Practical Strategies for the Treatment of Patients with Schizophrenia

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Dr. Rona Hu has served as a consultant for Alexza/Biovail and Sepracor/Sunovion.

Please take pretest now
Learning Objectives

• Recognize criteria for remission and recovery in patients with schizophrenia. Evaluate patients for the potential to achieve these outcomes and implement strategies directed towards these goals
• Recognize how clinical practice guidelines relate to the individualized treatment of patients with schizophrenia
• Integrate strategies that will help to improve the effective use of medications by patients with schizophrenia

Variable Functional and Symptomatic Outcomes ~ Who and Why?

N = 1449 patients
Based on endpoint values for 8 continuous measures: 5 PANSS factors, 2 QLS domains, + “useful work”

What Were the Predictors of Outcomes?

Cluster A (good outcome) vs Cluster E (poor outcome)
• Baseline variables
• Early change variables

Dimensions of Improvement in People with Schizophrenia

- Neurobiology
- Psychotic symptoms
- Cognitive symptoms
- Psychosocial functioning
- Quality of life
- Self-agency


Hierarchies of Outcome

Recovery
Remission
Stabilization


What do remission and recovery mean in the context of schizophrenia?
Symptomatic Remission
Remission in Schizophrenia Working Group

PANSS symptoms and signs mild or less (severity ≤ 3) for 6 months

- Positive symptoms
  - Delusions
  - Unusual thought content
  - Hallucinatory behavior

- Disorganization
  - Conceptual disorganization
  - Mannerisms/posturing

- Negative symptoms
  - Blunted affect
  - Social withdrawal
  - Lack of spontaneity


A Model for Functional Remission

- Domains
  - Productive activities
  - Residential and self-maintenance activities
  - Social relationships

- Criterion 1: Level of accomplishment
  - None
  - Attempts
  - Progress
  - Partial success
  - Full success

- Criterion 2: Breadth of accomplishment across functional domains
  - Making progress ≥ 1 domains
  - Partial success ≥ 1 domains
  - Full success ≥ 1 domains
  - Combinations


Criteria for Recovery?

- Symptom remission
- Vocational functioning
- Independent living
- Peer relationships
- Duration ≥ 2 years

Is recovery best viewed as an outcome or a process?

Recovery

- *Recovery from Illness*
  - Cure of illness, absence of illness

Vs

- *Recovery in Illness*: being in recovery
  - Process of managing illness more effectively
  - Having a meaningful life in the community
  - Moving ahead with one’s life despite illness

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**Factors Associated with the Potential for Positive Clinical and Functional Outcomes**

- Short duration of untreated psychosis
- Good early response to antipsychotic treatment
- Collaborative therapeutic alliance
- Supportive family/caregivers
- Access to comprehensive, coordinated, and continuous treatment
- Opportunities to engage in functional activities and receive specialized interventions
- Absence of substance abuse
Progressive Gray Matter Loss in Adolescent Patients With Schizophrenia Over 5 Years


Psychosis and Brain Volume Changes During the First 5 Years of Schizophrenia


Early Responders Show Early and Consistent Improvement—Clinical Outcomes

Early Responders Show Early and Consistent Improvement–Functional Outcomes


ER: early responders
ENR: early non-responders
SOFI: Schizophrenia Objective Functioning Instrument

Overall Living Instrumental Protective Social Situation Activity Activity Functioning

Least Squares Mean Change in SOFI Baseline to Endpoint

* P < 0.001

EPPIC Study
Early Psychosis Prevention and Intervention Centre

723 First-episode psychosis patients* treated for up to the first 2 years of illness
Median follow-up: 7.2 years; mean age @ follow-up: 28.7 years

<table>
<thead>
<tr>
<th>Remission/Recovery Criteria</th>
<th>Schizophrenia + Schizoaffective Disorder (%)</th>
<th>Total Cohort (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom remission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPRS</td>
<td>50</td>
<td>59</td>
</tr>
<tr>
<td>BPRS + SANS</td>
<td>29</td>
<td>37</td>
</tr>
<tr>
<td>Social/vocational recovery</td>
<td>22</td>
<td>31</td>
</tr>
<tr>
<td>Social/vocational recovery + symptom remission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPRS</td>
<td>18</td>
<td>26</td>
</tr>
<tr>
<td>BPRS + SANS</td>
<td>15</td>
<td>24</td>
</tr>
</tbody>
</table>

BPRS: Brief psychotic rating scale
SANS: Schedule for assessment of negative symptoms
*Includes schizophrenia, schizophreniform disorder, schizoaffective disorder, affective psychosis, and other psychotic

Psychosocial Interventions

• Locations with strong social psychiatry presence may help to positively influence outcomes
• Psychiatrists in the UK make house calls to individuals with chronic schizophrenia to ensure medication adherence
RAISE Recovery After an Initial Schizophrenia Episode

- NIMH research project that seeks to fundamentally change the trajectory and prognosis of schizophrenia through coordinated and aggressive treatment in the earliest stages of illness
  - RAISE Early Treatment Program
  - RAISE Connection Program
  - Each model integrates
    - Medication
    - Psychosocial therapies
    - Family involvement
    - Rehabilitation services
    - Supported employment


Long-term Treatment and Symptomatic and Functional Outcomes


*P < 0.05 vs HAL; **P < 0.01 vs HAL

Reduction of Functional Disability with Long-term Atypical Antipsychotic Treatment

Interpersonal Functioning  Role Functioning

### Schizophrenia Is a Neurodevelopmental Disorder

- Treatments are unlikely to reverse this illness of the brain
- Biomarkers or genetics may ultimately help to identify individuals likely to get schizophrenia
  - Disease-modifying treatments that arrest illness
  - Prevent onset
  - Prevent disease progression

### Cognitive Deficits Are the Bridge Between Brain Functioning and Functional Impairments in Day-to-Day Life

- Cognitive deficits are a frequent and robust feature of the illness
- Cognitive deficits are present at illness onset and persist throughout the illness
- Cognitive deficits directly contribute to poor functional outcome in schizophrenia

### Normative Data Compared to a Schizophrenia Sample on the RBANS Neuropsychological Test

<table>
<thead>
<tr>
<th>Total Scale Score</th>
<th>Schizophrenia (n = 575)</th>
<th>Normal controls (n = 540)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50</td>
<td>0.4%</td>
<td>0%</td>
</tr>
<tr>
<td>51-60</td>
<td>5.0%</td>
<td>2.2%</td>
</tr>
<tr>
<td>61-70</td>
<td>7.2%</td>
<td>4.0%</td>
</tr>
<tr>
<td>71-80</td>
<td>10.4%</td>
<td>7.0%</td>
</tr>
<tr>
<td>81-90</td>
<td>14.5%</td>
<td>9.0%</td>
</tr>
<tr>
<td>91-100</td>
<td>20.8%</td>
<td>11.0%</td>
</tr>
<tr>
<td>101-110</td>
<td>24.5%</td>
<td>12.0%</td>
</tr>
<tr>
<td>111-120</td>
<td>18.8%</td>
<td>10.0%</td>
</tr>
<tr>
<td>121-130</td>
<td>9.0%</td>
<td>4.0%</td>
</tr>
<tr>
<td>131-140</td>
<td>3.1%</td>
<td>0%</td>
</tr>
<tr>
<td>140+</td>
<td>0%</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

RBANS: Repeatable Battery for Assessment of Neuropsychological Status

Components of Psychosocial Rehabilitation

- Neurocognition
  - Attention
  - Processing
  - Memory
  - Reasoning
  - Visual learning

- Social Cognition
  - Emotion processing
  - Social perception
  - Attributional bias
  - Theory of mind

- Motivational Aspects
  - External
  - Intrinsic

- Outcomes
  - Functional
  - Subjective


Cognitive Remediation

- Behavioral treatments that specifically target:
  - Memory
  - Attention
  - Executive functioning
  - Reasoning

- Restorative cognitive techniques – drill and practice:
  - Paper & pencil tasks
  - Computerized training software
  - COGPACK, Povit Science Brain Fitness, etc.
  - Individual
  - Groups
  - Compensatory cognitive training – promote adaptive behavior

- Enhance daily functioning
  - School, work, social interactions, independent living

- Enhance skills pertinent to recovery goals


Work and Schizophrenia

- 20% employed
- 80% Unemployed
- 55 – 70% identify employment as a goal

Barriers

- Cognitive impairments
- Psychiatric symptoms
- Episodes of illness
- Stigma from employers
- Internalized stigma/low self-confidence
- Fear of losing disability benefits

**Vocational Rehabilitation**

- Skills training
- Sheltered workshops
- Transitional employment
- Supported employment

**Vocational rehabilitation + cognitive remediation → best results**

**Employment**

- Increased self esteem
- Reduction in symptoms and hospitalizations
- Enhanced social functioning
- Improvement in overall quality of life

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**Supported Employment**

**Basic Principles**

1. Zero exclusion; eligibility based on consumer choice
2. Focus on competitive jobs in integrated community settings
3. Rapid job search
4. Respect for consumers' preferences in terms of the nature of the job and types of support services
5. Ongoing job support
6. Close integration with a psychosocial rehabilitation team approach
7. Benefits counseling (disability benefits, social security, medical insurance)

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**Optimizing Employment Outcomes**

**Vocational Rehabilitation (VR) + Cognitive Remediation (CR)**

<table>
<thead>
<tr>
<th>Weeks Worked</th>
<th>Community Work</th>
<th>Internship</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VR</td>
<td>VR + CR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1000</td>
<td>1500</td>
<td>2000</td>
</tr>
<tr>
<td></td>
<td>1500</td>
<td>2000</td>
<td>2500</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Wages Earned</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community Work</td>
</tr>
<tr>
<td>VR</td>
</tr>
<tr>
<td>1000</td>
</tr>
<tr>
<td>1500</td>
</tr>
</tbody>
</table>

* P < 0.05; ** P < 0.01
VR + CR: Greater improvements in verbal learning, memory, executive functioning vs VR only


Management of Schizophrenia

- Patient-focused therapeutic alliance
- Individualized approach
- Reduce or eliminate symptoms
- Optimize quality of life
- Assist patients in attaining personal life goals (work, housing, relationships)
- Guidelines and algorithms provide a framework for decision making

Guideline/Algorithm Recommendations

<table>
<thead>
<tr>
<th></th>
<th>APA</th>
<th>TMAP</th>
<th>PORT</th>
</tr>
</thead>
<tbody>
<tr>
<td>First episode</td>
<td>SGA</td>
<td>SGA</td>
<td>SGA, FGA</td>
</tr>
<tr>
<td>Second choice</td>
<td>SGA, FGA, C</td>
<td>SGA, FGA</td>
<td>SGA, FGA</td>
</tr>
<tr>
<td>Third choice</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Fourth choice</td>
<td>(C+)</td>
<td>C+</td>
<td>–</td>
</tr>
<tr>
<td>Fifth choice</td>
<td>–</td>
<td>A, T</td>
<td>–</td>
</tr>
<tr>
<td>Combinations</td>
<td>–</td>
<td>CF</td>
<td>–</td>
</tr>
</tbody>
</table>

FGA: first-generation antipsychotic
SGA: second-generation (atypical) antipsychotic
C: Clozapine
C+: Clozapine augmentation
CF: Clozapine failure


PORT Psychosocial Treatment

Recommendations for:
- Assertive community treatment
- Supported employment
- Skills training
- Cognitive behavioral therapy
- Token economy interventions
- Family-based services
- Interventions for alcohol and substance abuse disorders
- Interventions for weight management

Survey of APA Practice Research Network: Schizophrenia Treatments

Real-World Antipsychotic Treatment Practices

- Second-generation antipsychotics are used in over 70% of individuals with schizophrenia (use may be higher in first-episode patients).
- Rate of clozapine use is much lower than the incidence of treatment-resistant schizophrenia.
- Antipsychotic polypharmacy
  - ~10 to 30% of individuals with schizophrenia
  - FGA + SGA most common combinations
- Use of adjunctive medications
  - Baseline data from CATIE
  - Antidepressants (38%), anxiolytics (22%), sedative hypnotics (19%), lithium (4%), other mood stabilizers (15%)
- Dosage of antipsychotic medications within therapeutic range 64 to 83% of the time during inpatient treatment


Atypical Antipsychotics for Schizophrenia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation (Approval)</th>
<th>Dose Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole (Abilify&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Oral (2002)</td>
<td>10-30 mg/day</td>
</tr>
<tr>
<td>Clozapine (Sparine&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Oral (1969)</td>
<td>150-200 mg/day</td>
</tr>
<tr>
<td>Haloperidol (Haldol&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Oral (1958)</td>
<td>30-150 mg/day</td>
</tr>
<tr>
<td>Lurasidone (Latuda&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Oral (2010)</td>
<td>40-80 mg once daily</td>
</tr>
<tr>
<td>Olanzapine (Zyprexa&lt;sup&gt;®&lt;/sup&gt;)</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&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Long-acting IM (2009)</td>
<td>150-600 mg IM every 2 weeks</td>
</tr>
<tr>
<td>Quetiapine (Seroquel&lt;sup&gt;®&lt;/sup&gt;, Seroquel XR&lt;sup&gt;®&lt;/sup&gt;)</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&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Oral (1993)</td>
<td>4-16 mg/day</td>
</tr>
<tr>
<td>Risperidone (Risperdal&lt;sup&gt;®&lt;/sup&gt; Consta&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Long-acting IM (2003)</td>
<td>25, 37.5, or 50 mg IM every 2 weeks</td>
</tr>
<tr>
<td>Ziprasidone (Geodon&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Oral (2001)</td>
<td>80-100 mg/day</td>
</tr>
<tr>
<td>Ziprasidone (Geodon PR&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Oral (1997)</td>
<td>10-20 mg/day</td>
</tr>
<tr>
<td>Ziprasidone (Geodon&lt;sup&gt;®&lt;/sup&gt; Consta&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Long-acting IM (2006)</td>
<td>200-400 mg/day</td>
</tr>
<tr>
<td>Ziprasidone (Geodon&lt;sup&gt;®&lt;/sup&gt; SR&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Long-acting IM (2006)</td>
<td>117 to 234 mg per month</td>
</tr>
<tr>
<td>Ziprasidone (Sylatif&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Oral – sublingual (2008)</td>
<td>5-10 mg twice daily</td>
</tr>
<tr>
<td>Ziprasidone (Fanapt&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Oral (2009)</td>
<td>6-12 mg twice daily</td>
</tr>
<tr>
<td>Ziprasidone (Luceva&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Oral (2010)</td>
<td>20-40 mg once daily</td>
</tr>
</tbody>
</table>


Recently Approved Schizophrenia Treatments

<table>
<thead>
<tr>
<th>Structure</th>
<th>Receptor Binding Profile</th>
<th>Approved Dosage</th>
<th>Commonly Observed Adverse Reactions*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asenapine</td>
<td>D₂, 5HT₂A, 5HT₁A, 5HT₁B, 5HT₂B, 5HT₆, 5HT₇, α₁, α₂, H₁ antagonist; Little/no affinity for M₁ receptors</td>
<td>5-10 mg sublingually, administered once daily</td>
<td>Akathisia, oral hypoesthesia, somnolence</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>D₂, 5HT₂A, 5HT₁A, α₁, α₂, H₁ antagonist; Little/no affinity for M₁ receptors</td>
<td>12-24 mg/day administered once daily, initiated with slow dose titration</td>
<td>Dizziness, dry mouth, fatigue, nasal congestion, somnolence, tachycardia, weight increase</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>D₂, 5HT₂A, 5HT₁A, α₂A antagonist; 5HT₁ partial agonist; Little/no affinity for H₁ or M₁ receptors</td>
<td>40-80 mg once daily</td>
<td>Somnolence, akathisia, nausea, parkinsonism, agitation</td>
</tr>
</tbody>
</table>

*Incidence ≥ 5% and 2-fold greater than placebo


Asenapine in Patients with Acute Exacerbation of Schizophrenia

<table>
<thead>
<tr>
<th>Treatment Day</th>
<th>Asenapine 5 mg BID (n = 109)</th>
<th>Asenapine 10 mg BID (n = 105)</th>
<th>Placebo (n = 122)</th>
<th>Haloperidol 4 mg BID (n = 112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-25</td>
<td>-20</td>
<td>-15</td>
<td>-10</td>
</tr>
<tr>
<td>7</td>
<td>-20</td>
<td>-15</td>
<td>-10</td>
<td>-5</td>
</tr>
<tr>
<td>14</td>
<td>-15</td>
<td>-10</td>
<td>-5</td>
<td>0</td>
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<td>21</td>
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<tr>
<td>42</td>
<td>5</td>
<td>10</td>
<td>15</td>
<td>20</td>
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</tbody>
</table>

†P < 0.05 vs placebo
‡P < 0.05 asenapine 10 mg vs placebo

PANSS: Positive and Negative Syndrome Scale

Mixed Model for Repeated Measures

Iloperidone in Patients with Acute Exacerbation of Schizophrenia

<table>
<thead>
<tr>
<th>Day</th>
<th>Iloperidone 24 mg/day (n = 283)</th>
<th>Ziprasidone 160 mg/day (n = 144)</th>
<th>Placebo (n = 144)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-18</td>
<td>-15</td>
<td>-12</td>
</tr>
<tr>
<td>7</td>
<td>-15</td>
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<td>-9</td>
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<tr>
<td>14</td>
<td>-12</td>
<td>-9</td>
<td>-6</td>
</tr>
<tr>
<td>21</td>
<td>-9</td>
<td>-6</td>
<td>-3</td>
</tr>
<tr>
<td>28</td>
<td>-6</td>
<td>-3</td>
<td>0</td>
</tr>
</tbody>
</table>

*P < 0.05 vs placebo
†P < 0.01 vs placebo

PANSS: Positive and Negative Syndrome Scale

Mixed Model for Repeated Measures

Lurasidone in Patients with Acute Exacerbation of Schizophrenia, Pearl 2

Baseline Day 4 Week 1 Week 2 Week 3 Week 4 Week 5 Week 6
Placebo (n = 114)
Lurasidone 120 mg (n = 118)
Lurasidone 40 mg (n = 118)
Diazepam 15 mg (n = 121)

P-values based on Mixed Model for Repeated Measures model of change from baseline

Typical and Atypical Antipsychotics: Are Newer Drugs More Effective?

CATIE (US): Clinical Antipsychotic Trials of Intervention Effectiveness
CUtLASS (UK): Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study


Typical Antipsychotics–Safety

*Side Effects Scale
Unusual: reported in a few patients
Not unusual: occurs in a significant minority
Common: many experience or can be in significant amount
Problematic: occurs frequently, can be in a significant amount, and may be a health problem in some patients
Ziprasidone  n = 183  15
Risperidone  n = 333  10
Quetiapine  n = 329  15
Olanzapine  n = 330  19
Perphenazine  n = 257  6

Mean modal dose
Ziprasidone  112.8 mg/day
Risperidone  3.9 mg/day
Quetiapine  543.4 mg/day
Olanzapine  20.1 mg/day
Perphenazine  20.8 mg/day

Mean Rx length: 114.7 weeks
Average dose: 80 mg/day CPZ equivalent
Mean age: 76.9 yrs
1-year incidence: 25%
N = 261


The Risk of Tardive Dyskinesia Is Not Trivial

5-Year Prospective Incidence in Elderly with Conventional Antipsychotics

Mean Rx length: 114.7 weeks
Average dose: 80 mg/day CPZ equivalent
Mean age: 76.9 yrs
1-year incidence: 25%
N = 261


Tardive Dyskinesia Systematic Review

Publications After 2004

12 Studies at least 1 year duration; n = 28,051, mean age 39.7 years

**Therapies in Development for Schizophrenia**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Receptor Binding Profile</th>
<th>Clinical Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cariprazine</td>
<td>(D_3, D_2) partial agonist, Preferential binding to (D_2) \text{SHT}_{1A} ) partial agonist</td>
<td>• Positive results from phase 2b study</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Phase 3 studies ongoing</td>
</tr>
<tr>
<td>Sertindole</td>
<td>(\text{SHT}<em>{1A}, \text{SHT}</em>{2C}, \text{alpha},) antagonist</td>
<td>• Positive efficacy data from phase 3 studies, however safety concerns (cardiac risks) are significant limitation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Phase IV studies ongoing</td>
</tr>
<tr>
<td>LY2140023</td>
<td>Metabotropic glutamate receptor (mGluR 2/3) presynaptic agonist</td>
<td>• Phase 2 studies ongoing</td>
</tr>
</tbody>
</table>

**Cognitive Enhancement—Many Mechanisms Explored**

<table>
<thead>
<tr>
<th>Pharmacological Mechanism</th>
<th>Compounds</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholinergic</td>
<td>Donepezil, galantamine, rivastigmine</td>
<td>Negative results</td>
</tr>
<tr>
<td>Nicotinic</td>
<td>DMX-B, AZD3480</td>
<td>Negative results</td>
</tr>
<tr>
<td>Glutamatergic</td>
<td>D-cycloserine, CX-516, lamotrigine</td>
<td>Complex system; suggestion of modest improvement with agents that normalize glutamatergic functions</td>
</tr>
<tr>
<td>Noradrenergic</td>
<td>Guanfacine, atomoxetine</td>
<td>Negative results</td>
</tr>
<tr>
<td>Gamma-aminobutyric acid</td>
<td>Fluoxetine, lorazepam</td>
<td>Positive results in small studies</td>
</tr>
<tr>
<td>Serotonin</td>
<td>Tianeptine, buspirone</td>
<td>Limited evidence of benefits</td>
</tr>
<tr>
<td>Dopaminergic</td>
<td>Tolcapone</td>
<td>Safety concerns</td>
</tr>
<tr>
<td>Stimulant</td>
<td>methylphenidate, pemoline</td>
<td>Long-term safety considerations?</td>
</tr>
<tr>
<td>Alertness agents</td>
<td>modafinil</td>
<td>Exacerbation of psychosis?</td>
</tr>
</tbody>
</table>


**Effective Use of Medication (Optimizing Adherence)**

- Medication is a tool that a person with schizophrenia can use to take greater control over his or her life
- The goal should be to maximize the effectiveness of medication to help the person live the kind of life that he or she wants to live
Medication Nonadherence

- Prevalence ~30 to 50% (and higher); rates vary depending on clinical setting, definitions, study duration, study population
- Relatively short gaps in medication coverage can increase the risk of relapse
- Nonadherence is associated with poor outcomes
  - Relapse
  - Hospitalization
  - Suicide attempts


Barriers to Medication Adherence in Schizophrenia

<table>
<thead>
<tr>
<th>Patients (n = 153) reporting barriers (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stigma</td>
</tr>
<tr>
<td>Adverse drug reactions</td>
</tr>
<tr>
<td>Homelessness/substance abuse</td>
</tr>
<tr>
<td>Forgetfulness</td>
</tr>
<tr>
<td>Lack of social support</td>
</tr>
<tr>
<td>Afraid of medication</td>
</tr>
<tr>
<td>Denial of illness</td>
</tr>
<tr>
<td>Lack of trust in provider</td>
</tr>
<tr>
<td>Difficulty with regimen</td>
</tr>
</tbody>
</table>


Factors that Contribute to Nonadherence

Patient-related Factors
- Persecutory delusions
- Lack of insight
- Health care beliefs
- History of substance abuse
- Previous nonadherence

Medication-related Factors
- Lack of efficacy
- Distressing side effects
- High doses
- Medication type
- Regime complexity

Environmental Factors
- Caregiver support
- Family and social support
- Financial cost
- Practical barriers

Clinician-related Factors
- Poor therapeutic alliance
- Attitude of staff

Monitoring Use of Medication Balancing Accuracy and Invasiveness

Variability in Adherence Assessment for Patients Prescribed Antipsychotics

57%
7%
5%
0 10 20 30 40 50 60
Nonadherence (%)

Electronic Monitoring Device Prescribers Patients

Theories Regarding Medication Adherence in Patients with Schizophrenia

1. Adherence is not a clinical outcome and only matters as it interferes with outcome
2. Adherence problems are often entangled with efficacy limitations of antipsychotic medications
3. Adherence can be viewed as a behavior or as an attitude
4. When considering adherence attitudes, patient belief is always reality
5. Adherence behavior changes and fluctuates over time and should be considered part of the illness

Strategies to Maximize Treatment Adherence

• Maintain a strong therapeutic alliance
• Address barriers
• Maximize efficacy, tailored treatment for each patient
• Maximize tolerability, patient-specific
• Long-acting depot formulations
• Psychosocial interventions
• Address cognitive deficits

Considerations for Discussing Use of Medication with Patients

• How you ask is important
• Your relationship with the patient is key
• Avoid appearing punitive or authoritarian
• Let the patient know that it is OK to disagree
• Be willing to take a flexible approach
• Exploring practical problems that interfere with adherence can help sort out reasons for less optimal medication response

Tailored Environmental Supports to Improve Medication Adherence

<table>
<thead>
<tr>
<th>Months to Relapse</th>
<th>Proportion Without Significant Relapse or Exacerbation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PharmCAT (n = 32)</td>
</tr>
<tr>
<td></td>
<td>CAT (n = 34)</td>
</tr>
<tr>
<td></td>
<td>Treatment as usual (n = 29)</td>
</tr>
</tbody>
</table>

CAT: cognitive adaptation therapy, environmental supports to cue behavior
PharmCAT: focuses on medication and appointment adherence

Long-Acting Injectable (LAI) Antipsychotics to Improve Medication Adherence

Balancing Advantages and Disadvantages

- Assured medication delivery
- Continuous antipsychotic coverage
- Reduced risk of relapse
- More frequent contact with treatment team
- Increasing number of options available

- Cost/insurance coverage
- More appointments
- Oral to LAI conversion
- Perceived stigma
- Negative perceptions by clinicians

Relapse Prevention with Risperidone Long-acting Injectable (RLAI) vs Oral Quetiapine

Paliperidone Palmitate Injectable Time to Relapse in Adults with Schizophrenia
Olanzapine Long-Acting Injection
24-Week Maintenance Study


High dose: 300 mg every 2 weeks
Medium dose: 405 mg every 4 weeks
Low dose: 150 mg every 2 weeks
Very low dose: 45 mg every 4 weeks

Optimizing Outcomes in Schizophrenia

- Develop a strong patient-focused therapeutic alliance
- Use an individualized approach
- Guidelines and algorithms provide a framework for decision making
- Treat early and comprehensively
  - Facilitate access to complete, coordinated, and continuous treatment
- Anticipate lapses in medication adherence
  - Employ strategies to optimize effective use of medication
- Partner with family and other social supports
- Encourage opportunities to engage in functional activities and receive specialized interventions
- Both symptomatic and functional remission are meaningful treatment goals
- Principles of recovery can be applied to all patients with schizophrenia
  “Having the best life possible, despite illness and symptoms”

Please take posttest now and complete the attestation/evaluation form
10 Components of Recovery
National Consensus Statement SAMHSA

1. Self-direction
2. Individualized and person-centered
3. Empowerment
4. Holistic
5. Non-linear
6. Strength-based
7. Peer support
8. Respect
9. Responsibility
10. Hope


Gray Matter Loss in Adult Patients With Schizophrenia at Baseline and 5-Year Follow-up


Excessive gray matter loss was related to increased number of hospitalizations (increased psychotic episodes).
Duration and Severity of Untreated Psychosis and Outcome in First-episode Schizophrenia

- Meta-analysis of 43 publications
- Prolonged duration of untreated psychosis prior to the initiation of treatment was associated with poorer symptomatic and functional recovery in initial episodes


APA Treatment Guidelines
Medication Choice in Acute Phase

APA Treatment Guidelines


Texas Medication Algorithm Project (TMAP)

- Choice of antipsychotic should be guided by considering the clinical characteristics of the patient and efficacy/side-effect profiles of medication.
- First-episode patients usually require lower antipsychotic dosing.
- Treatment adherence is an issue; assess contributing factors, consider long-acting preparation.
- Treatment refractory evaluation should be performed to re-examine diagnosis, substance abuse, medication adherence, psychosocial stressors.

FGA: first-generation antipsychotic
SGA: second-generation antipsychotic
ECT: electroconvulsive therapy


Texas Medication Algorithm Project (TMAP) Clinical Management

1. At baseline and throughout treatment, evaluate patients for psychosocial interventions.
2. Re-evaluate accuracy of diagnosis, presence of comorbidities for patients refractory to treatment.
4. Complete symptom ratings (such as Positive Symptoms Rating Scale, Brief Negative Symptom Assessment) at each medication visit for objective treatment decisions.
5. Document each algorithm stage and treatment choice.
6. Establish visit frequency for adequate monitoring of symptoms, adverse effects and dose adjustment for optimal therapeutic trial.
7. Initiate treatment with the form of recommended medication that is likely to be best tolerated by the patient (brand, generic, slow release, etc.), use an adequate dose and sufficient duration of treatment.
8. All patients should continue on maintenance treatment following satisfactory clinical response to treatment (minimal positive symptoms, remission).
9. Address medication acquisition cost considerations.

### Schizophrenia Patient Outcomes Research Team (PORT) Recommendations
#### Psychopharmacological Treatment

**Treatment of acute positive symptoms (acute exacerbation) in treatment-responsive schizophrenia**
- First-line treatment with an antipsychotic other than clozapine
- Treatment trials at least 2 weeks, with upper limit of 6 weeks to observe optimal response
- Antipsychotic choice: consider individual preference, prior treatment response, side effect experience; adherence history; relevant medical history and risk factors; medication side effect profile; long-term treatment planning

**Treatment of acute positive symptoms in first-episode schizophrenia**
- Antipsychotic treatment other than clozapine and olanzapine
- Starting antipsychotic doses should be lower than those recommended for multi-episode patients

### PORT Recommendations
#### Psychopharmacological Treatment

**Maintenance pharmacotherapy in treatment-responsive patients**
- Continued antipsychotic treatment to maintain symptom relief and reduce risk of relapse/worsening of symptoms

**Maintenance pharmacotherapy with long-acting antipsychotic treatment**
- Long-acting injectable (LAI) antipsychotic medication should be offered as an alternative to oral medication for maintenance treatment when LAI is preferable to oral preparations

**Maintenance with targeted, intermittent antipsychotic treatment**
- Not recommended in lieu of continuous antipsychotic treatment due to increased risk of symptom worsening and relapse

### PORT Recommendations
#### Psychopharmacological Treatment

**Residual positive symptoms in treatment-resistant patients**
- Clozapine should be offered when positive symptoms persist after 2 adequate trials of other antipsychotic agents
- A trial should last at least 8 weeks (300-800 mg/day)
- Clozapine plasma levels should be monitored in individuals with inadequate response; adjust dose to target > 350 ng/mL as tolerated

**Residual symptoms-hostility**
- Trial of clozapine should be offered

**Residual symptoms-suicidality**
- Trial of clozapine should be offered

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PORT Recommendations
Psychopharmacological Treatment

Prophylactic antiparkinson medication • For those treated with first-generation antipsychotics, prophylactic use of antiparkinson agents to reduce the incidence of extrapyramidal side effects should be determined on a case by case basis

Treatment of acute agitation • Oral or IM antipsychotic alone or in combination with a rapid-acting benzodiazepine

Intervention for smoking cessation • Bupropion SR (150 mg BID) for 10-12 weeks, with or without nicotine replacement therapy
• Smoking cessation education or support group

Acute treatment of persistent auditory hallucinations • Low frequency repetitive transcranial magnetic stimulation over the left temporoparietal cortex


Olanzapine vs Haloperidol
TD: 1-Year Prospective Incidence

<table>
<thead>
<tr>
<th>Drug</th>
<th>Year Incidence</th>
<th>N</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>7.45%</td>
<td>114</td>
<td>0.002 olanzapine vs. haloperidol</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>0.52%</td>
<td>513</td>
<td></td>
</tr>
</tbody>
</table>


Risperidone
TD: 1-Year Prospective Incidence in the Elderly

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Rx length</td>
<td>273 days</td>
</tr>
<tr>
<td>Mean age</td>
<td>82.5 years</td>
</tr>
<tr>
<td>1-year incidence</td>
<td>2.6%</td>
</tr>
</tbody>
</table>