S6735- Treatment of Schizophrenia
Course Director: Philip Janicak, M.D.
Saturday, May 14, 2016
Marriott Marquis - Marquis Ballroom D
Schizophrenia: Recent Diagnostic Advances, Neurobiology, and the Neuropharmacology of Antipsychotic Drug Therapy

Rajiv Tandon, MD
Professor of Psychiatry
University of Florida College of Medicine
Gainesville, Florida

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Disclosure Information

MEMBER, WPA PHARMACOPSYCHIATRY SECTION

MEMBER, DSM-5 WORKGROUP ON PSYCHOTIC DISORDERS

A CLINICIAN AND CLINICAL RESEARCHER
Pharmacological Treatment of Any Disease

- Know the Disease that you are treating
  - Nature; Treatment targets; Treatment goals;
- Know the Treatments at your disposal
  - What they do; How they compare; Costs;
- Principles of Treatment
  - Measurement-based; Targeted; Individualized

Program Outline

- Nature and Definition of psychosis?
  - Clinical description
  - What is wrong in psychotic illness
    - Dimensions of Psychopathology
    - Neurobiological Abnormalities
- Mechanisms underlying antipsychotic effects?
  - What contributes to Efficacy
  - Basis of Side-effect differences

DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS
FIFTH EDITION
DSM-5
AMERICAN PSYCHIATRIC ASSOCIATION
Challenges in DSM-IV Construct of Psychotic Disorders

- Indistinct Boundaries
  - With Other Disorders (e.g., with OCD)
  - Within Group of Psychotic Disorders (e.g., between schizophrenia and schizoaffective disorder)
- Unclear Relationship with Other Conditions
  - Eg., Catatonia
- Heterogeneity poorly described
- Limited utility in treatment decisions

Psychotic Disorders in DSM-5

- Concept
  - Definition of psychosis
  - Relationship between different psychotic disorders
  - Dimensions of psychosis and their measurement
- Addition and Deletion of Disorders
  - Catatonia NEC;
  - Schizophrenia subtypes;
- Changes in Criteria
  - Schizophrenia, Schizoaffective Disorder

Definition of Psychosis

- Core Features
  - Delusions
  - Hallucinations
  - Disorganized speech (thought disorder)
- Accompanying Features
  - Catatonia
  - Disorganized behavior
  - Negative symptoms
  - Mood Symptoms
Key Changes in Criterion A of Schizophrenia

• Eliminate special treatment of Schneiderian “first-rank” symptoms
  • Poor reliability of diagnosing “bizarre” delusions
  • No special prognostic or diagnostic value

• Add requirement that at least one characteristic symptom be a core psychotic symptom
  • Delusions, hallucinations, disorganized speech

New Learnings 1994-2013

- Schizophrenia
  • Multiple psychopathological dimensions
  • Distinct stages of illness
  • Need for early intervention/prevention
  • Mood symptoms can be prominent
  • Subtypes not stable

Heterogeneity better explained in terms of stages and dimensions rather than subtypes

New Findings: Stages and Dimensions of Illness
Tandon et al., Schizophrenia Research 2009; 110: 1-23
Schizophrenia Subtypes in DSM-5

- **ELIMINATE SUBTYPES**
  - No long-term stability
  - No diagnostic utility
  - No research utility
  - Poor reliability and validity

- **INTRODUCE DIMENSIONS** (To be rated on 0-4 scale)
  - Reality distortion (delusions, hallucinations)
  - Negative symptoms
  - Disorganization
  - Impaired cognition
  - Mood (depression, mania)
  - Psychomotor symptoms, including catatonia

### DIMENSIONS OF SCHIZOPHRENIA

- Disorganization
- Negative symptoms
- Positive symptoms
- Cognitive deficits
- Mood symptoms
- Motor symptoms

Different underlying pathophysiology and treatment response

### Diagnosis-Specific Severity Assessment: Symptom Domains

<table>
<thead>
<tr>
<th>Hallucinations</th>
<th>0 = Not Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delusions</td>
<td>1 = Equivocal</td>
</tr>
<tr>
<td>Disorganized Speech</td>
<td>2 = Present, but mild</td>
</tr>
<tr>
<td>Abnormal Psychomotor Behavior (incl. catatonia)</td>
<td>3 = Present &amp; moderate</td>
</tr>
<tr>
<td>Negative Symptoms</td>
<td>4 = Present &amp; severe</td>
</tr>
<tr>
<td>Impaired Cognition</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
</tr>
<tr>
<td>Mania</td>
<td></td>
</tr>
</tbody>
</table>
Clinical Application
Dimensions of Psychotic Disorders

- Precision in measurement-based care
- Specific targeting of distinct dimensions of schizophrenia and other psychotic disorders
- Individualizing treatment with more precise response-based treatment adjustments

Select Changes in DSM-5
Schizophrenia & Related Disorders

- Replace current subtypes with dimensions
- Include diagnosis of “attenuated psychosis syndrome” in Section 3 for further study
- Modify criteria for Schizoaffective Disorder
- Delink catatonia from schizophrenia

Neurobiological Basis
What Causes Schizophrenia?

- Genetic Factors of Central Importance
  - Contribute about 60-80% of liability
  - No major gene identified
  - Precise nature of genetic contribution??

- Environmental Factors Relevant
  - First and Second trimester insults
  - Cannabis and other substance abuse
  - Urbanicity and Migration
Neurobiological Basis
Nature of Brain Abnormalities in Schizophrenia

- CLEARLY A BRAIN DISEASE
  - Distinct abnormalities in brain structure, function, and neuropharmacology
  - Multiple brain areas and circuits implicated
  - Several cognitive functions and neurophysiological markers abnormal

- PRECISE etiology and pathophysiology still unclear

WHAT IS WRONG IN SCHIZOPHRENIA?
Nature of Brain Abnormalities

Structure
- cortical atrophy; ventricular enlargement
  - temporal and prefrontal cortex, hippocampus, thalamus
  - white matter tracts- myelination, connectivity

Function
- wide range of neurocognitive deficits,
  - abnormal activation patterns in PFC+ (fMRI)
  - broad array of electrophysiological markers

Pathology
- neurogenesis, migration, synaptogenesis, pruning
  - development; degeneration??

Neurobiological Basis
Neurochemical Abnormalities in Schizophrenia

- Dopaminergic abnormalities probable, but abnormalities in other systems likely as well

- Early model of “too much dopamine somewhere in the brain” overly simplistic
The Dopaminergic Pathways of the Brain

Dopaminergic Abnormalities in Schizophrenia: Current Status

- Limbic DA hyperfunction and Cortical DA hypofunction
- Tonic DA hypofunction and phasic DA hyperfunction

No consistent abnormalities in DA system delineated in schizophrenia

Other Neuropharmacological Abnormalities in Schizophrenia

- Glutamatergic deficiency (NMDA, Metabotropic,...)?
- Cholinergic deficiency (both muscarinic and nicotinic)?
- GABA-ergic deficiency?
- Abnormalities in various serotonin receptors
- Other neurotransmitter systems
Summary of Neuropharmacological Abnormalities in Schizophrenia

- Multiple neurotransmitters likely involved
- Dopaminergic abnormalities probable, but abnormalities in other systems likely as well
- In view of absence of definitive information, drug development is still empirical

How Do Antipsychotics Work?

- What is it that antipsychotics do that contributes to their therapeutic effect?
- What pharmacological properties explain their side-effect profiles?

Antipsychotic Therapies

<table>
<thead>
<tr>
<th>Prior to Antipsychotics</th>
<th>Conventional or Typical Antipsychotics (First Generation)</th>
<th>Atypical Antipsychotics (Second Generation)</th>
<th>Future Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>1952</td>
<td>Chlorpromazine, Haloperidol, Fluphenazine, Perphenazine, Trifluoperazine, Thiothixene</td>
<td>Clozapine, Risperidone, Olanzapine, Quetiapine, Ziprasidone, Paliperidone, Aripiprazole, Lurasidone</td>
<td></td>
</tr>
</tbody>
</table>
Defining Pharmacology Terms: Affinity vs. Intrinsic Activity

• **Affinity**
  • How well does the medication (ligand) bind to the receptor?
  • High, medium or low affinity

• **Intrinsic activity**
  • What does the drug do when it binds to the receptor?
  • If it does nothing (just sits there), it is an **antagonist**
  • If it does something, it is an **agonist**

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Intrinsic Activity (0-100) (at D₂ Receptors)

- **Intrinsic Activity Describes the Ability of a Compound to Stimulate Receptors**
  - D₂ receptor
  - **Full agonist** (dopamine)
    - Full receptor activity 100
  - **Antagonist** (e.g., haloperidol)
    - No receptor activity 0
  - **Partial agonist** (e.g., aripiprazole)
    - Partial receptor activity 1-99

---

All Known Antipsychotics Reduce Dopamine D2 Receptor Activity
### Clinical Implications of Blockade of Various Receptors by Antipsychotics

<table>
<thead>
<tr>
<th>Receptors</th>
<th>Possible Benefits</th>
<th>Possible Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dopamine D2 receptor</strong></td>
<td>Antipsychotic effect</td>
<td>Extrapyramidal movement disorders (EPS), (dystonia, Parkinsonism, akathisia, tardive dyskinesia)</td>
</tr>
<tr>
<td></td>
<td>Efficacy on positive sx</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Efficacy on agitation</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Endocrine changes (prolactin elevation causing galactorrhea, gynecomastia, menstrual changes, sexual dysfunction)</td>
</tr>
</tbody>
</table>

### Zooming in on the Dopamine D<sub>2</sub> Receptor Differences Between Antipsychotics

- Degree of binding at dopamine D<sub>2</sub> receptors
  - Different antipsychotics differ in the extent to which they block the dopamine-D<sub>2</sub> receptor at clinically relevant doses (reflected in % occupancy at the receptor)
    - > 60% occupancy believed to be necessary for antipsychotic effect
    - > 70% occupancy believed to be associated with elevated prolactin
    - > 80% occupancy believed to be associated with EPS
- Loose versus tight binding at dopamine D<sub>2</sub> receptor
  - Different antipsychotics differ with regard to how tightly they bind to the dopamine D<sub>2</sub> receptor
    - Quetiapine/Clozapine < Olanzapine < Ziprasidone < Risperidone / Conventional antipsychotics
    - Loose binding believed associated with greater ease of avoiding EPS

### Clinical Implications of Blockade of Various Receptors by Antipsychotics

<table>
<thead>
<tr>
<th>Receptors</th>
<th>Possible Benefits</th>
<th>Possible Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serotonin 5HT receptors</strong></td>
<td></td>
<td>---------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>5HT&lt;sub&gt;1A&lt;/sub&gt; receptor</td>
<td>Reduced EPS</td>
<td>Weight gain</td>
</tr>
<tr>
<td>5HT&lt;sub&gt;2C&lt;/sub&gt; receptor</td>
<td>Not definitely known</td>
<td>Weight gain</td>
</tr>
<tr>
<td>Histamine H&lt;sub&gt;1&lt;/sub&gt; receptor</td>
<td>Not definitely known</td>
<td>Sedation, weight gain</td>
</tr>
<tr>
<td>Muscarinic receptor</td>
<td>Not definitely known</td>
<td>Blurred vision, dry mouth, constipation, urinary retention, sinus tachycardia, memory dysfunction</td>
</tr>
<tr>
<td>α&lt;sub&gt;1&lt;/sub&gt;-Adrenergic receptor</td>
<td>Not definitely known</td>
<td>Postural hypotension, dizziness</td>
</tr>
</tbody>
</table>
The Clinical Benefits of Low EPS Risk

- Enhanced compliance
- Reduced negative symptoms
- Lower tardive dyskinesia risk
- Improved cognition
- Fewer motor side effects
- Less dysphoria

Dose-Response Curve: Antipsychotic Effects vs EPS


EPS: The Atypical Advantage

- EPS profiles differ among atypical agents
- Determined by combination of following attributes:
  - 5HT_{2A}/DA blockade
  - Affinity for dopamine D2 receptor and ease of dissociation from dopamine D2 receptor
  - Partial agonism at dopamine D2 receptor
  - Intrinsic anticholinergic activity
### Comparative Pharmacology of Antipsychotic Agents

![Diagram showing comparative pharmacology of antipsychotic agents](image)


### Conventional vs Atypicals Pharmacology & Side-Effect Profiles

<table>
<thead>
<tr>
<th></th>
<th>ZIP</th>
<th>ARI</th>
<th>HAL</th>
<th>CLZ</th>
<th>RIS</th>
<th>OLZ</th>
<th>QTP</th>
<th>PAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPS</td>
<td>±±</td>
<td>±±</td>
<td>++</td>
<td>0</td>
<td>±±</td>
<td>±±</td>
<td>±±</td>
<td>±±</td>
</tr>
<tr>
<td>TD</td>
<td>±±</td>
<td>±±</td>
<td>++</td>
<td>0</td>
<td>±±</td>
<td>±±</td>
<td>±±</td>
<td>±±</td>
</tr>
<tr>
<td>Anticholinergic</td>
<td>±±</td>
<td>±±</td>
<td>++</td>
<td>±±</td>
<td>±±</td>
<td>±±</td>
<td>±±</td>
<td>±±</td>
</tr>
<tr>
<td>Hypotension</td>
<td>±±</td>
<td>±±</td>
<td>++</td>
<td>±±</td>
<td>±±</td>
<td>±±</td>
<td>±±</td>
<td>±±</td>
</tr>
<tr>
<td>Sedation</td>
<td>±±</td>
<td>±±</td>
<td>++</td>
<td>±±</td>
<td>±±</td>
<td>±±</td>
<td>±±</td>
<td>±±</td>
</tr>
<tr>
<td>Weight gain</td>
<td>±±</td>
<td>±±</td>
<td>++</td>
<td>±±</td>
<td>±±</td>
<td>±±</td>
<td>±±</td>
<td>±±</td>
</tr>
</tbody>
</table>

Key: 0 = absent; ± = mild; + = moderate; ++ = severe

Adapted from Tandon et al, J Clin Psychiatry 1999;60(suppl 8);21-28

### Future Trends in Pharmacotherapy of Schizophrenia

- New Molecular Targets
- Rational Polypharmacy
- Phase-specific Treatments
- Better Individualizing Treatment
- Soon-to-be-available Agents
DEVELOPING BETTER TREATMENTS FOR SCHIZOPHRENIA
Hypothesis-Driven Targets of Treatment
Adapted from Tandon et al., "Schizophrenia, Just the Facts, Circa 2008" Schizophrenia Research, 2008, 100:4-19

Pathophysiology may involve cascade of sequential, cumulative events

Targets of Treatment:
Stages of Illness
Can different treatments be useful at different stages of treatment?
• Vulnerability factors: can specific individual-specific targeting of vulnerability factors prevent onset of illness?
• Prodrome: can treatment prevent onset of illness? - omega-3 fatty acids
### Targets of Treatment: Stages of Illness

<table>
<thead>
<tr>
<th>Early Stage</th>
<th>Later Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Can early aggressive treatment limit extent of deterioration?</td>
<td>Targeting various objectives</td>
</tr>
<tr>
<td>Antipsychotic</td>
<td>Prevention of relapse- antipsychotic?</td>
</tr>
<tr>
<td>Glutamatergic (eg., sarcosine)</td>
<td>Cognitive deficit- cholinergic agent?</td>
</tr>
</tbody>
</table>

### Better Individualizing Treatment

<table>
<thead>
<tr>
<th>Matching Drug and Dose to Patient</th>
<th>Targeting Different Pharmacogenomic Targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacogenetics</td>
<td>Different diseases with their markers</td>
</tr>
<tr>
<td>Receptor Imaging</td>
<td>Distinct susceptibility and protective genes</td>
</tr>
</tbody>
</table>

### Addressing The Challenges

#### Better Understanding of Schizophrenia
- Distinct dimensions of Illness
- Distinct stages of illness
- Elucidation of neurobiology
- More precise delineation of etiology

#### More Refined Treatment Development
- Directed at specific dimension-endophenotype
- Stage-specific treatments
- Novel treatment targets: Beyond dopamine!
# Treatment of Schizophrenia

*Circa 2014*

We have made much progress. But there is much more to do!

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## Reference

Reference


Management of Acute Psychosis

Philip G. Janicak, MD
Northwestern University Feinberg School of Medicine
Chicago, Illinois

Annual Meeting of the American Psychiatric Association
Toronto, Canada
May 16, 2015

Disclosure Information for Philip G. Janicak, M.D.

• Grant-Research Support
  • Cervel Neurotech, Inc.; Janssen/Ortho-McNeil; Neuronetics; Otsuka; The Research Foundation for Mental Hygiene, Inc.

• Consultant
  • Neuronetics

• Royalties
  • Lippincott, Williams & Wilkins
  • UpToDate
Major Points

• Diagnostic indications
• Symptom assessments
• Antipsychotics
  • Dosing strategies
• Stages of illness
  • High-risk, prodromal, first-episode and early-onset
  • Multipisode
• Treatment-resistant psychosis

Diagnostic Indications

• Schizophrenia
• Schizoaffective disorder
• Delusional disorder
  • Mood disorders
  • Major neurocognitive disorder with psychosis
  • Delirium
  • Psychosis secondary to another medical condition
  • Intellectual disability with psychosis and/or aggression
  • Tourette’s disorder

Schizophrenia:
Psychopathological Dimensions
Positive and Negative Syndrome Scale (PANSS): Clinical Significance

- Delineate and describe target symptoms
- 3 subscales and 30 items including
  - 7 items of the Positive scale
  - 7 items of the Negative scale
  - 16 items of the General Psychopathology scale
- Individual item values range from 1 to 7
- Assess severity of symptoms
- Quantify severity of relapse
- Potentially quantify response to treatment interventions
- Provide a comprehensive list of clinically important symptoms

Aripiprazole vs Placebo: Factor Analysis*

<table>
<thead>
<tr>
<th>Mean Change from Baseline</th>
<th>Aripiprazole (5-30 mg/ d) N=817</th>
<th>Placebo (N=406)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>1.33</td>
<td>-0.25***</td>
</tr>
<tr>
<td>Negative</td>
<td>0.96</td>
<td>-1.62***</td>
</tr>
<tr>
<td>Disorganized Thought</td>
<td>0.63</td>
<td>-1.84***</td>
</tr>
</tbody>
</table>

*LOCF
***p<0.001 vs. placebo.


Risperidone vs Haloperidol: Factor Analysis‡

<table>
<thead>
<tr>
<th>Factors</th>
<th>Risperidone 6 mg/d (n=255)</th>
<th>Haloperidol 20 mg/d (n=85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total PANSS</td>
<td>-2.03†</td>
<td>-1.78†</td>
</tr>
<tr>
<td>Disorganized Thought</td>
<td>-1.98†</td>
<td>-1.85†</td>
</tr>
<tr>
<td>Anxiety</td>
<td>-1.35‡</td>
<td>-1.55‡</td>
</tr>
<tr>
<td>Negative Symptoms</td>
<td>-1.62‡</td>
<td>-1.78‡</td>
</tr>
<tr>
<td>Positive Symptoms</td>
<td>-1.55‡</td>
<td>-1.71‡</td>
</tr>
</tbody>
</table>

‡LOCF = last observation carried forward.

*P<0.01 risperidone vs haloperidol; †P≤0.05.

‡‡LOCF = last observation carried forward.

### NIMH Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS)

- Consensus Cognitive Battery*
  - Speed of processing (3 tests)
  - Verbal learning (1 test)
  - Working memory
    - Nonverbal (1 test)
    - Verbal (1 test)
  - Reasoning and problem solving (1 test)
  - Visual learning (1 test)
  - Social cognition (1 test)
  - Attention/vigilance (1 test)


### Outcome Evaluations

- **Clinical**
  - Response (e.g., PANSS)
  - Remission (e.g., minimal to no symptoms; ≥ 6 months)
  - Improved functioning (e.g., PSP)
  - Recovery (e.g., QOL)

- **Statistical**
  - P value
  - Effect size
  - NNT/NNH/LHH

### First Generation Antipsychotics

<table>
<thead>
<tr>
<th>Class/Trade Name</th>
<th>Generic Name</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phenothiazines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aliphatics</td>
<td>Chlorpromazine</td>
<td>100-1000 mg</td>
</tr>
<tr>
<td>Albenzine</td>
<td>Promazine</td>
<td>25-1000 mg</td>
</tr>
<tr>
<td>Sparine</td>
<td>Thioridazine</td>
<td>20-180 mg</td>
</tr>
<tr>
<td>Sevazine</td>
<td>Trifluoperazine</td>
<td>20-180 mg</td>
</tr>
<tr>
<td>Velspar</td>
<td>Droperidol</td>
<td>2.5-10 mg</td>
</tr>
<tr>
<td>Prolixin</td>
<td>Fluphenazine</td>
<td>5-40 mg</td>
</tr>
<tr>
<td>Trilafon</td>
<td>Perphenazine</td>
<td>2-60 mg</td>
</tr>
<tr>
<td><strong>Dibenzepines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Navane</td>
<td>Thiothixene</td>
<td>6-60 mg</td>
</tr>
<tr>
<td>Taractan</td>
<td>Chlorprothixene</td>
<td>10-600 mg</td>
</tr>
<tr>
<td><strong>Dibenzothepines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loxapine</td>
<td></td>
<td>20-235 mg</td>
</tr>
<tr>
<td><strong>Butyrophenones</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haldol</td>
<td>Haloperidol</td>
<td>3-30 mg</td>
</tr>
<tr>
<td>Inapsine</td>
<td>Droperidol</td>
<td>2.5-10 mg</td>
</tr>
<tr>
<td><strong>Dibenzoazepines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molinax</td>
<td></td>
<td>15-225 mg</td>
</tr>
</tbody>
</table>

© Janicak
### Second Generation Antipsychotics

<table>
<thead>
<tr>
<th>Class/Trade Name</th>
<th>Generic Name</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dibenzodiazepines</td>
<td>Clozaril</td>
<td>Clozapine</td>
</tr>
<tr>
<td>Risperdal</td>
<td>Risperidone</td>
<td>2-8 mg</td>
</tr>
<tr>
<td>Fanapt</td>
<td>Iloperidone</td>
<td>12-24 mg</td>
</tr>
<tr>
<td>Latuda</td>
<td>Lurasidone</td>
<td>40-160 mg</td>
</tr>
<tr>
<td>Benzisoxazole</td>
<td>Zyprexa</td>
<td>Olanzapine</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Seroquel</td>
<td>75-800 mg</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Geodon</td>
<td>40-160 mg</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Saphris</td>
<td>10-20 mg</td>
</tr>
</tbody>
</table>

### Iloperidone (12-24 mg/day)

**Potential Advantages**
- Impact on various 5-HT receptors
- Impact on D3 receptor
- Minimal
- Metabolic effects
- EPS/akathisia
- Cholinergic effects
- Prolactin increase
- Pharmacogenomic panel (?)

**Potential Disadvantages**
- Dizziness, headache, nausea, dry mouth, insomnia most common AEs
- Need to titrate
- QTc prolongation
- Mild weight increase
- Cost

### Asenapine (10-20 mg/day)

**Potential Advantages**
- Novel receptor profile
- May benefit persistent negative symptoms (PNS) and cognition
- Placebo-level weight gain and metabolic changes
- Mild elevation of prolactin levels
- Low EPS (dose dependent)
- Bipolar disorder indication

**Potential Disadvantages**
- Insomnia, somnolence, nausea most common AEs
- Limited maintenance data
- Sublingual administration 5-10 mg BID
- Hypoesthesia/parasthesia
- Dysgeusia
- Cost
Lurasidone (40-160 mg/day)

Potential Advantages
• Novel receptor profile
• Rapid onset of effect
• Placebo-level weight gain and metabolic changes
• Minimal H₁ or NE₁, M₁ effects
• Minimal increase in QTc duration
• Bipolar depression indication

Potential Disadvantages
• GIT symptoms
• Nausea
• Somnolence
• Parkinson’s; akathisia
• Prolactin elevation
• Cost

Antipsychotic Drug Strategy

• Goal is to achieve optimal outcome with lowest effective dose
• Phases of treatment (acute; stabilization; maintenance)
• Problems
  • Delay in response
  • Indefinite nature of response
• Sources of guidance
  • Dose/plasma level-response data
  • Imaging data
  • Pharmacogenetics/pharmacogenomics

Antipsychotic Dose/Plasma Level–Effect Relationship

Concept of Therapeutic Window

Clinical Response

Toxicity

Dose/Plasma level of antipsychotic drugs
**Dopamine-2 (D₂) Receptor Occupancy of Haloperidol***

- PET-D₂ study with haloperidol (1-5 mg/d)
- Receptor occupancy ranged from 38%-87%
  - ≥65% increased likelihood of clinical response
  - ≥72% increased likelihood of hyperprolactinemia
  - ≥78% increased likelihood of extrapyramidal symptoms (EPS)

*First Episode


---

**Pharmacogenetics/Pharmacogenomics**

- Consider how inheritance and subtle acquired genetic variants impact a drug’s effectiveness
- Focus on SNPs in a single candidate gene to test for phenotypic associations
- Examine thousands of SNPs randomly distributed across the genome

---

**High Risk/Prodromal Stages: Symptoms**

**High risk**
- Attenuated; brief intermittent symptoms
- Trait vulnerability
- Psychosocial decline

**Prodromal symptoms**
- High levels of unusual content
- High suspicion/paranoia
- Substance abuse
High-Risk/Prodromal Stages: Treatment

- Intensive community care
- Family education
- Psychotherapy (e.g., CBTp)
- Pharmacological
  - Omega 3 FAs
  - NAC
  - Antipsychotics (?)

First-Episode/Early-Onset Stages: Symptoms

- Progression occurs early, during the first 5 years following first psychotic episode
- Patients are at high risk for:
  - Relapse
  - Persistent symptoms of psychosis
  - Neurocognitive impairment
  - Deficits in social and vocational performance
  - Suicidality


First-Episode/Early-Onset Stages: Treatment

- Intensive early-intervention program (OPUS)
- Treatment and Intervention in Psychosis Early-Detection Study (TIPS)
- Comparison of Atypicals for First Episode Psychosis (CAFÉ)
- Effectiveness of Antipsychotic Drugs on First Episode Schizophrenia and Schizophreniform Disorder (EUFEST)
- Treatment of Early Onset Schizophrenia Spectrum Disorders (TEOSS)
Multiepisode Patients

Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)

• NIMH-sponsored trial in 1460 patients
  • **Phase I** compared perphenazine to various SGAs in terms of overall effectiveness over 18 months
    • 1A-TD: no perphenazine
    • 1B- switch to SGA vs perphenazine
  • **Phase 2** random assignment to open label clozapine/or blinded alternate SGA
  • **Phase 3** subjects choose one of 8 open label options


CATIE

Phase I: Design

• 57 US sites: conducted between January 2001 and December 2004
• Chronic schizophrenia diagnosis (no history of resistance)
• Randomized to:
  • Perphenazine*
  • Olanzapine, risperidone, quetiapine, or ziprasidone**
  • Concomitant psychotropics (except for other antipsychotics), medical conditions and substance use disorders allowed

* TD excluded; ** Added later

**Phase I: Results**

- *Majority discontinued (74%)* due to lack of efficacy, adverse effects, or other reasons.
- *OLZ most effective* in terms of rates of discontinuation (64%); *most problematic* in terms of weight and metabolic-related issues.


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**Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUTLASS): Band I**

- *One-year* trial; 14 community settings in U.K.
- Compared FGAs (primarily sulpiride) with SGAs (primarily OLZ).
- 227 patients with chronic schizophrenia
  - 14 years mean illness duration
  - Mean PANSS baseline score of 72
- *Quality of life* was primary outcome measure
- *No significant differences* among various agents


---

**Strategies for Treatment-Resistant Psychosis**

- Clozapine
- Antipsychotic polypharmacy
- Novel approaches
Clozapine

Advantages
- May benefit treatment-refractory patients
- May reduce suicidal, aggressive or violent behavior
- May increase life expectancy
- Diminished extrapyramidal side effects
- Minimize risk for or improve tardive dyskinesia
- Minimize hyperprolactinemia

Disadvantages
- Box Warnings
  - Agranulocytosis
  - Seizures
  - Myocarditis
  - Orthostasis
  - Increased mortality in dementia
- Other Adverse Effects
  - Weight gain/metabolic syndrome
  - DKA
  - GIT hypomotility

CATIE: Phase 2E
- Discontinuation for lack of efficacy
  - Clozapine was significantly better than olanzapine, risperidone, and quetiapine
- Discontinuation for all cause
  - Clozapine was significantly better than risperidone or quetiapine

CUtLASS: Band II
- Clozapine versus other SGAs
- 136 treatment-refractory schizophrenia patients
- Clozapine superior in reducing psychotic symptoms
- Clozapine not superior in improving quality of life
Antipsychotic Polypharmacy

**Advantages**
- Ease transition from one agent to another
- Supplement long-acting agents during initiation or exacerbation
- Improve specific symptoms
- Need for lower doses of two agents due to safety or tolerability issues with standard doses of a single agent
- Augment efficacy of first antipsychotic

**Disadvantages**
- Increase risk for adverse effects
- Increase risk for drug interactions
- Adherence problems
- Increase cost
- Inadequate data to support augmentation benefit

Risperidone Augmentation of Clozapine: BPRS Total Scores

![Graph showing BPRS scores over weeks with risperidone augmentation compared to placebo.](image)

*Significantly different from the score at 12 weeks for clozapine/placebo treatment per ANCOVA with baseline BPRS total score as the covariate (F=3.15, df=2, 74, p<0.05). Josiassen et al. Am J Psychiatry. 2005;162:130-136.

Dopamine/Serotonin Systems

- **Dopamine** receptors
  - DA1 receptors in PFC modulate working memory
  - DA2, DA4 antagonists
- **Serotonin** receptors
  - 5-HT1A agonists
  - 5-HT2A inverse agonists/antagonists; 5-HT2C agonists
  - 5-HT3 antagonists
  - 5-HT4 agonists
  - 5-HT6 and 5-HT7 antagonists
- **Combined** actions
  - 5-HT/DA antagonist ratio
  - DA2/DA3 and 5-HT1A partial agonists (e.g., cariprazine)
Norepinephrine (NE) System

- Modulation may improve vigilance, moderate stress reaction and enhance cognition and mood
- Alpha NE modulation
  - Asenapine; iloperidone; lurasidone
- Selective reuptake inhibitors
  - Reboxetine
  - Atomoxetine
  - Norquetiapine

Glutamate System

- Primary excitatory neurotransmitter
  - Synthesized from glutamine
- PCP and ketamine produce psychosis
- Receptor types:
  - Ionotropic (NMDA; AMPA; Kainate):
    - Glycine agonists/reuptake inhibitors at NMDA
    - Modulators of AMPA
  - Metabotropic
    - mGlu I (1/5)
    - mGlu II (2/3)
    - mGlu III (4/6/7/8)

Glutamate System Modulators

- Ionotropic receptor modulators
  - NMDA
    - Lamotrigine
    - Glycine
    - N-acetylcysteine
    - Memantine
    - Nitroprusside
  - AMPA
    - Ampakines
    - Minocycline
- Metabotropic receptor modulators
  - mGlu 2/3
# Lamotrigine: Combination Trials

- **Glutamate and NE modulation**
- **Attenuates ketamine-induced behavioral changes**
- **Early trials** encouraging
- **Negative trials**
  - LTG plus AP
  - Two large trials
- **Positive trials**
  - Meta-analysis of five trials
  - LTG superior to placebo (plus CLZ) in 161 resistant patients

Goff et al., 2007.; Tiihonen et al., 2009.

---

# Glycine

- **Negative/cognitive symptoms**
- **Glycine site** of the NMDA ionotropic receptor
  - The Cognitive and Negative Symptoms in Schizophrenia Trial (CONSIST)
    - 16-week, DB, RCT with adjunctive
      - Glycine
      - D-cycloserine
      - Placebo
  - **Meta-analysis** of glycine plus nonclozapine antipsychotics supportive
- **Glycine transport inhibitors**
  - Sarcosine; RG1678 (bitopertin)


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# N-Acetylcysteine (NAC)

- **Increases glutathione** (GSH) levels
  - Primary antioxidant (intracellular free radical scavenger) which maintains oxidative balance in normal cells
- **Modulates Glu and DA pathways**
  - Increases extracellular Glu and stimulates mGlu 2 receptor, reducing synaptic release
  - Alters DA release
- **Reduces inflammatory cytokines**
- **Augmented APs** (primarily CLZ) at doses of 2,000 mg/day in a 6-month RCT (n=140)

### Memantine

- Weak (vs. ketamine), selective NMDA antagonist
- Small, DB-PC trial found memantine superior to placebo in 21 patients with treatment refractory schizophrenia

---

### Sodium Nitroprusside

- Increases nitric oxide and cGMP production
- May modulate NMDA receptor activity
- RCT (n=20)
  - Early-onset stage
  - Single IV dose (0.5 ug/kg/min for 4 hrs)
  - Rapid improvement which persisted for 4 wks

---

### Ampakines

- **CX516**
  - AMPA receptor positive modulator
- DB-PC, 4-week trial
  - 900 mg TID as adjunct to CLZ (n=52), OLZ (n=40) or RISP (n=13)
  - Failed to improve cognition/psychotic symptoms

---
Minocycline

- Tetracycline derivative
- AMPA receptor modulator
  - Neuroprotective
  - Antiinflammatory
  - Antioxidant
- DB-PC, 6-month trial
  - 200 mg/day augmented antipsychotics for early phase schizophrenia (negative/cognitive symptoms)


Pomaglumetad Methionil (mGlu 2/3)

- Metabotropic presynaptic glutamate receptor selective agonist
- Study 1
  - Positive trial
  - 4 week trial in 196 schizophrenia patients
  - Similar to OLZ and > placebo in reducing PANSS scores
  - High dropout rate
- Study 2
  - Failed trial
  - 4 week trial in 669 schizophrenia patients
  - 5, 20, 40 or 80 mg BID versus placebo; OLZ (15 mg) as control
  - Did not separate from placebo
  - High placebo response; 4 seizures
- Study 3
  - Negative trial
  - 40 and 80 mg BID did not separate from placebo
  - Risperidone as active control did separate from placebo


GABA System

- Primary inhibitory neurotransmitter
- Cortical and subcortical GABA activity is disrupted in schizophrenia (e.g., first-episode patients)
- Preclinical and clinical data support GABA agonists which activate interneurons, decrease mesolimbic DA hyperactivity and potentially improve positive symptoms

Divalproex ER Plus SGA or Placebo


Mean Change in PANSS Over Study Duration

- Antipsychotic monotherapy
- Combination therapy

Change in PANSS From Baseline

- Day 3
- Day 5
- Day 7
- Day 10
- Day 14
- Day 21
- Day 28
- Day 35
- Day 42
- Day 49
- Day 56
- Day 63
- Day 70
- Day 77
- Day 84

(n=402)

Valproate for Schizophrenia

Advantages
- Modulates DA, GABA, GLU
- Neurotransmission
- Intracellular signaling
- May benefit hostility/anxiety early in treatment as adjunct to antipsychotics (e.g., OLZ, RISP)

Disadvantages
- Adverse effects
- Teratogenicity
- Valnoctamide (analogue)
- PCO, PCOS (?)
- May worsen metabolic effects depending on specific antipsychotics (e.g., OLZ vs. RISP)

GABA A Receptor Hypothesis

- Working memory and cognitive control deficits associated with impairments in PFC function
- Synchronization of pyramidal cell activity in part dependent on GABA A receptors (alpha 2 subunits)
- Selective agonists may improve cognition

GABA

**GABA<sub>A</sub> Agonist: Proof of Concept Trial**

- **MK-0777** versus placebo (RCTs)
  - **Trial 1** (n=15); 4 weeks
    - 3-8 mg BID
    - Enhanced GABA<sub>A</sub> activity at α<sub>2</sub> subunit improved
      - Cognition
      - Electrophysiological measure of PFC function
  - **Trial 2** (n=60); 4 weeks
    - 3 or 8 mg BID
    - MCCB
    - Placebo>MK-0777


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Choline

**Acetylcholine System**

- **Imbalances in muscarinic and/or nicotinic signaling** may underlie symptoms of schizophrenia (e.g., perinatal choline; cholinesterase inhibitors)
- **Receptor types**
  - **Nicotinic ionotropic receptors**
    - Modulate DA, NE, GLU, GABA
  - **Muscarinic** metabotropic receptor (M<sub>1</sub>-M<sub>5</sub>)
    - Nonselective
    - Selective

---

Choline

**Nicotinic Receptor**

- **α<sub>7</sub> nicotinic receptor agonists**
  - DMXB-A: (75 mg BID or 150 mg BID)
  - Four-week, two-site, double-blind, placebo-controlled, crossover, study (n=31)
    - Improved attention/vigilance and working memory domains (MATRICS)
    - Improved negative symptoms (anhedonia and alogia subscales) (SANS)
- **α<sub>4</sub>β<sub>2</sub> receptor agonists** (e.g., varenicline)

Muscarinic Receptor

- **Xanomeline**
  - $M_1/M_4$ agonists
  - Improved psychosis and negative symptoms
  - Also has affinity for $M_2$, $M_3$, $M_5$ receptors

- **Allosteric modulators**
  - Selective potentiators of $M_1$ or $M_4$ (e.g., VU10010)
  - Dramatically enhance receptor activation by Ach

- **Allosteric agonists**
  - $M_1$ (e.g., TBPB)

Antidepressants

- **First generation agents**
  - Amoxapine
  - Selegiline

- **Second generation agents**
  - Mirtazapine (30 mg/day)
    - Augmenting benefit for depressive, negative and
cognitive symptoms with FGAs and SGAs
  - Duloxetine
    - In one RCT improved negative and positive
      symptoms as an adjunct to CLZ
  - SSRIs
    - Not helpful for cognitive or negative symptoms

- **DHEA**
  - May improve mood/negative symptoms

Steroids

- **Glucocorticoids**
  - MOA
    - HPA axis implicated in the pathophysiology and stress vulnerability of
      schizophrenia
  - Mifepristone is a glucocorticoid receptor antagonist; (600-1200 mg/day)
    may benefit schizophrenia

- **Neurosteroids**
  - MOA
    - Neuroprotective effects
    - HPA axis modulation
    - Increase GABA(A) receptor response
    - Modulate NMDA receptors
  - Pregnenolone has multiple effects (e.g., neuroprotective)
    - Pilot studies demonstrated adjunctive pregnenolone decreased negative
      and positive symptoms, improved cognition, and decreased EPS
  - DHEA may improve mood/negative symptoms

References:
Other Potential Treatments

- Histamine
  - H $_2$ inverse agonists/antagonists
- Antiinflammatory agents
  - NSAIDs
  - Minocycline
- Cannabinoids
  - CB$_2$ receptor antagonists (cannabinol, SR141716)
- Hormonal
  - Estradiol; raloxifene
  - Oxytocin
- Purinergic
  - Allopurinol

Nutraceutical Strategies

- Omega fatty acids
  - Schizophrenia may involve dysfunctional fatty acid metabolism
  - Omega-3 fatty acids may prevent psychosis in young individuals with subthreshold syndromes
- Folate
  - Reduces homocysteine levels
  - May benefit depressive symptoms in schizophrenia
- Vitamin D
  - Nutritional deficiencies may increase risk of schizophrenia
  - Vitamin D supplementation during first year may reduce risk

Alternate Treatment Approaches: Therapeutic Neuromodulation

- Electroconvulsive therapy
- Transcranial magnetic stimulation
  - Negative symptoms
  - Refractory auditory hallucinations
  - Cognition (e.g., WVM)
- Transcranial direct cortical stimulation
- Deep brain stimulation
  - Tardive dyskinesia/dystonia
- Optogenetics
Alternate Treatment Approaches: Psychosocial

- Psychoeducation: patient and family
- Social skills training (SST)
  - Active instruction
  - Behavioral rehearsal
  - Social reinforcement
  - Assigned homework
- Vocational rehabilitation
  - Supported employment (SE)
    - Immediate job placement
    - Consider patient preference
    - Employment specialists
  - Long-term follow-up
- Psychotherapy (e.g., cognitive remediation; cognitive remediation plus skills training)

Major Points

- Diagnostic indications
- Symptom assessments
- Antipsychotics
  - Dosing strategies
- Stages of illness
  - High-risk, prodromal, first-episode and early-onset
  - Multiepisode
  - Treatment-resistant psychosis

Reference

Treatment of Schizophrenia: Long-Term Management

Stephen R. Marder, MD
Director, Mental Illness Research, Education and Clinical Center
VA Greater Los Angeles Healthcare System
Professor, Director of the Section on Psychosis
Semel Institute of Neuroscience at UCLA
Annual Meeting of the American Psychiatric Association
New York
May 2014

Disclosure Information for Stephen R. Marder, MD

- Consulting
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- Research Support
  - Psychogenics; Amgen; Sunovion

Phases of Schizophrenia and Goals of Treatment

- **Acute** – Reduce acute symptoms
- **Stabilization** – Minimize the likelihood of relapse; enhance adaptation to community; consolidate remission
- **Stable** – maintain or improve level of function and quality of life; prevent relapse; monitor for adverse treatment effects.
Stabilization Phase: Management

- If a patient responds to a medication they should continue on a therapeutic dose for at least 6 months
- Psychotherapeutic interventions should be supportive
- This phase may be a good time for educating patients and families

Relapse Prevention With Ziprasidone: 1-Year Kaplan-Meier Estimate

Maintenance Antipsychotic Treatment of Schizophrenia

- Antipsychotics reduce relapse risk
- Patients who relapse when they are receiving antipsychotic medications have episodes that are less severe than those in patients who discontinue their drugs
- Patients may require as long as 6 months to fully recover from a psychotic episode
Drug Discontinuation Among Successfully Maintained Schizophrenic Outpatients

<table>
<thead>
<tr>
<th>Study</th>
<th>Time in Remission</th>
<th>Length of Follow-up</th>
<th>Off Drug</th>
<th>Relapse Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hogarty et al, 1976</td>
<td>2–3 y</td>
<td>12 mo</td>
<td>65%</td>
<td></td>
</tr>
<tr>
<td>Johnson, 1976</td>
<td>1–2 y</td>
<td>6 mo</td>
<td>53%</td>
<td></td>
</tr>
<tr>
<td>Dencker et al, 1980</td>
<td>2 y</td>
<td>24 mo</td>
<td>94%</td>
<td></td>
</tr>
<tr>
<td>Cheung, 1981</td>
<td>3–5 y</td>
<td>18 mo</td>
<td>62%</td>
<td></td>
</tr>
<tr>
<td>Johnson, 1981</td>
<td>1–4 y</td>
<td>18 mo</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>Wistedt, 1981</td>
<td>6 mo</td>
<td>12 mo</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Unweighted mean</td>
<td></td>
<td></td>
<td></td>
<td>76%</td>
</tr>
</tbody>
</table>

Relapse Following a First Episode of Schizophrenia

<table>
<thead>
<tr>
<th>Author</th>
<th>Duration of Follow-up (years)</th>
<th>Percentage Relapsed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kane et al, 1982</td>
<td>3.5</td>
<td>69</td>
</tr>
<tr>
<td>Rabiner et al, 1986</td>
<td>1</td>
<td>29</td>
</tr>
<tr>
<td>Crow et al, 1986</td>
<td>2</td>
<td>55</td>
</tr>
<tr>
<td>Prudo &amp; Blum, 1987</td>
<td>5</td>
<td>80</td>
</tr>
<tr>
<td>McCreaddie et al, 1988; 1992</td>
<td>5</td>
<td>70</td>
</tr>
<tr>
<td>Rajkumar &amp; Thara, 1989</td>
<td>3</td>
<td>59</td>
</tr>
<tr>
<td>Zhang et al, 1994</td>
<td>1.5</td>
<td>35</td>
</tr>
<tr>
<td>Linszen et al, 1994</td>
<td>1.5</td>
<td>17</td>
</tr>
<tr>
<td>Robinson et al, 1999</td>
<td>5</td>
<td>82</td>
</tr>
</tbody>
</table>

Long-term Antipsychotic Treatment and Brain Volumes

**A Longitudinal Study of First-Episode Schizophrenia**

**Hypothesis:** Progressive brain volume changes in schizophrenia might contribute to the clinical course of schizophrenia. Specifically, it was hypothesized that antipsychotic treatment would slow brain atrophy in schizophrenia patients and that this effect would be more pronounced and sustained over a longer period of treatment in patients with more severe symptoms at baseline.

**Methods:** Subjects were patients with first-episode schizophrenia treated with antipsychotics. Brain volumes were assessed using MRI scans at baseline and follow-up visits. The study included 50 patients, 25 receiving antipsychotics and 25 receiving no treatment. Follow-up visits were at 6 months, 1 year, and 2 years.

**Results:** Antipsychotic treatment was associated with slower brain volume decline compared to untreated controls. The antipsychotic group showed a significant increase in brain volume over the 2-year follow-up period, while the untreated group showed a significant decrease.

**Conclusion:** Antipsychotic treatment may have a beneficial effect on brain volume in patients with first-episode schizophrenia.
Relapse Rate Differences Between Oral and Depot Formulations

<table>
<thead>
<tr>
<th>Study</th>
<th>Total Number of Patients</th>
<th>Duration</th>
<th>% Difference (oral – depot)</th>
</tr>
</thead>
<tbody>
<tr>
<td>del Giudice et al</td>
<td>82</td>
<td>1 yr</td>
<td>48</td>
</tr>
<tr>
<td>Crawford and Forrest</td>
<td>29</td>
<td>40 wks</td>
<td>27</td>
</tr>
<tr>
<td>Schooler et al</td>
<td>214</td>
<td>1 yr</td>
<td>9</td>
</tr>
<tr>
<td>Rifkin et al</td>
<td>51</td>
<td>1 yr</td>
<td>2</td>
</tr>
<tr>
<td>Falloon et al</td>
<td>41</td>
<td>1 yr</td>
<td>-16</td>
</tr>
<tr>
<td>Hogarty et al</td>
<td>105</td>
<td>2 yrs</td>
<td>24</td>
</tr>
</tbody>
</table>

Mantel-Haenszel Test P < 0.002; Davis et al, 1988.

Survival Rates on Oral and Depot Fluphenazine

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

Methods: Data on the effectiveness of antipsychotics in the treatment of schizophrenia in Finland were obtained from the nationwide registry of hospital discharges, which records all hospitalizations in the country. Patients were followed from their first hospitalization for schizophrenia until their next hospitalization or the last day of follow-up, whichever occurred first. The effectiveness of antipsychotics was measured by the risk of readmission within 1 year of discharge. Patients were stratified by the type of antipsychotic used (oral, depot, or both) and by the duration of follow-up (1 year). The primary outcome was the risk of readmission within 1 year of discharge.

Results: A total of 2,384 patients were included in the study. The risk of readmission within 1 year of discharge was lower for patients who received depot antipsychotics compared to those who received only oral antipsychotics (hazard ratio 0.75, 95% CI 0.65-0.87). The difference was statistically significant (p < 0.001).

Conclusions: Depot antipsychotics are associated with a lower risk of readmission within 1 year of discharge compared to oral antipsychotics. This finding supports the use of depot antipsychotics in the management of schizophrenia.
Risperidone Microspheres:
Mean Active Moiety Concentrations

<table>
<thead>
<tr>
<th>ng/ml</th>
<th>Day</th>
<th>Oral (n = 21)</th>
<th>Consta (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2</td>
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<td>5</td>
<td>3</td>
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<td></td>
</tr>
<tr>
<td>24</td>
<td>11</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

RIS-INT-32; Data on file, Janssen Pharmaceutica Products, L.P.

Paliperidone Palmitate
*Invega Sustenna™*

- Usually prescribed once each month
- Release of paliperidone begins one day after injection indicating that it can be used for acute treatment
- There are no studies comparing it to other long-acting antipsychotics

Olanzapine Pamoate
*Zyprexa Relprevv™*

- Therapeutic plasma levels for 2-4 weeks.
- Associated with a risk of a postinjection delirium sedation syndrome
- Patients should be observed for three hours after each injection.
Long-Acting Aripiprazole (Abilify Maintena)

- Approved March 1, 2013
- Usual dose is 300-400 mg q month
- Recommendation is for a 14 day overlap with oral aripiprazole
- Lyophilized powder that is reconstituted with sterile water to form an injectable suspension

Special Considerations for Depot Drugs

- Parenteral drugs are more bioavailable
  - Avoid conversion formulas
  - Dose conservatively
- Parenteral drugs require **3-6 months to reach steady state** and are excreted slowly
  - Cross titrate with oral drug during conversions

Recently reported results

- McEvoy et al reported results from an NIMH trial at the Schizophrenia International Research Society meeting
- Haloperidol Decanoate and Paliperidone Palmitate showed similar efficacy
- Greater weight gain with paliperidone and greater akathisia with haloperidol
Special Issues In First-Episode Patients

- Diagnostic uncertainty
- Concerns about delaying treatment
- How long to treat
- High rates of suicide
- Resistance to settings that serve chronically mentally ill

Duration of Untreated Psychosis

- The first treatment contact is preceded by an average of one year of psychotic symptoms as well as years of prodromal symptoms
- There is evidence that a longer duration is associated with a poorer course, more severe symptoms and poorer functioning.
Recovery in Remitted First-Episode Psychosis at 7 Years of Follow-up of an Early Dose Reduction/Discontinuation or Maintenance Treatment Strategy

Long-term Follow-up of a 2 Year Randomized Clinical Trial

- 7 year follow-up of a 2 year randomized trial in first episodes
- Those randomized to dose reduction had higher recovery rates and higher functioning.
- 17 out of 103 patients discontinued antipsychotics. These individuals showed better functioning at 7 years

Approaches to Weight Gain and Insulin Resistance

- Cochrane review supports changing antipsychotics
- Early elevations of triglycerides and weight predict later elevations
- Life style interventions work!
- Consider metformin
Metformin and Lifestyle Intervention for Antipsychotic Weight Gain

- 128 pts with schizophrenia who gained 10% of weight on antipsychotics
- Randomized to placebo, lifestyle intervention, metformin (750 mg/day), or metformin plus lifestyle intervention
- 12 week weight change:
  - Placebo - +4.8%,
  - Metformin w/ lifestyle - -7.3%
  - Metformin - -4.9%
  - Lifestyle alone - -2.2%

(Wu et al., JAMA 2008)

Stable Phase: Assessment

- Consider positive, negative, cognitive, and mood symptoms as well as side effects
- Evaluate level of adherence
- Examine for tardive dyskinesia
- Regular assessment of prodromal symptoms
- Evaluate weight, cardiovascular risk factors, etc
For Patients With Persistent Symptoms

- Are there differences among the SGA’s and FGA’s?
- When should clozapine be prescribed?
- When to intervene for metabolic disturbances

CATIE Schizophrenia Study

Time to Discontinuation for Any Cause

CATIE Phase 2: Clinical Antipsychotic Trials of Intervention Effectiveness

- **Phase 2T** (n=444) was recommended for those who discontinued for tolerability. Compared olanzapine, quetiapine, risperidone, or ziprasidone.
- **Phase 2E** (n=99) was recommended for those who discontinued for lack of efficacy. Groups were open-label clozapine or double-blind olanzapine, quetiapine, or risperidone.
Phase 2E: Discontinuations

- **All cause** discontinuation
  - Clozapine 56%
  - Olanzapine 71%
  - Risperidone 86%
  - Quetiapine 93%
  - Clozapine was significantly better than risperidone or quetiapine

---

Phase 2E: Discontinuations

- Discontinuation for **lack of efficacy**
  - Clozapine 11%
  - Olanzapine 35%
  - Risperidone 43%
  - Quetiapine 43%
  - Clozapine was significantly superior to olanzapine, risperidone, and quetiapine

---

**Effectiveness of Switching From Antipsychotic Polypharmacy to Monotherapy**

Suara M. Emsick, Ph.D.
Nina E. Schule, Ph.D.
T. Scott Stroup, M.D., M.P.H.
Joseph P. McEvoy, M.D.
Ingrid Hajas
Carlos Jackson, Ph.D.
Nancy H. Covel, Ph.D.
The Schizophrenia Trials Network

Objectives: This randomized trial addressed the risks and benefits of switching from antipsychotic polypharmacy or switching among antipsychotics for patients who were receiving antipsychotic medication.

Methods: Adults with schizophrenia or schizoaffective disorder were randomized to switch to monotherapy with a non-preferential antipsychotic or continuing polypharmacy. The primary outcome was discontinuation due to clinical worsening.

Results: Of the 473 patients who completed the study, 235 were randomized to monotherapy and 238 to polypharmacy. At 6 months, the discontinuation rate was significantly lower in the monotherapy group (13%) compared to the polypharmacy group (26%).

Conclusions: Switching from antipsychotic polypharmacy to monotherapy is associated with a lower risk of discontinuation due to clinical worsening compared to continuing polypharmacy.

DOI: 10.1002/jup.2017.0050007020

12
Schizophrenia PORT 2009

Recommendation. Clozapine should be offered to people with schizophrenia who continue to experience persistent and clinically significant positive symptoms after 2 adequate trials of other antipsychotic agents. A trial of clozapine should last at least 8 weeks at a dosage from 300 to 800 mg/day.
Schizophrenia PORT 2009

Clonazepam for the Treatment of Residual Symptoms: Monitoring Clozapine Plasma Levels

Recommendation. If a person treated with clonazepam has failed to demonstrate an adequate response, then a clonazepam level should be obtained to ascertain whether the clonazepam level is above 350 ng/ml. If the blood level is less than 300 ng/ml, then the dosage should be increased, to the extent that side effects are tolerated, to achieve a blood level above 350 ng/ml.

Schizophrenia PORT -- 2009

Anticonvulsants and Lithium for Treatment-Resistant Positive Symptoms

Summary Statement. A substantial proportion of people with schizophrenia treated with antipsychotic medications continue to exhibit residual positive symptoms. Lithium and anticonvulsants are used extensively to augment antipsychotic treatment of these symptoms. However, few studies have been conducted to formally evaluate the efficacy of these approaches. Of the anticonvulsants, carbamazepine, valproate/valproic acid, lamotrigine, and topiramate have been the most extensively studied, but none of these agents have demonstrated sufficient efficacy to support a recommendation in people with residual positive symptoms. There is little evidence to support the efficacy of lithium for these symptoms.

Schizophrenia PORT -- 2009

Antipsychotic Polypharmacy

Summary Statement. Many individuals with schizophrenia have an incomplete symptom response to antipsychotic monotherapy. The use of combinations of antipsychotic medications (antipsychotic polypharmacy) has become an increasingly common treatment approach for people who have failed to adequately respond to previous antipsychotic treatment. The majority of studies of combinations of antipsychotic medications have examined the efficacy and safety of a single combination: clozapine and risperidone. These studies have failed to document sufficient efficacy and safety of this combination to support a recommendation in people with treatment-resistant schizophrenia.
Differential Diagnosis of Depression in Schizophrenia

- Antipsychotic-induced akinesia
- Dysphoria from akathisia
- Demoralization syndrome
- Negative symptoms

Management of Depression in Schizophrenia (Siris)

- Assure that depression is not part of a psychotic decompensation
- Rule out EPS, particularly akinesia; change to an SGA
- Add an antidepressant

Recovery in Schizophrenia

- Focuses on restoration of function rather than stabilization
- Patients are at the center of the process and are partners in setting goals and planning treatment
- Restores hope and optimism in the recovery process
Schizophrenia: Core Symptom Clusters

I. Positive symptoms
- Delusions
- Hallucinations
- Disorganisation

II. Negative symptoms
- Blunted affect
- Alogia
- Avolition
- Anhedonia

III. Cognitive symptoms
- Attention
- Memory
- Executive functions (e.g., abstraction)

IV. Affective symptoms
- Dysphoria
- Suicidality
- Hopelessness

Social / occupational dysfunction
- work interpersonal relationships
- self-care

Cognitive Impairment in Schizophrenia

- Patients tend to have deficits in multiple areas of cognitive functioning, suggesting generalized impairment
- Cognitive impairment can be detected in preschizophrenic children as early as first grade
- First-episode patients: Impairment consistent with those seen in more chronic patients

Magnitude of Cognitive Deficits in Schizophrenia

Meta-Analysis; 204 studies, 7420 patients and 5865 controls

Healthy Comparison Mean

Characteristic profile in schizophrenia: maximal impairment in memory, attention, and executive function; relative preservation of old learning and visual perceptual skills.
**MATRICS Ranking of Targets**

<table>
<thead>
<tr>
<th>Target</th>
<th># of nominations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-7 nicotinic receptor agonists</td>
<td>31</td>
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<tr>
<td>D1 receptor agonists</td>
<td>30</td>
</tr>
<tr>
<td>AMPA glutamatergic receptor agonists</td>
<td>14</td>
</tr>
<tr>
<td>Alpha 2-adrenergic receptor agonists</td>
<td>14</td>
</tr>
<tr>
<td>NMDA glutamatergic receptor agonists</td>
<td>12</td>
</tr>
<tr>
<td>Metabotropic glutamate receptor agonists</td>
<td>12</td>
</tr>
<tr>
<td>Glycine reuptake inhibitors</td>
<td>8</td>
</tr>
<tr>
<td>M1-muscarinic receptor agonists</td>
<td>7</td>
</tr>
<tr>
<td>GABA A R subtype selective agonists</td>
<td>5</td>
</tr>
</tbody>
</table>

---

**Hierarchical Model of Negative Symptoms**

- Negative Symptoms
  - Diminished Expression
  - Social Dysfunction
    - Experiential (pleasure, drive) Deficits
    - Behavioral Deficits

---

**Five consensus based NS**

- NIMH Consensus Conference (Jun 16, 2006)

- Affective flattening: Face, voice, gestures, spontaneous movement
- Alogia: Speech quantity, spontaneous elaboration
- Anhedonia: Inability to experience pleasure
- Avolition: Productive self-care, work motivation
- Asociality: Family, friends, romantic

- Diminished expression
- Diminished motivation & emotion
Rummel, Kissling, Leucht, 2005

<table>
<thead>
<tr>
<th>Study</th>
<th>AP vs AD N</th>
<th>AP vs PBO N</th>
<th>SMD (random) (95% CI)</th>
<th>SMD (random) (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Silver and Kanter, 1992</td>
<td>15</td>
<td>15</td>
<td>-1.07 (-1.05, -0.38)</td>
<td></td>
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<tr>
<td>Sykes et al., 1994</td>
<td>14</td>
<td>16</td>
<td>-1.07 (0.05, 0.69)</td>
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<tr>
<td>Jenkins-Sherhill et al., 2000</td>
<td>11</td>
<td>14</td>
<td>-0.39 (-1.21, 0.43)</td>
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<tr>
<td>Hayashi et al., 1987</td>
<td>13</td>
<td>13</td>
<td>-0.56 (-1.31, 0.23)</td>
<td></td>
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<tr>
<td>Hayashi et al., 1989</td>
<td>12</td>
<td>12</td>
<td>-0.44 (-1.13, 0.24)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>66</td>
<td>71</td>
<td>-0.71 (-1.09, -0.34)</td>
<td></td>
</tr>
</tbody>
</table>

Results: SANS Total Score

D-cycloserine vs. placebo, t= -0.11, df=550, p=0.92
Glycine vs. placebo, t=0.47, df=550, p=0.64

Proof of Concept Trial With a GlyT1 Inhibitor: Bitopertin

- Bitopertin increases CSF glycine – dose dependent
- 323 pts with predominant neg symptoms randomized to 10, 30, 60 mg or placebo
- Significant improvement in PANSS Marder factors on 10 and 30 mg, but not 60 mg
- A larger Phase 3 trial found no advantage of Bitopertin over placebo
Effective Psychosocial Treatments: Schizophrenia (PORT)*

- Illness education
- Family interventions that provide education and support
- Supported employment
- Assertive community treatment
- Skills training
- Cognitive behaviorally oriented psychotherapy

*PORT = Patient Outcomes Research Team.

Psychosocial Approaches to Specific Targets

- Facial affect recognition can be enhanced with special training\(^1\)
- Cognitive training can improve working memory\(^2\)
- Attention can be improved with specialized training\(^3\)
- Cognitive enhancement therapy improved neurocognition and processing speed\(^4\)

Neuroplasticity-Based Training in Schizophrenia

Meta-Analysis of Cognitive Remediation for Schizophrenia

Cognitive Training: Effects on Employment Rate
Tenets of Cognitive Model of Psychotic Illness

- Psychotic experiences are common—reported by 40% of population
- Problem is how psychotic experiences are interpreted; “normals” correct for odd experiences
- Faulty appraisals leading to diagnosable illness result from specific developmental history
- Faulty appraisals are maintained by logical errors (e.g. generalization, minimization)

Common Elements of CBT for Psychosis

- engagement and assessment
- developing a shared understanding of the experience of psychosis (i.e. case formulation)
- normalizing experiences of first symptoms
- establishing a functional goal
- coping enhancement
- working on delusions and hallucinations, often using gentle challenging (automatic thought records and behavioral experiments)
- addressing mood and negative self-evaluations
- managing the risk of relapse and social disability (social functioning)

Many Manuals Available

- Chadwick et al (1996)
- Nelson (1997)
- Kingdon & Turkington (2005)
- Wright et al (2008)
### Strong Supportive Data

1. 34 published RCTS on CT/CBT for psychosis
2. 4 meta-analyses showing moderate to large effect sizes on some measure of positive symptoms—usually BPRS or SANS;
3. More recent meta-analysis have less robust (but still powerful) findings
4. Variability in results with better designed trials (e.g., use of active controls, blind raters etc) yielding lower effect sizes. Blinding of raters is a big issue—studied masked studies have an effect size of .307; unmasked .492 (Wykes et al, 2008)

### Strong Supportive Data con't

1. Group and individual seem to have similar effects, but not extensively studied
2. Effects on hospitalization and social functioning less clear
3. Durability of effects is an issue—some studies find stronger effects at follow-up—Sensky et al.; others find diminution of effects—Tarrier

---

![Graph showing effectiveness of Cognitive Behavioral Therapy](image)
Baseline Demographic and Clinical Characteristics

Table 1. Baseline Demographics and Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CT (n = 50)</th>
<th>SS (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>34.3 (10.6)</td>
<td>41.5 (10.6)</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>27 (54.0)</td>
<td>19 (38.0)</td>
</tr>
<tr>
<td>Race/Ethnicity, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>19 (38.0)</td>
<td>18 (36.0)</td>
</tr>
<tr>
<td>White</td>
<td>10 (20.0)</td>
<td>8 (16.0)</td>
</tr>
<tr>
<td>Asian American</td>
<td>5 (10.0)</td>
<td>6 (12.0)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (18.0)</td>
<td>9 (18.0)</td>
</tr>
<tr>
<td>Employment status, No. (%)</td>
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</tr>
<tr>
<td>Full-time</td>
<td>26 (52.0)</td>
<td>25 (50.0)</td>
</tr>
<tr>
<td>Part-time</td>
<td>24 (48.0)</td>
<td>25 (50.0)</td>
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<tr>
<td>Education, years of</td>
<td></td>
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</tr>
<tr>
<td>High School</td>
<td>16 (32.0)</td>
<td>15 (30.0)</td>
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<tr>
<td>College</td>
<td>18 (36.0)</td>
<td>17 (34.0)</td>
</tr>
<tr>
<td>Graduate School</td>
<td>16 (32.0)</td>
<td>18 (36.0)</td>
</tr>
</tbody>
</table>
| Global Functioning

Global Functioning

Graph showing the mean GAF score over time for different groups: CT alone (n=50), CT with ST (n=50).
Summary

- The **goals of maintenance** treatment include preventing relapse and improving functional outcome.
- These goals usually require combining **pharmacological and psychosocial** treatments.
- Clinicians should also address the **health risks** associated with schizophrenia.
- Patients should not be considered poor responders until they have received a **clozapine trial**.
Adverse Effects of Antipsychotics

Jeffery T. Rado, MD
Northwestern University

Annual Meeting of the American Psychiatric Association
Atlanta, GA
May 2016

Disclosure Information for Jeffery T. Rado

• Research Support: Neuronetics and Otsuka.

Effectiveness = Efficacy + Safety/Tolerability
### Adverse Effects of Antipsychotics

<table>
<thead>
<tr>
<th>Effect</th>
<th>HDO</th>
<th>CLO</th>
<th>RIS</th>
<th>OLZ</th>
<th>QTP</th>
<th>ZIP</th>
<th>ARP</th>
<th>PAL</th>
<th>ILQ</th>
<th>ASR</th>
<th>LUR</th>
<th>BRX</th>
<th>CAR</th>
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</thead>
<tbody>
<tr>
<td>Metabolic</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>Q/+</td>
<td>Q/+</td>
<td>++</td>
<td>++</td>
<td>Q/+</td>
<td>Q/+</td>
<td>Q/+</td>
<td>Q/+</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>+</td>
<td>Q/+</td>
<td>++</td>
<td>Q/+</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>Q/+</td>
<td>0</td>
<td>Q/+</td>
<td>0</td>
<td>Q/+</td>
<td>0</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Q/+</td>
<td>++</td>
<td>++</td>
<td>Q/+</td>
<td>++</td>
<td>Q/+</td>
<td>Q/+</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
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<tr>
<td>Endocrine</td>
<td>++</td>
<td>Q/+</td>
<td>+++</td>
<td>Q/+</td>
<td>++</td>
<td>Q/+</td>
<td>Q/+</td>
<td>++</td>
<td>++</td>
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<td>0</td>
<td>Q/+</td>
<td>Q/+</td>
<td>++</td>
<td>Q/+</td>
<td>++</td>
<td>Q/+</td>
<td>++</td>
<td>Q/+</td>
<td>Q/+</td>
<td>Q/+</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Sedation</td>
<td>+</td>
<td>+++</td>
<td>Q/+</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
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</tr>
</tbody>
</table>

*All appropriate doses; 0 = none; + = mild; ++ = moderate; +++ = substantial

---

### Related Issues

- Advanced age
- Clozapine
- Other serious adverse effects
- Adherence

---

### Schizophrenia: Life Expectancy

- **25% shorter life expectancy** versus general population
- **Mortality rate** is 1.5 to 3 times higher
  - **Cardiovascular disease**
    - Exacerbated by many antipsychotics
    - But even higher without treatment
- **Suicide** is also a contributor (5-10%)
Metabolic

- Weight gain
  - Recognized problem since chlorpromazine
  - More common with certain SGAs
- Long-term weight-associated complications
  - Elevated triglycerides and cholesterol
  - Hypertension; heart, CNS and renal disease; cancer
- Diabetes mellitus
  - More problems managing DM
  - New-onset cases of DM
  - Ketoadiposis

CATIE: Metabolic Syndrome and Risk Factors in Schizophrenia vs General Population

<table>
<thead>
<tr>
<th>Phase 1</th>
<th>Males CATIE N=509</th>
<th>NHANES N=509</th>
<th>Females CATIE N=180</th>
<th>NHANES N=180</th>
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</thead>
<tbody>
<tr>
<td>Metabolic Syndrome Prevalence</td>
<td>36.0%</td>
<td>19.7%</td>
<td>51.6%</td>
<td>25.1%</td>
</tr>
<tr>
<td>Waist Circumference Criteria</td>
<td>35.5%</td>
<td>24.8%</td>
<td>76.3%</td>
<td>57.0%</td>
</tr>
<tr>
<td>Triglyceride Criteria</td>
<td>50.7%</td>
<td>32.1%</td>
<td>42.3%</td>
<td>19.6%</td>
</tr>
<tr>
<td>HDL Cholesterol Criteria</td>
<td>48.9%</td>
<td>31.9%</td>
<td>63.3%</td>
<td>36.3%</td>
</tr>
<tr>
<td>BP Criteria</td>
<td>47.2%</td>
<td>31.1%</td>
<td>46.9%</td>
<td>26.8%</td>
</tr>
<tr>
<td>Glucose Criteria</td>
<td>14.1%</td>
<td>14.2%</td>
<td>21.7%</td>
<td>11.2%</td>
</tr>
</tbody>
</table>

Lieberman, et al. NEJM 2006

Criteria and Consequences of the Metabolic Syndrome

Heart attack
Diabetes
PAD
Insulin resistance
Atherosclerosis
Stroke
Acute coronary syndrome

Metabolic Syndrome
3 or more risk factors required for definition
Risk Factor | Defining Level | Metabolic Syndrome
Abdominal obesity
Men | Waist circumference >102 cm (>40 in)
Women | >88 cm (>35 in)
HG cholesterol
Men | <40 mg/dL
Women | <50 mg/dL
Blood pressure | <130/85 mm Hg
Fasting glucose | <110 mg/dL

Prevalence and Relative Risk of Modifiable CVD Risk Factors

<table>
<thead>
<tr>
<th>Modifiable risk factors</th>
<th>Prevalence, % (RR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>45-55 (1.5-2)</td>
</tr>
<tr>
<td>Smoking</td>
<td>50-80 (2-3)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10-15 (2)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>19-58 (2-3)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>25-69 (≤5)</td>
</tr>
<tr>
<td><strong>Metabolic syndrome</strong></td>
<td><strong>37-63 (2-3)</strong></td>
</tr>
</tbody>
</table>


Risks Interact Exponentially

Antipsychotics Increase Risk Factors and Do it Quickly

- 50% on antipsychotics weigh >20% above recommended body weight
- Increases diabetes risk by 600%
- Average 5% weight gain in short-term studies
  - Triglycerides increase 50%
- **Dose-related** with clozapine/olanzapine
  - Weight increases about 1.5 lbs/month
Risks Vary Across Agents: CATIE Phase I

- Weight Change/Mo lbs × 10
- Glucose Change mg/dl
- Glycosalated Hg % × 100
- Cholesterol mg/dl
- Triglycerides mg/dl

* Different from group

Many Patients Do Not Receive Treatment for Metabolic Syndrome

Many Patients Do Not Receive Treatment for Metabolic Syndrome

Ongoing Management I

- **Weight assessed** at weeks 4, 8, 12, then quarterly
- **Plasma glucose and BP** assessed at baseline and 12 weeks for first year, then at least annually.
- **Lipids** at baseline and 12 weeks, then at 1-year intervals.
- **Treat or refer**

Diabetes Care, February 2004
Ongoing Management II

- Behavioral
  - Nutrition and physical activity counseling; weight management program
  - Monitor for signs/symptoms of diabetes or DKA

- Medication
  - Choice of antipsychotic
  - Choice of concomitant medications
    - Metformin prophylaxis
  - Decrease polypharmacy

Diabetes Care, February 2004

Ongoing Management III

- Metformin
  - Most extensively studied
  - Wu: 12-week weight change (%):
    - Placebo (+4.8%)
    - Metformin (750 mg/day) plus lifestyle (-7.3%)
    - Metformin (750 mg/day) alone (-4.9%)
    - Lifestyle intervention alone (-2.2%)
  - Dyslipidemia and insulin resistance normalize
  - Prophylaxis?
  - Topiramate


Ongoing Management IV

- Mediterranean diet
  - Whole grains, vegetables, fruits, nuts, olive oil
- Smoking cessation
- Moderate alcohol consumption
- Moderate exercise: STRIDE
  - 1.5 hr/week
  - >2 miles/day

STRIDE weight loss and lifestyle intervention

![Graph showing weight loss and lifestyle intervention over time]

Green, Am J Psy. 2015, 71-81

Cardiovascular
- Drug induced Hypotension/ Orthostasis
- Myocarditis
  - Flu-like syndrome
  - ECG:CPK
- Arrhythmogenic potential
  - Torsade de pointes
  - QTc utility?
  - Sudden death
  - At risk patients
    - Female; CVD; familial LQTS; multiple drugs; hypokalemia

© Janicak

Mean Change from Baseline in QTc Interval* for Antipsychotics†

- Thioridazine 300 mg: +35
- Zip 100 mg: +21
- Ria 16 mg: +12
- Qtp 750 mg: +15
- Ria 4-6 mg: +9
- O1z 25 mg: +7
- Hal 10 mg: +4
- Ari 15 mg‡: −3.3

*Based on correction: †Study 054 as presented to FDA, 2000.
‡Proposed USPI data for aripiprazole; Data on file, Bristol-Myers Squibb.
Causes of QTc Prolongation

- Daily activities
  - Sleeping (~13 msecs)
  - Eating/drinking (~16 msecs)
  - Athletic training
  - Alcohol
  - Obesity
- Psychotropics

Does QTc Prolongation Cause TdP?

- Drug-associated QTc prolongation has not been linked to TdP
  - Except for overdoses
- Other risk factor for TdP in over 90%
- 20% of TdP, QTc was < 500 ms

Sudden Cardiac Death Risk Linked to Antipsychotic Dose

<table>
<thead>
<tr>
<th></th>
<th>Low dose</th>
<th>Moderate dose</th>
<th>High dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGA</td>
<td>1.3</td>
<td>2.01</td>
<td>2.42</td>
</tr>
<tr>
<td>SGA</td>
<td>1.59</td>
<td>2.13</td>
<td>2.86</td>
</tr>
</tbody>
</table>

**Sudden Death: Causes and Associations**

- **Cause:**
  - Myocardial infarction
  - Other arrhythmias
  - Cardiomyopathy
  - Stroke
  - Drug OD

- **Association:**
  - Hip fracture
  - Acute Renal Failure

---

**Taiwanese Study of 55,000: Case-crossover design**

- MI risk dose related
  - 2.5 times greater
  - Higher (ns) in 2nd gen.
  - Greater in males, elderly, dementia
  - Healthier persons at higher risk
  - Dose related
  - Short term effect?

*Circulation. 2014;130:235-243*

---

**Ongoing Management**

- **ECG** before and after starting antipsychotic treatment if elderly, on lithium, or other risk factors
- **No ziprasidone** recent MI; + FH
- **Cautious use** with elderly; recent MI; antiarrhythmics; bulimia; diuretics; heart disease
- Attend to **syncope; electrolytes**
- Avoid **haloperidol IV** (> 2 mg/day) in ICU
Neurological Movement Disorders

Acute EPS

<table>
<thead>
<tr>
<th>Maximum</th>
<th>Minimum</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIGH POTENCY</td>
<td>RISPERIDONE</td>
</tr>
<tr>
<td>FGAs</td>
<td>PALPERIDONE</td>
</tr>
<tr>
<td>ILOPERIDONE</td>
<td>QUETIAPINE</td>
</tr>
<tr>
<td>BREXIPRAZOLE</td>
<td>LURASIDONE</td>
</tr>
<tr>
<td>CARIPRAZINE</td>
<td>ARIPIPRAZOLE</td>
</tr>
<tr>
<td>ASENAPINE</td>
<td></td>
</tr>
</tbody>
</table>

Ongoing Management

- **Akathisia**
  - Dose reduction, β blockers (propranolol 20 TID), benzodiazepines (clonazepam 0.50 bid), mirtazapine (15 mg)
- **Other EPS**
  - Anticholinergics (1-4 mg benztropine; 5-15 trihexyphenidyl); amantadine 100-400
  - Central and peripheral effects vs psychosis
Tardive Dyskinesia: Incidence and Morbidity

- **Incidence** about 5% per year; 15-30% cross section in chronic patients
- **Mortality rate doubled**
- **Risk factors**
  - Age; affective disorder; smoking; acute EPS; organic mental disorder; high dose; choice and duration of drug treatment
  - Be aware of variants (e.g. dystonia)
  - Approach differs

Risperidone vs Haloperidol
Incidence of TD: low but not 0

<table>
<thead>
<tr>
<th></th>
<th>Risperidone (n=177)</th>
<th>Haloperidol (n=188)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of patients with TD symptoms at 1 year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
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<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean age: 40 years

Data from Csernansky J et al. WWS, Davos, February 2000.

Endocrine

Hyperprolactinemia
Prolactin: Incidence and Adverse Effects

- 65% of women, 43% of men have elevated prolactin levels
  - Women >25 ng/ml; men 15 ng/ml
  - Signs and symptoms not always correlated

Short-term AEs
- Amenorrhea
- Lactation/breast engorgement
- Gynecomastia
- Sexual dysfunction

Long-term AEs
- Osteoporosis
- Cancer risk

Prolactin Changes in CATIE

<table>
<thead>
<tr>
<th>Drug</th>
<th>Maximum</th>
<th>Minimum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Clozapine</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Olanzapine</td>
<td></td>
<td></td>
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<tr>
<td>Brexpiprazole</td>
<td></td>
<td></td>
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<tr>
<td>Asenapine</td>
<td></td>
<td></td>
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<tr>
<td>Quetiapine</td>
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<td></td>
</tr>
<tr>
<td>Ziprasidone</td>
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<td></td>
</tr>
<tr>
<td>Iloperidone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lurasidone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cariprazine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Different from group
Menstrual irregularities

- Menstrual irregularities and other problems predicted by agent
  - Lurasidone and iloperidone, not asenapine
- Switch drug
- Birth control pills
- Bromocriptine
- GI and psychosis risks

* Different from group  

---

Sexual Dysfunction Troubling but Treatable

- 50% men, 33% women
- Only 1 in 3 volunteer information
- Risk factors
  - FGA, clozapine, risperidone
  - FGA depot more problematic for women
  - Recent data establish stronger link with prolactin levels and AP dose

---

Risperidone and High Potency Antipsychotics

* Different from group  
Management

- **Aripiprazole** improves sexual function
- Also lowering dose or bromocriptine

- **Sildenafil** (25 or 50 mg) vs placebo
  - Erections 4 times as likely to occur
  - Intercourse 3.75 times as satisfying

Anticholinergic Effects

- More common with:
  - Clozapine, olanzapine, quetiapine
  - Low-potency FGAs

- Peripheral and central effects

Sedation

<table>
<thead>
<tr>
<th>Maximum</th>
<th>Minimum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>Olanzapine</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Ziprasidone</td>
</tr>
<tr>
<td>Asenapine</td>
<td>Paliperidone</td>
</tr>
<tr>
<td>Low Potency FGAs</td>
<td>Iloperidone</td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>Aripiprazole</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>Cariprazine</td>
</tr>
</tbody>
</table>

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Sedation: Potential Consequences

- Impairs psychomotor and cognitive activities¹
- Impairs ability to function²
- Can lead to discontinuation from antipsychotic medication³

Sedation Was the Third Most Common Reason for Discontinuation Due to Adverse Events in CATIE³

Interactive psychotic disorder involves a complex interplay between genetic factors, environmental stressors, and epigenetic influences. Various neurotransmitter systems are implicated in the development and maintenance of these disorders, including dopamine, serotonin, and glutamate systems.


Related Issues

Advanced Age

- Significance
  - Not as benign as in younger adults
  - Pneumonia; falls; fractures; renal failure; PE; CHF; sudden death
  - QTc prolongation and increased clotting
- Risks
  - Dementia
  - FGAs > SGA?

Management

- Avoid in those with vascular dementia
- Avoid with TIA; hypertension; Afib
- Use low divided doses
- Monitor for hypotension; sedation; EPS

Problems, Drug Impact and Management

Draft: 1-20-14 15
Use of Antipsychotics in Dementia With Psychosis

- Box warning
- Recommendations
  - When feasible, attempt non-pharmacological interventions
  - Use low doses (e.g., risperidone 0.25 mg)
  - Increase by lowest possible amount
  - Give in divided schedule
  - Monitor for hypotension, sedation, EPS

Related Issues

Pregnancy

Respiratory Distress and Withdrawal Symptoms Common

Table 4: Babies at birth.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of babies (percent)</th>
<th>Expected rate in Australia (‰)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth wt 2.0 kg</td>
<td>0 (0%)</td>
<td>1.6%</td>
</tr>
<tr>
<td>Birth wt &lt; 2.0 kg</td>
<td>2 (0.9%)</td>
<td>1.6%</td>
</tr>
<tr>
<td>Birth wt &gt; 3.0 kg</td>
<td>2 (1.6%)</td>
<td>1.6%</td>
</tr>
<tr>
<td>Respiratory distress at birth</td>
<td>2 (1.6%)</td>
<td>20.0%</td>
</tr>
<tr>
<td>Abnormal Apgar score at 1 minute</td>
<td>4 (3.2%)</td>
<td>1.2%</td>
</tr>
<tr>
<td>Abnormal Apgar score at 5 minutes</td>
<td>1 (0.8%)</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

# Related Issues

## Clozapine

### Advantages

- May benefit treatment-refractory patients
- May reduce suicidal, aggressive or violent behavior
- May increase life expectancy
- Diminished extrapyramidal side effects
- Minimize risk for or improve tardive dyskinesia
- Minimize hyperprolactinemia

### Disadvantages

**Box Warnings**
- Agranulocytosis
- Seizures
- Myocarditis (0.7%)
- Orthostasis
- Increased mortality in dementia

**Other Adverse Effects**
- Weight gain/metabolic syndrome
- DKA
- GIT hypomotility

### Hematological Effects

- Clozapine-induced **agranulocytosis**
  - Management
    - Stop agent
    - Reverse isolation; supportive measures
    - GSCF (filgastrim)
  - **Rechallenging** strategies

---

### Problems, Risks and Recommendations

- Neutropenia/agranulocytosis
- Polyserositis/myocarditis
- Constipation → Bowel obstruction
  - Stool softeners
- Seizures are dose related
  - Valproic acid, lamotrigine, gabapentin
- Orthostasis → syncope → vascular collapse
  - Risks: fast titration; benzodiazepines
- Sialorrhea
  - Glycopyrrrolate; atropine drops sublingual

### Related Issues

#### Other Serious Adverse Effects

- Neuroleptic Malignant Syndrome (NMS)
  - Fever; rigidity; elevated WBC; LFTs; mental state
  - No rigidity, tremor with clozapine, quetiapine
- Venous Thrombosis → pulmonary emboli
  - DVT, PE OR 3.5-10 fold: clozapine, olanzapine hi
  - Consider anticoagulation with catatonia, restraints
- Laryngeal spasm
  - Life-threatening EPS
- Hepatitis
  - Allergic or toxic
- Hyponatremia
Related Issues

Adherence

Most Striking Finding in CATIE

Risk Factors for Medication Nonadherence

- Illness-related
  - Substance use comorbidity\(^1,2\)
  - Symptom severity\(^3\)
  - Lack of insight\(^4\)
  - Subjective well being\(^5\)

- Treatment-related
  - Tolerability\(^6\)
  - Efficacy\(^7\)
  - Regimen complexity\(^8\)
  - Therapeutic alliance\(^9\)
  - System factors\(^10\)
  - This Talk

- Patient-related
  - Previous medication adherence\(^1\)
  - Demographic characteristics\(^2\,11\)
  - Subjective response to medications\(^11\)
  - Medication supervision\(^11\)

---

Intolerable Side Effects: CATIE Phase I

* Different from group

Intolerable Side Effects: CATIE Phase 2 Tolerability

* Different from group

Strategies That May Improve Adherence

- Educational
  - Provide information regarding disease state
  - Inform the patient about the purpose and potential side effects of medications

- Behavioral
  - Simplify regimens and use adherence aids
  - Enable cognitive restructuring of attitudes toward medication and disease state
  - Empower patients and caregivers to take an active role in managing their disease

- Affective
  - Facilitate a supportive environment
  - Encourage counseling and family reporting of adherence to therapy

Adherence

- Assessment of **capacity**
- Working **model**
- Adequate **communication**
- Promote **active involvement**

---

Adherence

- **Assess frequently** for nonadherence
- **Psychoeducation**
- Observe for and treat emergent **adverse effects**
- **Simplify regimen**
  - Once-daily dosing; extended half-life medications
  - Long-acting formulations

---

‘Finding an antipsychotic regimen that patients can live with comfortably is an essential part of an effective management strategy’

*Steve Marder, MD March ’07*
References I


References II