Management of Negative Symptoms in Schizophrenia

EPI GUIDE

The Canadian Consortium for Early Intervention in Psychosis (CCEIP) clinical guidance documents provide clinicians with evidence-based recommendations for the diagnosis, assessment, and management of psychosis. This guidance is developed by an expert panel of clinicians who evaluate the available literature and develop consensus-based recommendations.

Recognize

- Negative symptoms are among the most important **determinants of functioning** in schizophrenia.[1,2]
- **Be vigilant for negative symptoms** as they are associated with a higher burden of illness but are often overlooked or not the reason a person would seek care.[3,4]
- After urgent symptoms are addressed, **take time to focus** exclusively on negative symptoms.[4]

Assess

- **Administer the NSA-4** or other tool to systematically evaluate negative symptoms and monitor progress.[4]

Manage

- **Prioritize optimal management** of negative symptoms, even when positive symptoms are minimal or absent.[3]
- **Differentiate between primary and secondary negative symptoms** and personalize the management approach based on the underlying cause.[4]
- **Consider early intervention programs** to address negative symptoms during the critical period to optimize outcomes[2,5]

Negative symptoms in schizophrenia

Negative symptoms (NS) are a reduction or absence of usual behaviour related to motivation, interest, or expression. Although often the first symptom of schizophrenia, NS can occur at any point in the course of illness. They are unlikely to be recognized as pathological, contributing to delays in diagnosis, and can be challenging to manage.[3,4,6–8] When NS are present at baseline, they tend to be persistent, although severity can fluctuate.[1] More severe NS have been observed in males, in patients who developed schizophrenia at a younger age, and in those with a longer duration of untreated psychosis.[1] NS can be primary or secondary, require different approaches, and are categorized by five interrelated symptom domains.[3,4,9]

Prevalence of negative symptoms [1, 9]

- **~60%** have predominantly NS
- **90%** in first episode psychosis have ≥1 NS
- **35-70%** of patients continue to have clinically significant NS, despite treatment

Prioritize management of negative symptoms due to significant burden on patients

Optimal management of NS should be a priority of care. Clinicians should be especially vigilant for their presence as they are associated with significant burden and are seldom spontaneously reported by patients:[3,10]

Personal

- ↓ quality of life[11]
- ↓ personal relationships[12]
- ↑ substantial familial burden[13]
- ↓ household/recreational functioning[14]
- ↓ rates of remission[15]

Life

- ↓ levels of insight[16]
- ↓ work/school performance[12]
- ↓ educational attainment levels[12,17]
- ↓ long-term functioning/disability[18]

Health

- ↑ antipsychotic dose[19]
- ↑ risk and duration of hospitalizations[13]
- ↑ risk of obesity/metabolic syndrome[13]
- ↑ overall healthcare costs[13]

Recognize negative symptoms: definitions and characteristics[3,4,9,20]

Primary
Intrinsic

A diagnosis of exclusion, related to the **underlying pathophysiology** of schizophrenia due to the dysfunction of neural circuits that **regulate motivation and reward.**

Secondary
Caused by other factors

Positive symptoms
Social withdrawal induced by persecutory delusions, mind reading, thought insertion

Psychiatric comorbidities
Depression, substance use, PTSD, anxiety

Antipsychotic medication side effects
Sedation, EPS, amotivation

Medical comorbidities
Neurological disorders, sleep apnea, chronic pain

Environmental factors
Understimulation, stigma, social deprivation

Factors	Symptom domain	Definition
Diminished expression	Alogia	Reduction in quantity of words spoken and spontaneous speech. Short or monosyllable answers to questions, avoids communication, uses few words.
	Blunted affect	Diminished intensity and range of facial and vocal expressions, poor eye contact, minimal use of gestures.
Avolition/ apathy	Anhedonia	Reduced experience of pleasure. Difficulty or inability to anticipate future pleasure, few leisure activities, lack of interest in sexual activity.
	Asociality	Diminished interest in, motivation for, and appreciation of social interactions with others. Few or poor relationships with friends and reduced social interaction.
	Avolition	Reduced goal-directed activity due to decreased motivation. Emotional withdrawal, apathy, poor grooming and hygiene, less involvement due to apathy and lack of energy.

How to accurately assess negative symptoms

Patients often do not spontaneously report negative symptoms due to lack of awareness.[10] After urgent symptoms are addressed, take time to focus exclusively on accurate assessment of the presence, cause, severity, and impact of NS.[3] Use validated scales to systematically evaluate NS and monitor progress, such as the Clinical Assessment Interview for Negative Symptoms (CAINS),[21] 4-item Negative Symptom Assessment (NSA-4),[22] and the Positive and Negative Syndrome Scale (PANSS-6).[23]

At a clinical level both types of NS often appear to have similar or even identical phenomenology. Therefore, they are not easily distinguished with NS scores without additional information about other symptom dimensions or environmental factors. [24]

Assess	**Assess affect and behaviour** that may suggest NS, such as:[3,15] • Communication difficulties, flat affect, limited emotion, social inactivity, low motivation, and retarded psychomotor activity. • Evaluate body language, facial expressions, levels of interaction or engagement. • Ask patients and informants about daily activities, social life, and interests. • Compare the patient's level of impairment expected from a healthy age- and sex-matched individual.	Questions should be phrased to elicit broad responses to demonstrate whether a patient is able to:[3] • Elaborate on a response without prompting. • Participates in enjoyable activities to assess for anhedonia. • Has social contacts to assess social drive. • Is goal oriented and productive
Screen	**Screen for comorbidities** that may present as/or aggravate NS: • Medical comorbidities, such as obstructive sleep apnea, chronic insomnia, hypothyroidism, iron deficiency anemia.[3] • Psychiatric comorbidities, such as depression using the Calgary Depression Scale for Schizophrenia.[25]	
Evaluate	**Evaluate potential antipsychotic medication side effects** that may present as/or aggravate NS, such as sedation, amotivation, or extrapyramidal symptoms, using the Extrapyramidal Symptom Scale or the Monitoring Antipsychotic Side Effects tool.[3,15,26,27]	

Management of negative symptoms remains a challenge

With no medications specifically indicated for the treatment of NS, appropriate therapy can vary considerably based on the underlying cause. Guidance is limited and based on expert consensus.[4,15] Combining pharmacological and psychosocial treatments should be initiated as early as possible in the course of illness, as early intervention services were associated with superior outcomes in NS severity compared with treatment as usual.[5]

Therapeutic options for all negative symptoms[3,10,15]

- Optimize current medications to treat/maintain stability of psychotic/positive symptoms
- Minimize medication side effects that may aggravate NS
- Adjust medication or switch to a medication with efficacy in treating NS
- Treat comorbid medical and psychiatric conditions if possible, such as depression, substance use, or sleep apnea
- Refer to specialist for treatment of a comorbid condition if necessary, and to a psychologist for psychosocial intervention
- Encourage self-care, social interaction, and environmental stimulation
- Suggest exercise, especially aerobic exercise[15,28]
- Recommend family psychoeducation to increase awareness of NS and alleviate concerns that the patient is "lazy" or "not trying".

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Primary negative symptom therapeutic options[8,10,29,30]

Medication optimization	• Primary NS typically do not improve with currently available antipsychotic treatment with dopamine D2 antagonists or partial D2 agonists. • Clozapine, olanzapine, amisulpride and asenapine may confer benefits in treating NS. However, it is difficult to distinguish whether these improvements are related only to secondary NS.[31–33] • Cariprazine in first-episode psychosis may be effective based on a pilot study with a small sample.[34] • Future potential considerations may offer options, such as pimavanserin, roluperidone, or glycine transporter 1 inhibitors.[13,14]
Adjunctive pharmacotherapy[29]	Limited evidence is available for adjunctive pharmacotherapy, and may be impacted by the primary antipsychotic agent (e.g. risperidone + tropisetron, clozapine + duloxetine).[35] • **Antidepressants:** Modest effect, e.g. fluoxetine, paroxetine, seligiline, citalopram, reboxetine, fluvoxamine, or mirtazapine.[35,36] • **Serotonin 5-HT_3 receptor antagonists:** Benefit shown with tropisetron, ondansetron, and granisetron and are well tolerated.[29]
Cognitive therapy	• **Cognitive behavioural therapy:** Moderate benefit.[15,37,38] • **Cognitive remediation therapy:** Meaningful benefits, programs involving strategy discussion and transfer activities have stronger effects on functioning and NS.[15,38–40]
Neurostimulation	• **Repetitive transcranial magnetic stimulation (rTMS)**: Significant medium to large effect sizes, however, must be interpreted with caution due to significant heterogeneity[15,41] • **Transcranial direct current stimulation (tDCS)**: Significant medium to large effect sizes, however, must be interpreted with caution due to significant heterogeneity[41] • **Electroconvulsive therapy (ECT)**: Recent literature review showed benefit (18/35 studies), but interpretation limited by small numbers and methodological issues[29,42]

Secondary negative symptom therapeutic options[4,15,24,43]

Secondary NS are more likely to improve as underlying factors are treated, and should be treated as per available guidelines as there is no evidence for a specific approach in patients presenting with NS.[15] Specific guidance is provided below:

Depression	• Switch to an antipsychotic agent with antidepressant properties (e.g., quetiapine, cariprazine, aripiprazole, clozapine, olanzapine, or lurasidone[31,44]) • Add-on antidepressant treatment • Integrate cognitive behaviour therapy
Positive symptoms	• Dose range optimization of pharmacotherapy (increase in the antipsychotic drug dose); or • Change of agent, e.g. switch to clozapine for treatment-resistant positive symptoms • Integrate cognitive behaviour therapy
Medication side effects	• Dose range optimization of pharmacotherapy (reduction in the drug dose); or • Switch to agent with lower risk of the symptom
Environmental factors	• Community based treatment, graded increase in social activities, skills training[24]

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