenia


ECT  Reserpine  Chlorpromazine  Thioridazine  Loxapine  Haloperidol  Fluphenazine  Perphenazine  Clozapine  Risperidone  Olanzapine  Quetiapine  Ziprasidone  Aripiprazole  Asenapine  Illoperidone  Lurasidone

First Generation Antipsychotics  Second Generation Antipsychotics
<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation (Approval)</th>
<th>Dose Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole (Abilify)</td>
<td>Oral (2002)</td>
<td>10-30 mg/day</td>
</tr>
<tr>
<td>Aripiprazole Monohydrate</td>
<td>Long-acting IM (2013)</td>
<td>300 to 400 mg per month</td>
</tr>
<tr>
<td>Olanzapine (Zyprexa)</td>
<td>Oral (1996)</td>
<td>10-20 mg/day; higher doses are often used if treatment refractory</td>
</tr>
<tr>
<td>Olanzapine (Zyprexa Relprevv)</td>
<td>Long-acting IM (2009)</td>
<td>150-300 mg IM every 2 weeks</td>
</tr>
<tr>
<td>Quetiapine (Seroquel, Seroquel XR)</td>
<td>Oral (1997, 2007)</td>
<td>150-800 mg/day; higher doses are often used if treatment refractory</td>
</tr>
<tr>
<td>Risperidone (Risperdal)</td>
<td>Oral (1993)</td>
<td>4-16 mg/day</td>
</tr>
<tr>
<td>Risperidone (Risperdal Consta)</td>
<td>Long-acting IM (2003)</td>
<td>25, 37.5, or 50 mg IM every 2 weeks</td>
</tr>
<tr>
<td>Ziprasidone (Geodon)</td>
<td>Oral (2001)</td>
<td>80-160 mg/day</td>
</tr>
<tr>
<td>Clozapine (Clozaril)</td>
<td>Oral (1989)</td>
<td>300-900 mg/day</td>
</tr>
<tr>
<td>Paliperidone (Invega)</td>
<td>Oral (2006)</td>
<td>6-12 mg/day</td>
</tr>
<tr>
<td>Paliperidone (Invega Sustenna)</td>
<td>Long-acting IM (2009)</td>
<td>117 to 234 mg per month</td>
</tr>
<tr>
<td>Asenapine (Saphris)</td>
<td>Oral – sublingual (2009)</td>
<td>5-10 mg twice daily</td>
</tr>
<tr>
<td>Iloperidone (iloperidone)</td>
<td>Oral (2009)</td>
<td>6-12 mg twice daily</td>
</tr>
<tr>
<td>Lurasidone (Latuda)</td>
<td>Oral (2010)</td>
<td>40-160 mg once daily</td>
</tr>
</tbody>
</table>

Advances in Psychopharmacology of Schizophrenia

• New information on “old” therapies
• Most recently approved oral antipsychotics
• Recently approved long-acting formulations
• Treatment selection
• In the pipeline
Recent Approvals of Oral Antipsychotics

• Asenapine (Saphris)
  – Approved and available in late 2009
• Iloperidone (Fanapt)
  – Approved in 2009 and available 2010
• Lurasidone (Latuda)
  – Approved late 2010 and available in early 2012
<table>
<thead>
<tr>
<th><strong>Asenapine (Saphris)</strong></th>
<th><strong>Iloperidone (Fanapt)</strong></th>
<th><strong>Lurasidone (Latuda)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indications</strong></td>
<td>Adults with schizophrenia + bipolar</td>
<td>Adults with schizophrenia</td>
</tr>
<tr>
<td><strong>Comparable in efficacy trials</strong></td>
<td>~ risperidone, haloperidol</td>
<td>~ risperidone, haloperidol, ziprasidone</td>
</tr>
<tr>
<td><strong>Tablet strengths</strong></td>
<td>5mg and 10mg in a clamshell package for sublingual</td>
<td>1mg, 2mg, 4mg, 6mg, 8mg, 10mg and 12mg strengths</td>
</tr>
<tr>
<td><strong>Starting dose</strong></td>
<td>Label is 5mg twice a day but most clinicians start just at bedtime</td>
<td>1mg twice a day with up-titration to 12mg within 4 days but many clinicians will do a slower up-titration and just at bedtime</td>
</tr>
<tr>
<td><strong>Target dose</strong></td>
<td>5-10mg twice a day (10-20 total daily dose)</td>
<td>12-24mg/day (total daily dose). Lower target dose if patient on a CYP2D6 or CYP3A4 inhibitor</td>
</tr>
<tr>
<td><strong>Dose-response characteristics</strong></td>
<td>Unknown; suggestion that lower dose range (e.g. 5mg twice a day) is preferable for acute treatment of schizophrenia</td>
<td>Robust dosage efficacy within the lower doses (e.g. between 8 and 16mg/day total daily dose). Dose-response at higher end of dose range not well characterized</td>
</tr>
<tr>
<td><strong>Problems</strong></td>
<td>Sublingual Bad taste Rapidly sedation Some akathisia and weight gain</td>
<td>Significant orthostatic hypotension Needs up-titration tp get therapeutic QTc labeling</td>
</tr>
<tr>
<td><strong>Possible advantage(s)</strong></td>
<td>Bypass GI absorption Need to get to therapeutic dose right away Need for rapid sedation When there is a strong CYP3A4 inducer like carbamazepine (Tegretol)</td>
<td>Best in class for EPS and akathisia without the sedation or dyslipidemia associated with quetiapine</td>
</tr>
</tbody>
</table>
Advances in Psychopharmacology of Schizophrenia

• New information on “old” therapies
• Most recently approved oral antipsychotics
• Recently approved long-acting formulations
• Treatment selection
• In the pipeline
Development of Long-Acting Treatments for Schizophrenia*


First Generation Antipsychotics
- Fluphenazine Enanthate
- Fluphenazine Decanoate

Second Generation LAI Antipsychotics
- Haloperidol Decanoate
- Risperidone LAI
- Aripiprazole LAI
- Paliperidone LAI
- Olanzapine LAI

*Approved for use in U.S. by FDA
Olanzapine Pamoate

- Olanzapine pamoate monohydrate
- Practically insoluble in water
- Pamoic acid not pharmacologically active
- Crystalline pamoate salt formulation that slowly dissolves into olanzapine (base) and pamoic acid at the injection site

Olanzapine Pamoate: Post-injection Delirium/Sedation Syndrome

- Dizziness, confusion, disorientation, extreme sedation/reduced consciousness
  - Incidence rate per injection = 0.07%
  - Incidence rate per patient = 1.4%
  - Approximately 1 event per 1,400 injections
- Clinicians reluctant to use
- ? Preceding clozapine

Meyer, JM. *CNS Spectrums*. 2013;18:55-68
Paliperidone Palmitate Formulation and Mechanism of Action

- Paliperidone palmitate is a palmitate ester of paliperidone

- The palmitate ester of paliperidone is nearly insoluble
- Uses technology to create an aqueous suspension for IM administration
- After IM injection, paliperidone palmitate slowly dissolves at the injection site

Long-acting Paliperidone Palmitate in Maintenance Phase

Kaplan–Meier plot of time to recurrence – final analysis

The hazard ratio (placebo/long-acting paliperidone palmitate was 3.60 (95% CI: 2.45, 5.28)

Paliperidone Palmitate Injectable 3 Month Formulation FDA Trial

- Phase III randomized, double-blinded trial, 509 patients with schizophrenia
- Paliperidone palmitate vs. Placebo injection
- Patients initially stabilized on once monthly paliperidone injectable and then switched to the 3-month formulation
- Trial halted early by IDMC due to significant efficacy in delaying time to relapse
Clinical Pearls: Paliperidone Palmitate

• Efficacy established for acute phase of illness without oral supplementation

• Relative ease of use
  – Monthly injection
  – No refrigeration requirement
  – Small injection volumes (all doses 1 mL or less, except for 234 mg {1.5 mL})

• Lower potential for drug-drug interactions due to renal excretion
Aripiprazole Long-Acting Injectable

- Lyophilized powder for intramuscular gluteal injection
- Pros
  - Q 4 wk dosing
- Cons
  - Not indicated for acute psychotic episode
  - Relatively complex preparation prior to injection
  - Gluteal only
  - Oral overlap for first 2 weeks
Time to Impending Relapse for Aripiprazole LAI vs Placebo

Relapse was defined as clinical worsening, psychiatric hospitalization, increased risk of suicide, or violent behavior.

Clinical Pearls: Aripiprazole

- Starting dose of 400 mg but still need oral overlap
- At steady state 400 mg every 4 weeks is effective
  - Provides plasma levels comparable to ~ 15 to 20 mg/d oral
  - Dose reduction to 300 mg if 400 mg not tolerated
  - Dose reduction options also defined for those on CYP 2D6 and 3A4 inhibitors
- Relatively favorable side effect profile of oral aripiprazole is helpful for patients who cannot tolerate other LAIs due to prolactin, EPS, weight gain or sedation

Advances in Psychopharmacology of Schizophrenia

• New information on “old” therapies
• Most recently approved oral antipsychotics
• Recently approved long acting formulations
• Treatment selection
• In the pipeline
Idealized Patient Profiles

- Responds well and takes medication
- Takes medication but does not respond well
- Responds well but does not take and goes on to relapse
Matching Profile to Medication

First-line oral antipsychotic

Clozapine

Long-acting formulation
Matching Profile to Medication

First-line oral antipsychotic

Clozapine

Long-acting formulation
Implications of Phase of Illness Model in Medication Selection

• All antipsychotics can be used for all phases of schizophrenia
• Relative advantages and disadvantages of specific antipsychotics may change across different phases
• Antipsychotics are not interchangeable for individual patients
How Phase of Illness Influences Medication Priorities

Advantageous in acute phase
- Reach therapeutic dose quickly
- Well tolerated as dose increased
- Short-acting formulations
- No serious short-term side effects that would jeopardize immediate safety or clinical response

Advantageous in maintenance phase
- Better at relapse prevention
- Fewer distressing side effects
- Simple regimen
- Does well with other drugs*
- Long-acting version available
- Long-term medical safety

* “our” drugs = adjunctive pharmacologic agents
  “their” drugs = marijuana, alcohol
First-line Antipsychotics  
Selection Based on Side Effect Burden

- Patients with schizophrenia do not get a “day off” from side-effect burden
- All antipsychotics have significant side effects but relative burden differs across medications
- Side effect differences predictable and can be used to predict what will happen after switching
- Major improvements in reducing side effect burden
- No longer “catch 22” of high EPS vs. high metabolic problems

Weiden and Buckley 2007
Evidence to Reject Theories Associating Antipsychotic Side Effects and Efficacy

<table>
<thead>
<tr>
<th>Theory</th>
<th>Era</th>
<th>Evidence for Rejection</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPS and efficacy</td>
<td>1960-1980</td>
<td>Clozapine most effective</td>
</tr>
<tr>
<td></td>
<td>1990s</td>
<td>Other atypicals = haloperidol</td>
</tr>
<tr>
<td>Weight gain and efficacy</td>
<td>1960s</td>
<td>Haloperidol = chlorpromazine</td>
</tr>
<tr>
<td></td>
<td>2000-</td>
<td>Ziprasidone &amp; aripiprazole = olanzapine</td>
</tr>
<tr>
<td>Sedation and efficacy</td>
<td>1970s</td>
<td>Haloperidol = chlorpromazine</td>
</tr>
<tr>
<td></td>
<td>1980s</td>
<td>No benefit from massive doses of haloperidol</td>
</tr>
<tr>
<td></td>
<td>2000-</td>
<td>IM aripiprazole = IM olanzapine</td>
</tr>
</tbody>
</table>
Reverberations From Side Effects
How Patient and Clinician Responses May Differ

- Side effect appears
- Subjective Distress
- Objective Severity
- Safety & Risk
- Adherence Impact

Influencing patient response
Influencing clinician response

Matching Profile to Medication

First-line oral antipsychotic

Clozapine

Long-acting formulation
Potential Advantages of Long-acting Injectable Antipsychotics

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

Potential Obstacles to Long-acting Injectable Antipsychotics

• Systems barriers
  – Logistic barriers (appointments, staffing)
  – Administrative barriers

• Pharmacologic barriers
  – Oral/LAI conversion
  – Fewer choices among antipsychotics

• Attitudinal barriers
  – Perceived stigma
  – Anti-injection attitudes among clinicians

What Does the Research Tell Us?

- Two generations of research
  - 1970-1985
  - 1990s – present
- Inconsistencies in findings
  - RCTs are less likely to show favourable results
  - Cohort studies tend to favour long-acting route
- Relative effectiveness of long-acting formulations depends on more than the direct benefits of the long-acting medication
  - More variation in services context for long acting than for pills

Relapse and Atypical Antipsychotics: RCTs show Relapse Still Happens with Depot Formulations

Figure 2. Time to Hospitalization after Randomization.
In this analysis, data on patients who withdrew from the study were censored at the time of withdrawal from the study.

Long-Acting Risperidone and Oral Antipsychotics in Unstable Schizophrenia
Finish study following first admission for schizophrenia

- Prospective cohort study using national registers in Finland
- 2588 consecutive patients admitted for first time with schizophrenia (2000–2007)
- Followed up according to first drug dispensed post-discharge
- Mean follow-up 2 years
- Rates of discontinuation and rehospitalisation calculated for patients treated with the four most widely used depots in Finland
  - Risperidone depot
  - Zuclopenthixol decanoate
  - Haloperidol decanoate
  - Perphenazine decanoate
- And patients treated with the same four antipsychotics in oral form

Early Intervention with LAI may Prevent or Delay Rehospitalization

FIGURE 1. Risk of Rehospitalization After a First Hospitalization for Schizophrenia, by Antipsychotic Treatment Pattern (N=2,588)*

- Haloperidol, depot
- Clozapine
- Olanzapine
- Other antipsychotics
- Risperidone, depot
- Perphenazine, depot
- Polypharmacy
- Zuclopenthixol, depot
- Risperidone, oral
- Perphenazine, oral
- Quetiapine
- No treatment
- Haloperidol, oral
- Zuclopenthixol, oral

* This is an illustration of the fully adjusted hazard ratios reported in Table 2.
The PRIDE Trial

(Paliperidone Palmitate Research in Demonstrating Effectiveness)

- First prospective randomized clinical trial looking at real world consequences of relapse
- Fifteen month trial of 444 adults with one incarceration in the previous two years
- Once monthly injection vs. daily oral antipsychotics (aripiprazole, haloperidol, olanzapine, paliperidone, perphenazine, quetiapine and risperidone)
- Results:
  - Significantly delayed time to relapse vs. oral
  - Reduced overall relapse (relapse rates 1.4 times higher in oral group)
Summary on Use of LAI

• We often miss nonadherence in our patients; this can sabotage assessment of pharmacologic response
• LAI is an excellent adherence tracking method
• LAI can be an adherence tracking intervention, especially for patients who WILL NOT take medication down the road
• LAI can be a direct adherence intervention, especially for patients who CANNOT take their oral antipsychotic consistently
Matching Profile to Medication

First-line oral antipsychotic

Clozapine

Long-acting formulation
Clozapine
Clinical Uses

- Persistent symptoms after failing several first-line antipsychotics (~30%)
- High suicide risk (~10%)
- Aggression and violence (~5%)
- EPS and tardive dyskinesia (~2%)
- Other serious complications (e.g. polydispsia) (~2%)

What does “treatment-resistant” mean?
How to disentangle from poor adherence or substance abuse
Patient keeps changing treatment settings
Patient too disorganized to follow up with monitoring
Clinician not trained or too overwhelmed

Clozapine Underutilization and Discontinuation in African Americans Due to Leucopenia

Deanna L. Kelly¹, Julie Kreyenbuhl, Lisa Dixon, Raymond C. Love, Deborah Medoff, and Robert R. Conley

The Maryland Psychiatric Research Center, Box 21247, Baltimore, MD 21228 and the Center for Mental Health Services Research

Table 1. Reasons for Discontinuation by Racial Group

<table>
<thead>
<tr>
<th>Reason</th>
<th>African American (%)</th>
<th>Caucasian (%)</th>
<th>Test Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>48.6, N = 286</td>
<td>44.9, N = 578</td>
<td>Chi square = 2.26, df = 1, P = 0.13</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>9.18, N = 54</td>
<td>11.27, N = 145</td>
<td>Chi square = 1.85, df = 1, P = 0.17</td>
</tr>
<tr>
<td>Agranulocytosis</td>
<td>0</td>
<td>0.62, N = 8</td>
<td>Chi square = 3.67, df = 1, P = 0.06</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>5.27, N = 31</td>
<td>2.41, N = 31</td>
<td>Chi square = 10.55, df = 1, P = 0.001</td>
</tr>
<tr>
<td>Other hematologic adverse effect</td>
<td>0.34, N = 2</td>
<td>0.31, N = 4</td>
<td>Chi square = 0.01, df = 1, P = 0.92</td>
</tr>
<tr>
<td>Other nonhematologic adverse effect</td>
<td>5.27, N = 31</td>
<td>6.22, N = 80</td>
<td>Chi square = 0.65, df = 1, P = 0.42</td>
</tr>
<tr>
<td>Nonadherence</td>
<td>14.6, N = 86</td>
<td>12.5, N = 161</td>
<td>Chi square = 1.58, df = 1, P = 0.21</td>
</tr>
<tr>
<td>Death</td>
<td>1.36, N = 8</td>
<td>1.63, N = 21</td>
<td>Chi square = 0.19, df = 1, P = 0.66</td>
</tr>
<tr>
<td>Other</td>
<td>3.23, N = 19</td>
<td>3.41, N = 44</td>
<td>Chi square = 0.04, df = 1, P = 0.83</td>
</tr>
<tr>
<td>Unknown</td>
<td>9.35, N = 55</td>
<td>6.52, N = 84</td>
<td>Chi square = 4.70, df = 1, P = 0.03</td>
</tr>
</tbody>
</table>

Kelly DL. Schiz Bull. 2007;33(5):1221-1224
Current Challenges with Reducing Treatment Burden with Antipsychotic Medications

- Persistent psychosis
- Persistent anxiety
- Depressive symptoms
- Suicide risk
- Negative symptoms
- Cognitive and attentional problems
Pimavanserin (ACP-103) is a drug developed by Acadia Pharmaceuticals which acts as an inverse agonist on the serotonin receptor subtype 5-HT2A, with 10x selectivity over 5-HT2C, and no significant affinity or activity at 5-HT2B or dopamine receptors... and is in Phase II trials for adjunctive treatment of schizophrenia alongside an antipsychotic medication. It is expected to improve the effectiveness and side effect profile of antipsychotics.

Wikipedia accessed October 19, 2013
Nicotinic Systems
Example of Nicotinic Receptor Modulation

EVP-6124: Is an Alpha-7 Nicotinic Partial Agonist and Co-agonist with Acetylcholine. It is currently in Phase III trials for treatment of cognitive dysfunction in persons with schizophrenia (and also Alzheimer’s disease)
Summary

• Use our current medications wisely
  – Clozapine underused
  – Long-acting injections underused

• Newer medications and formulations
  – Can use differential efficacy to help more patients
  – Reduce side-effect burden overall

• Future developments
  – Refining dopamine model while also…
  – Moving away from dopamine
  – Improving formulations