Beyond the Positive: The Role of Cognitive and Negative Symptoms of Schizophrenia
Learning Objectives

• Recognize the impact of cognitive and negative symptoms on functioning and outcomes in patients with schizophrenia

• Assess and monitor the cognitive and negative symptoms of patients over time

• Incorporate psychosocial strategies into the overall care of patients with schizophrenia

• Enable patients to participate in their own recovery by establishing life goals
Ian is a 24-year-old patient with schizophrenia and prominent negative symptoms, including amotivation and alogia. Which of the following statements is true regarding anhedonia in patients with schizophrenia?

1. Patients with schizophrenia are unable to experience pleasure
2. Patients with schizophrenia are unable to anticipate the experience of pleasure
3. Both of the above
Pretest Question 2

Marie is a 37-year-old homeless patient with schizophrenia who was recently hospitalized. Although she was diagnosed at age 22, she has never taken an antipsychotic. A longer duration of untreated schizophrenia has been associated with:

1. Increased negative symptoms
2. Less improvement in verbal memory
3. Worse positive symptoms
4. 1 and 2 only
5. 2 and 3 only
A 42-year-old patient with treatment-resistant schizoaffective disorder is currently enrolled in a cognitive enhancement therapy (CET) program. Recent evidence suggests that CET may be effective in treating:

1. Cognitive symptoms of schizophrenia
2. Negative symptoms of schizophrenia
3. Both of the above
Symptom management
Physical health
Reduced hospitalization
Reduced criminal activity
Reduced substance abuse
Stable housing
Employment
Community involvement
Family involvement
Treatment alliance
Cognitive ability
Empowerment

RECOVERY
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

Successful treatment of positive symptoms is not predictive of social functioning or independent living skills

Negative Symptoms

• 2005 NIMH MATRICS consensus includes 5 negative symptom domains
  – Blunted affect
  – Alogia
  – Asociality
  – Avolition
  – Anhedonia

• These domains may be categorized into 2 factors: diminished expression and amotivation

• Negative symptoms may be primary or secondary

### 5 Domains of Negative Symptoms

<table>
<thead>
<tr>
<th>Domain</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AMOTIVATION</strong></td>
<td></td>
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<tr>
<td>AVOLITION</td>
<td>Deficits in initiation and maintenance of goal-directed behaviors</td>
</tr>
<tr>
<td>ANHEDONIA</td>
<td>Reduced ability to anticipate pleasure</td>
</tr>
<tr>
<td>ASOCIALITY</td>
<td>Diminished interest in social interactions</td>
</tr>
<tr>
<td><strong>DIMINISHED</strong></td>
<td></td>
</tr>
<tr>
<td>BLUNTED AFFECT</td>
<td>Reduced intensity and range of emotional expression</td>
</tr>
<tr>
<td>ALOGIA</td>
<td>Decreased quantity of speech</td>
</tr>
</tbody>
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Anticipatory Anhedonia

• 2 components of hedonic experience
  – Anticipatory hedonia (wanting the experience)
  – Consummatory hedonia (enjoying the experience)

• Patients with schizophrenia are able to experience pleasure but display anticipatory anhedonia

• Possibly attributable to impairments in reward neurocircuitry
  – Difficulty processing reward information
    • Overlap with cognitive impairment

New Conceptualization of Negative Symptoms

- Attentional impairment, poverty of speech, and inappropriate affect may be categorized as part of the disorganized symptom domain rather than the negative symptom domain.
Cognitive Symptoms

• Present in 80% of patients with schizophrenia

• 2005 NIMH MATRICS consensus identified 7 cognitive domains
  – Verbal learning and memory
    • Most consistent and severe cognitive impairment in schizophrenia
  – Visual learning and memory
  – Working memory
  – Speed of processing
  – Reasoning and problem solving
  – Attention
  – Social cognition

Cognitive Symptoms Throughout the Course of Schizophrenia

- Cognitive deficits often evident during the prodromal period (prior to the first episode of psychosis)
- Improvement in cognitive deficits over time?
- Progressive decline over time?
- Most studies suggest that cognitive impairment remains stable over time
- Cross-sectional studies: progressive decline
- Longitudinal studies: cognitive impairment remains stable during the chronic phase

Distinguishing Negative and Cognitive Symptoms

• Correlation between negative and cognitive symptoms, including impaired social cognition?
  – A confounding issue of commonly used assessment tools (eg, PANSS)?

• Negative symptoms may mediate the relationship between cognitive impairment and functional outcomes
  – Do neurocognition (what one can do) and negative symptoms (what one wants to do) act independently on functional outcomes?

Prognosis in Schizophrenia

- Poor functional outcomes
  - Quality of life, psychosocial and occupational functioning

- Severity of negative symptoms predicts social functioning
  - Especially motivational deficits (rather than emotional blunting)

- Severity of cognitive symptoms predicts residential and vocational functioning
  - Especially verbal memory

Duration of Untreated Psychosis (DUP)

• 3-year longitudinal study of patients with short vs. long DUP
• Level of negative symptoms did not differ between patients with short vs. long DUP at intake
• Long DUP was associated with:
  – Increased negative symptoms
  – Less improvement in verbal memory
• Patients with short vs. long DUP did not differ in positive symptom severity at any time point
• Longer DUP may result in greater brain structural deficits

Gray Matter Loss Is Worse in Patients With a Longer Duration of Untreated Psychosis

Colored voxels depict brain areas of significantly greater gray matter loss in patients with a long duration of untreated psychosis (>18 wks) compared to those with a short duration (<18 wks)

Progressive Gray Matter Loss in Adolescent Patients With Schizophrenia Over 5 Years

Loss of Gray Matter in Unmedicated Patients With Schizotypal Personality Disorder or Schizophrenia

Reduced Gray Matter Volume in Antipsychotic-Naïve Patients With First-Episode Schizophrenia Correlates With Functional Deficits

Temporal Lobe Abnormalities

Correlate with:
- Global Assessment of Functioning (GAF) Scale
- PANSS Positive Symptoms
- PANSS Thought Disturbance
- PANSS Activation
- PANSS Paranoia
- PANSS Impulsive Aggression
- PANSS General Psychopathology

Anterior Cingulate Gyrus Abnormalities

Correlate with:
- Global Assessment of Functioning (GAF) Scale
- PANSS Positive Symptoms
- PANSS Thought Disturbance
- PANSS Activation
- PANSS Paranoia
- PANSS Impulsive Aggression

ASSESSMENT AND MONITORING OF NEGATIVE AND COGNITIVE SYMPTOMS
Measuring Negative Symptoms

- Older rating scales may not be accurate
  - PANSS (Negative Symptoms Subscale) and SANS both include measures of attentional deficits
  - PANSS (Negative Symptoms Subscale) does not cover all negative symptoms

- Brief Negative Symptom Scale (BNSS)

- Clinical Assessment Interview for Negative Symptoms (CAINS)

- Schedule for the Deficit Syndrome (SDS)

- Negative Symptom Assessment (NSA-16; NSA-4)

Measuring Cognitive Symptoms

- Brief Assessment of Cognition in Schizophrenia (BACS)
- MATRICS Consensus Cognitive Battery (MCCB)
- Schizophrenia Cognition Rating Scale (SCoRS)
- UCSD Performance-Based Skills Assessment Battery (UPSA; UPSA-Brief)

Measuring Functional Outcomes

• Self-reports: the worst way to measure functioning?
  – For instance, patients who have never had a job may report competence in employment skills

• Quality of Life Scale (QLS)
• Specific Level of Functioning (SLOF)
• Social Skills Performance Assessment (SSPA)
• Motor-Affective-Social-Scale (MASS)

PHARMACOLOGICAL MANAGEMENT OF NEGATIVE AND COGNITIVE SYMPTOMS
Antipsychotics

• Second-generation antipsychotics (SGAs): better for treating negative and cognitive symptoms than first-generation antipsychotics (FGAs)?

• Clozapine may be best
  – However, no antipsychotic has shown robust effects on negative or cognitive symptoms

• Antipsychotics may actually worsen negative symptoms and cognitive impairments

• No robust evidence for the efficacy of adjunctive agents

Time as a Drug

• Therapeutic effects on non-positive symptoms may require time
• Long-term treatment often leads to steady improvement in schizophrenia symptoms
• Some patients with schizophrenia show an early robust response to treatment
• For most, response may take time, especially in treatment-resistant patients
• Superior efficacy of one antipsychotic over another may require time

Some Patients May Require a Year Before Responding to Treatment

13% of patients did not show 20% improvement on the Heinrichs-Carpenter Quality of Life Scale until 1 year of clozapine treatment

Efficacy of Antipsychotics on Positive and Negative Symptoms of Schizophrenia

Efficacy of Antipsychotics on Negative Symptoms of Schizophrenia

Long-term Differences Between an Atypical and a Conventional

Efficacy of Antipsychotics on Symptoms of Schizophrenia

Efficacy of Antipsychotics on Cognitive Symptoms of Schizophrenia

Antipsychotic Treatment Improves Cerebral Functioning

Baseline untreated patients with first-episode schizophrenia have decreased amplitude of low-frequency fluctuations.

Patients treated for 6 wks with antipsychotics have increased amplitude of low-frequency fluctuations compared to baseline.

Patients treated for 6 wks with antipsychotics have increased amplitude of low-frequency fluctuations compared to controls.

NONPHARMACOLOGICAL MANAGEMENT OF NEGATIVE AND COGNITIVE SYMPTOMS
Psychosocial Interventions

- Psychosocial support may lead to long-lasting improvements in cognition
  - Better treatment adherence
  - Fewer relapses
  - Improved "real world" functioning

Cognitive Behavioral Therapy (CBT)

- Psychotherapy with emphasis on current thoughts, emotions, and behaviors
- Focus on undoing old learning and teaching new behaviors
- Patients receiving CBT usually report significant improvement after developing strategies to modify unhelpful situational cognitions; however, change is usually observed when unhelpful core beliefs are identified and modified
- Effects are moderate at best, yet CBT is recommended in most treatment guidelines
- Individual therapy is more effective than group therapy

Cognitive Remediation Therapy

• Designed to improve neurocognitive abilities, including attention and memory
• Pencil/paper tasks; computer exercises; can be tailored to address individual areas of weakness
• Improvement in executive functioning predicts improved daily functioning
• May protect against gray matter loss
• Beneficial for negative and disorganized symptoms?

Penades et al. Schizophr Res 2006;87:323-31;
Eack et al. Arch Gen Psychiatry 2010;67(7):674-82; Cella et al. Schizophr Res 2014;156-60;
Cognitive Remediation Therapy

Cognitive Enhancement Therapy (CET)

- Designed to address core social and non-social cognitive deficits
- Improvement in overall negative symptoms, especially social withdrawal, affective flattening, and motor retardation

Cognitive Enhancement Therapy May Protect Against Gray Matter Loss in Schizophrenia

Eack SM. Arch Gen Psychiatry 2010;67(7):674-82.

CET = cognitive enhancement therapy: computer-based neurocognitive training focused on the remediation of social and non-social deficits in schizophrenia

EST = enriched supportive therapy: individual psychotherapy focused on illness management through psychoeducation and coping skills
Neurostimulation

• Electroconvulsive therapy (ECT): effective in treating some negative symptoms

• Transcranial magnetic stimulation (TMS)
  – Improves negative symptoms
  – Possibly by eliciting dopamine release in the caudate nucleus

• High-frequency (>10 Hz) repeated TMS of the DLPFC
  – Effective for negative symptoms (except alogia)

Exercise

• Physical exercise has been linked to:
  – Increased neurogenesis, synaptogenesis
  – Increased growth factors
  – Improved hippocampal plasticity
  – Improved memory

• Aerobic exercise may increase benefits of cognitive therapies

Exercise May Improve Cognition

MDD exercise
MDD control
MDD relaxation
Schiz control
Schiz relaxation
Schiz exercise

Exercise May Improve Negative Symptoms

ACT Now!
Recovery Is Going Fast!
Assertive Community Treatment (ACT)

- Goal: replace crisis-oriented clinical care with intensive community-based intervention
- Integrative care is available 24/7 for as long as needed
- Team approach
- Most cost-effective for patients who are:
  - Severely disabled by their illness
  - Have had numerous hospitalizations
  - At high risk for relapse

ACT Services

Element of Recovery

Symptom management

Physical health

Reduced hospitalization

Reduced criminal activity

Reduced substance abuse

Stable housing

Employment

Community involvement

Family involvement

Treatment alliance

Cognitive ability

Empowerment

RECOVERY

- Medication prescription, administration, and monitoring
- Illness management and recovery skills
- Continuous assessment and intervention

- Crisis assessment and intervention
- Illness management and recovery skills
- Medication prescription, administration, and monitoring

- Illness management and recovery skills
- Medication prescription, administration, and monitoring
- Individual supportive therapy

- Substance abuse treatment
- Illness management and recovery skills
- Individual supportive therapy

- Housing support services

- Employment support services
  - Transportation

- Intervention with support networks
  - Transportation

- Intervention with support networks
  - Individual supportive therapy

- Frequent interaction with ACT team members
  - Integration of patient's wishes in treatment planning

- Individual supportive therapy
  - Assistance with activities of daily living
  - Case management

- Integration of patient's wishes in treatment planning
  - Incorporation of recovering patients as peer specialists on ACT team
NOVEL TREATMENTS UNDER INVESTIGATION
Novel Pharmacological Targets

- Glutamatergic modulation
- GABAergic modulation
- Cholinergic modulation
- Inflammation
- Cannabinoids
- Oxytocin
- Dopamine D1 receptors

Glutamatergic Neurotransmission

EAAT = Excitatory amino acid transporter
vGlu-T = Vesicular glutamate transporter
NMDA = N-methyl-D-aspartate
NMDA Receptors: A Closer Look

GABA inter-neuron

GABA

Mg²⁺

glutamate neuron

glutamate neuron

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NMDA Receptors: A Closer Look

Ca^{2+}

Glutamate

Glycine

Mg^{2+}
Glutamatergic Modulation

- Glutamate hypofunction may contribute to all symptom domains of schizophrenia
- NMDA receptor antagonists
- Glycine agonists
- Glycine reuptake inhibitors
- mGluR 2/3 agonists
Cholinergic Modulation

- Increasing cholinergic neurotransmission may improve cognition
  - Adrenergic $\alpha_1$ receptors
  - Adrenergic $\alpha_{2A}$ and $\alpha_{2C}$ receptors
  - Nicotinic $\alpha_4\beta_2$ receptors
  - Nicotinic $\alpha_7$ receptors
  - Muscarinic M1 and M4 receptors

Summary

• Recovery in schizophrenia encompasses far more than remission of positive symptoms; negative and cognitive symptoms of schizophrenia have the most detrimental effects on functional outcomes; unfortunately, they are also the most challenging symptoms to treat

• Increasing recognition of the importance of negative and cognitive symptoms and evidence of their distinct but often overlapping characteristics has sparked re-evaluation of the categorization and assessment of these symptom domains

• There are currently no FDA-approved agents for the treatment of negative or cognitive symptoms of schizophrenia; available antipsychotics and adjunctive treatments show little efficacy, especially in the short term

• Nonpharmacological approaches show some promise for the treatment of both negative and cognitive symptoms

• Novel treatment strategies specifically targeting negative and cognitive symptoms are actively being investigated