Treating the Patient with Schizophrenia: Striking a Balance Between Symptom Control and Tolerability

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Objectives

To understand the impact of schizophrenia (SCZ) on cognitive and social functioning

To describe how persistent SCZ symptoms and loss of function may impact patients and caregivers

To understand the trade-off between symptom control and tolerability issues that must be balanced with current therapy

To understand how optimizing therapy can help some patients achieve long-term symptomatic improvement
SCHIZOPHRENIA CAN BE A PROGRESSIVE, CHRONIC, DEBILITATING DISEASE

Rebecca Roma, MD, MBA
A Patient’s Journey With Schizophrenia: Loss of Interpersonal Connection and Decreased Satisfaction With Life

“I have lost all form of desire. I have no contact to myself. I feel like a zombie; I am unable to feel pleasure; everything appears indifferent. I am not a part of this world; I have a strange ghostly feeling as if I was from another planet. I am almost nonexistent.”

—Patient with schizophrenia*

*From a study of patients in the prodromal phases of schizophrenia and schizotypal conditions

Patients’ Experience With SCZ Can Involve a Variety of Positive, Negative, and/or Cognitive Symptoms\(^1,2\)

### Positive Symptoms

“Positive” refers to overt symptoms that should not be present. These include:
- Hallucinations
- Delusions
- Disorganized speech

### Negative Symptoms

“Negative” does not refer to a person’s attitude but instead to a lack of characteristics that should be present. These include:
- Reduced speech
- Lack of emotional/facial expression
- Diminished ability to begin and sustain activities
- Decreased ability to experience pleasure
- Social withdrawal

### Cognitive Deficits

Difficulties with the following aspects of cognition can make it hard to live a normal life or earn a living:
- Memory
- Attention
- Planning
- Decision making

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The onset and trajectory of SCZ progression may be influenced by genetics, developmental risk factors, and social adversity.
The Theoretical Course of SCZ Progression May Lead to Functional Decline\textsuperscript{1-4}

SCZ Is Associated With an Increased Prevalence of Psychiatric and Physical Comorbidities


<table>
<thead>
<tr>
<th>Condition</th>
<th>Schizophrenia Population (%) N=26,279</th>
<th>Control Population (%) N=1,936,876</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressive disorder*</td>
<td>3.7%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Affective psychoses*</td>
<td>2.0%</td>
<td>6.9%</td>
</tr>
<tr>
<td>Personality disorders*</td>
<td>2.0%</td>
<td>13.6%</td>
</tr>
<tr>
<td>Neurotic disorders</td>
<td>5.1%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Alcohol dependence syndrome</td>
<td>10.2%</td>
<td>4.0%</td>
</tr>
<tr>
<td>Nondependent abuse of drugs</td>
<td>24.1%</td>
<td>7.3%</td>
</tr>
</tbody>
</table>

*Prevalence in control population ≤2%.

- Schizophrenia patients also had longer hospitalizations
Patients With SCZ Are More Likely to Have Physical Comorbidities

Prevalence of Physical Comorbidities in SCZ Patients (mean age, 40.2 y) and Control Subjects (mean age, 37.7 y) from the Wellmark Blue Cross/Blue Shield of Iowa Database

- 33.2% of schizophrenia patients had ≥3 comorbidities compared with 12.1% of controls (P<0.0001)
- 29% of schizophrenia patients had no comorbidities compared with 54.7% of controls (P<0.0001)
- Schizophrenia patients required significantly more months of follow-up care and more healthcare visits

*The adjusted odds ratio was not significant (OR 0.99, 95% CI 0.81-1.20).

SCZ patients are more likely to:
- Become unemployed and homeless
- Lose the ability to work competitively
- Isolate from friends and family

Disease impact extends beyond the patient:
- Caregiver fatigue, discouragement, and resource utilization
- Healthcare, social, and criminal justice costs

DISCUSSION
THE IMPACT OF PERSISTENT SYMPTOMS ON PATIENTS

Georgia Stevens, PhD, APRN, PMHCNS-BC
Despite Availability of Therapy, SCZ Continues to Represent a Major Source of Disability* in the US\textsuperscript{1-3}

*In the IHME study, disability was defined as any short- or long-term health loss.\textsuperscript{1}

DALYs, disease-adjusted life years: The sum of years lost due to premature death (YLLs) and years lived with disability (YLDs). DALYs are also defined as years of healthy life lost.\textsuperscript{1}

Significant Correlations Between Measures of Cognition, Symptomatology, and Functionality in a Study of Patients With Schizophrenia

Post hoc path analysis of multiple measures in a single patient population (N=384).

*Except for the correlation between cognition and negative symptoms in relation to motivation/sense of purpose (P < 0.01).

On Average, Only 2 of 10 Patients Receiving Pharmacologic Therapy for SCZ May Achieve Symptom Remission for ≥ 6 Months

Percent of Patients Achieving Symptom Remission Over 18 Months Irrespective of Switching Medications (N = 1122)*

- Patients in the CATIE trial were initially randomized to double-blind treatment with an atypical antipsychotic (for 18 months). Premature discontinuation resulted in a series of switches between antipsychotics that were studied for the remainder of the 18 months.
- Remission was defined as a score of mild or lower on 8 specific items (delusions, conceptual disorganization, hallucinatory behavior, blunted affect, social withdrawal, lack of spontaneity, mannerisms/posturing, and unusual thought content) of PANSS. Patients were considered to be not in remission at baseline.

*Data are shown as the percentage of dropouts and completers who did not remit, showed any remission, showed ≥ 3 months’ remission, or showed ≥ 6 months’ remission.

CATIE, Clinical Antipsychotic Trials of Intervention Effectiveness; PANSS, Positive and Negative Syndrome Scale.
Despite Pharmacologic Therapy, 22% of Patients Experience Symptom Relapse in Studies of Varying Lengths

Relapse Rate* During Maintenance Therapy with Antipsychotic Medication (Meta Analysis of 62 studies)

In 62 studies of varying lengths, the overall rate of relapse was 22% for patients receiving antipsychotics vs 57% for patients receiving placebo/no treatment

1. *Relapse criteria were clinical judgment (26 studies), need of medication (17 studies), rating-scale-based definitions (15 studies), admission to hospital (3 studies), and dropout due to worsening of symptoms (2 studies); in 2 studies the relapse criteria were not indicated; 2. Leucht S, et al. *Lancet*. 2012;379:2063-2071.
SCZ Symptom Relapse May Predict Decreased Responsiveness to Therapy Through 32 Weeks

Post hoc analysis of 97 patients in a multinational relapse prevention:
- At baseline, PANSS total scores were 70.0 for prerelapse patients and 78.2 following relapse ($P < 0.001$)
- At week 32, PANSS total scores were 54.5 for prerelapse patients and 56.7 following relapse ($P = 0.026$); this 2.2-point difference suggests a small but significant increase in residual symptoms following relapse
- At week 48 after reinitiating therapy, the difference in PANSS scores was no longer apparent, which may indicate symptoms resolve to prerelapse levels if therapy remains consistent

PANSS, Positive and Negative Syndrome Scale; SE, standard error.

DISCUSSION
MANAGING THE PATIENT WITH SCHIZOPHRENIA: THE BALANCE BETWEEN SYMPTOM CONTROL AND SIDE EFFECTS OF THERAPY

Rebecca Roma, MD, MBA
"It took a lot of convincing for him to put me on lower doses of things because my body is sensitive and I know that. But I guess the normal dose for something, maybe of my body weight or whatever was what he was trying to give me…. It was very stressful and kind of scary because the medication would make me feel weird…"

—*Patient with schizophrenia*

*This patient was enrolled in the first-episode psychosis program Specialized Treatment Early in Psychosis (STEP), based at the Connecticut Mental Health Center. Patients included in this study ranged in age from 20–35 years.

The Current Standard of Care for SCZ Is Characterized by the Impact and Limitations of Treatment\(^1,2\)

<table>
<thead>
<tr>
<th>Antipsychotic Classification</th>
<th>Functional Impact</th>
<th>Treatment Limitations</th>
</tr>
</thead>
</table>
| First generation (Typical)  | • Decrease frequency and severity of psychotic episodes  
                            • Improve functional capacity | • Adverse effects (EPS symptoms)  
                            • Suboptimal outcomes |
| • Dopamine D\(_2\)-receptor antagonism |                        |                       |

| Second generation (Atypical) | All the efficacy goals of first-generation antipsychotics plus:  
                            • Reduced EPS-symptom profile  
                            • Increased rates of relapse prevention and treatment continuation | • No clear superiority over first-generation medication in improving positive, cognitive, and social outcomes  
                            • Side effects (metabolic, weight gain, sedation)  
                            • Adverse events (agranulocytosis) |
| • Dopamine D\(_2\)-receptor antagonism / partial agonism  
• Serotonin 5HT-2A antagonism and 5-HT1a partial agonism |                        |                       |

EPS, extrapyramidal symptoms.
Bothersome Side Effects Are Commonly Reported by Patients During SCZ Therapy

Bothersome Medication Side Effects Reported by >10% of Current Medication Users (N = 876)

- Difficulty thinking/concentrating
- Restlessness/feeling jittery
- Insomnia
- Sleepiness
- Weight gain
- Decreased interest in sex
- Agitation
- Sedation
- Dizziness
- Constipation
- Tremors
- Sexual dysfunction
- Nausea/vomiting

- Among patients with SCZ, 86.2% overall reported the presence of any medication side effect in this cross-sectional study.

Data based on a nationwide survey of adults with a self-reported diagnosis of SCZ and who were currently using an antipsychotic medication.

Treatment Limitations of Current Therapy May Lead to Discontinuation

Reasons for Treatment Discontinuation During the CATIE Trial

Antipsychotic-induced Akathisia May Result in Cognitive Deficits, Anxiety, and Impaired Coping\textsuperscript{1,2}

Comparison of FCQ Scores Between Subjects With and Without Akathisia*†

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Akathisia (n = 25)</th>
<th>Non-akathisia (n = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Disorder of selective attention</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Deterioration of discrimination</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Perceptual disorder</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Disorder of coping responses</td>
<td>7</td>
<td>6</td>
</tr>
</tbody>
</table>

- An expert review paper reported that the risk for extrapyramidal symptoms, including akathisia, correlated with an atypical antipsychotic’s binding affinity for multiple receptors (eg, D\textsubscript{2}, 5-HT\textsubscript{2A}, muscarinic, and histamine)\textsuperscript{2}

\*P <.05. †This study took place in a Korean population but used the Barnes Akathisia Rating Scale to assess treatment-related akathisia.

Difference in FCQ scores for psychomotor disorder, cognitive floating, blocking symptoms, language disorder, and automatic behavior disorder not significant.

FCQ, Frankfurt Complaint Questionnaire.
Antipsychotic-induced Sedation May Impair Quality of Life and Functional Capacity, Which Can Cause Treatment Dissatisfaction\textsuperscript{1-3}

- In another study, it was found that patients with persistent sedation may complain that they have no energy, that they constantly feel tired, or that they cannot think clearly\textsuperscript{3}
- It was also found that the risk for somnolence and sedation correlates with the H\textsubscript{1}-receptor-binding affinity of each atypical antipsychotic\textsuperscript{3}:
  - Higher H\textsubscript{1}-receptor affinities may lead to increased rates of somnolence\textsuperscript{3}

Chronic SCZ Patients on Established Antipsychotic Therapy Demonstrate Multiple Risk Factors for Metabolic Syndrome

Summary of individual metabolic syndrome risk factors in a meta-analysis of 21 studies of unmedicated SCZ patients (n = 8593), 26 studies of first-episode SCZ patients (n = 2548), and 78 studies of medicated patients with chronic SCZ (n = 24,892)

- Among patients with chronic SCZ:
  - 1 in 2 are overweight (waist size: men > 102 cm, women, > 88 cm)
  - 2 in 5 have high blood pressure (>130/85 mmHg)
  - 1 in 10 have diabetes
- First-episode SCZ patients had significantly fewer metabolic risk factors than those on established antipsychotic medication

*Data from a meta-analysis of 32 publications. BP, blood pressure; HDL, high-density lipoprotein; IFG, impaired fasting glucose.
DISCUSSION
OPTIMIZING CURRENT THERAPY MAY LEAD TO LONG-TERM SYMPTOMATIC IMPROVEMENT FOR SOME PATIENTS$^{1,2}$

Georgia Stevens, PhD, APRN, PMHCNS-BC

Selecting Therapy Based on Clinical Circumstances: Recommendations From the APA Work Group on SCZ

Choose medication based on clinical circumstances from following:

- Group 1: First-generation antipsychotics
- Group 2: Second-generation antipsychotics*
- Group 3: Clozapine
- Group 4: Long-acting injectable antipsychotics

**Acute Phase**

- **For intolerable side effects:** choose a different medication from Group 1 or 2.
- **Good response without intolerable side effects?**
  - **Yes:** Continue acute-phase medication treatment.
  - **No:** Continue acute-phase medication treatment.

**Stabilization Phase**

- **For intolerable side effects:** choose a different medication from Group 1 or 2.
- **For residual or intercurrent symptoms:** consider a different medication from Group 2 or 3 or appropriate adjunctive medication.
- **For treatment nonadherence:** consider a different medication from Group 4.

*Second-generation antipsychotics on the market at the time of the publication. APA, American Psychiatric Association; ECT, electroconvulsive therapy.

Important to Consider Clinical Benefits Against Side Effects Throughout the Course of Disease

Clinical benefits¹,²:
• Efficacy against positive, negative, and cognitive symptoms
• ↓ relapse risk
• ↑ stability

Side effects (examples)¹,²*:
• EPS (incl. akathisia)
• Sedation
• Weight gain
• Metabolic effects
• Hyperprolactinemia / sexual side effects

• Antipsychotics vary in their clinical efficacy and in their side-effect profiles²
• In patients with schizophrenia, stable disease is associated with better quality of life, whereas relapse is strongly associated with reduced quality of life³
• Side effects are associated with a reduced quality of life, with some side effects (eg, EPS, diabetes) having a more pronounced effect than others³,⁴
• Treatment decisions change based on stage of disease and tolerability of current medication¹

*Prevalence dependent on class of antipsychotic being used.
Early Response to Antipsychotic Therapy May Be Predictive of Improved Long-term Treatment Response in Some Patients

252 Patients With Schizophrenia Followed for up to 18 Months

- Early response (n=136)
- Delayed response (n=50)
- Nonresponse (n=66)

Greatest Percent Total Improvement, %

- Statistically significant differences between early and delayed responders were observed from week 5 to week 12 (P < 0.05), aside from week 8, on the PANSS general psychopathology subscale
- There was no difference in percent change in PANSS score between early and delayed responders after week 12
- Compared with nonresponders, early responders maintained significantly greater PANSS total percent change from week 5 to 44, and delayed responders from week 5 to 20

Early responders achieved a 20% PANSS total change over 2 weeks of treatment; delayed responders achieved a 20% PANSS total change during weeks 3-4; nonresponders did not achieve a 20% PANSS total change through week 4.

A 3-Year Study Showed Significantly Improved Remission and Quality of Life With an Atypical Antipsychotic

Post hoc analysis of data from a 40-week randomized, double-blind study followed by a 3-year double-blind extension (186 patients in analysis).


\[ P < 0.01 \text{ (atypical antipsychotic vs conventional antipsychotic, slope)} \]
\[ *P < 0.05 \text{ (atypical antipsychotic vs conventional antipsychotic)} \]
“[I don’t feel as] anxious anymore. And that takes years. It’s not something automatic. You have to learn to cope with your problems… and talking helps. Being out in public helps. But for me the most important thing I tell people is that you have to do something that makes you feel you accomplished something.”

—Patient with schizophrenia*

*This patient was enrolled in the first-episode psychosis program Specialized Treatment Early in Psychosis (STEP), based at the Connecticut Mental Health Center. Patients included in this study ranged in age from 20–35 years.
DISCUSSION
Conclusions

- SCZ is a significant and progressive disorder associated with both psychiatric and medical comorbidities
- Negative symptoms and cognitive deficits are predictors of poor daily functioning
- Persistent symptoms and rehospitalizations are common in patients with schizophrenia
- Use of current pharmacologic therapy for SCZ involves finding a balance between symptom control and alleviating common side effects such as weight gain, metabolic effects, EPS, and sedation
- Optimizing therapy could offer some patients a pathway towards long-term symptomatic improvement

QUESTIONS
CLOSING
Managing the Patient with Schizophrenia:

Striking a Balance Between Symptom Control and Tolerability

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