



## Literature Review

# Negative Symptoms Management in Schizophrenia

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### ARTICLE INFO

Received: July 9, 2020

Revised: September 10, 2020

Accepted: September 19, 2020

Published: May 31, 2021

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#### Keywords:

management

negative symptoms

schizophrenia

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### Abstract

Clinicians often overlook the presence of negative symptoms in treating schizophrenia. The burden borne by patients, families, and society is quite heavy. These symptoms not only have high costs, but also affect the functional prognosis in independence and socializing. There is a need for adequate therapy of negative symptoms of schizophrenia which can improve the patient's quality of life. Negative symptoms are characterized by blunt affect, alogia, avolition, anhedonia, and asociality. Knowing the difference between the primary and secondary types of negative symptoms of schizophrenia can bring big impact on the therapy. The primary type of negative symptoms is an integral part of schizophrenia, while the secondary one is caused by external conditions of schizophrenia, such as depression. Management of negative symptoms of schizophrenia includes psychopharmaceuticals and non-psychopharmaceuticals. Atypical antipsychotics remain the drug of choice due to their affinity not only to D2 receptor, but also to serotonin, glutamate, histamine,  $\alpha$  adrenergic, and muscarinic receptors. In addition, the higher dissociation rate of D2 receptors of atypical antipsychotics allow for minimal motor side effect. Cariprazine has been approved by The Food and Drug Association and The European Medicines Agency to treat primary and persistent negative symptoms due to its minimal side effect. Non-pharmacological therapies such as Cognitive Behavioral Therapy (CBT) and Motivation and Engagement Training (MOVE) can optimize the treatment efficacy. These therapies will enhance the cognitive improvement, adaptation, and social skill development of the patients.

**INTRODUCTION**

Negative symptoms are considered as the main aspect of schizophrenia since Kraepelin described the weakening of the wellspring of volition or avolition as the main psychopathology of *dementia praecox* [1]. These symptoms often become the parameter of the patients’ functional prognosis [2]. Not only the negative symptoms last longer than positive symptoms [3], they also affect the independency of the patients in performing activities of daily living, socializing, work, or school [2]. In the end, negative symptoms will become an economic burden for the patient, family, and the community [4].

Although clinicians are familiar with the term negative symptom, there is still a misunderstanding and uncertainty on the appropriate identification and management [5]. Concerning this matter, the authors hope that this article can aid clinicians to further understand the management of the negative symptoms of schizophrenia.

**1. Schizophrenia**

Eugen Bleuler coined the term schizophrenia to describe a discord of mind, emotion, and behavior of those affected by this disorder. He created the fundamental theory for this discordance in the form of association disorder, affective disorder, autism, and ambivalence, which is summarized into four As. He added a secondary symptom which increases the understanding of schizophrenia [6]. This disorder is characterized by five major symptoms, i.e. positive symptoms, negative symptoms, cognitive symptoms, aggressive symptoms, and affective symptoms [7].

**2. Negative symptoms**

Negative symptoms are the non-existence of otherwise normal behavior in the normal population [8][3]. They are considered intrinsic symptoms of schizophrenia [8]. Based on the 2005 MATRICS Consensus, negative symptoms are described with 5As, which are divided into two clusters. The first one (reduced expression) consists of blunted affect and alogia. The second cluster (amotivation) consists of avolition, anhedonia, asociality [9][8][10][4]. This description is in line with the concept of negative symptoms in DSM V as limited affect and limited avolition or limited asociality [11].

**Table of characteristics of negative symptoms of schizophrenia**

Cluster	Characteristic	Description
Cluster I (reduced expression)	Blunted affect	Reduced expression and emotion. The patient looks immobile, lifeless, rigid wood-like expression, minimum eye contact, monotonous tone of speech [4].
	Alogia	Reduced speech and answers to questions [4].
Cluster II (amotivation)	Avolition	Reduced motivation, goal, or ability to follow-up with plans [4].
	Anhedonia	Reduced pleasure felt compared to before affected by the disease [4].
	Asociality	Social withdrawal, reduced interest, and happiness in social interaction, neglect self-care, and ADL (Activity Daily Living) [4].

Most literature divides negative symptoms into two parts, primary and secondary. Primary symptoms are caused by the intrinsic factor of schizophrenia, while secondary symptoms are caused by factors outside schizophrenia, such as EPS, depression, substance abuse, and mental retardation. Determining primary or secondary symptoms affects the appropriate choice of therapy for this condition [12].

Within the course of schizophrenia, we will find negative symptoms in the prodromal phase, residual phase, and several times in between episodes. Negative symptoms are prominent in hebephrenic schizophrenia, simplex schizophrenia, and residual schizophrenia [4].

Clinicians in the outpatient setting can assess negative symptoms using the NSA-4 (Negative Symptom Assessment – 4 items). It is a shorter form of the NSA-16 to screen and measure the severity of negative symptoms of schizophrenia independent of differences in geography, clinicians’ credential levels, or previous experience with rating scale instrument [13]. Outside the

psychometry, we can recognize negative symptoms through observation and several simple questions. Several important markers of negative symptoms during observation include reduced speech quality and quantity, poor self-care, and limited eye contact during conversation. Simple questions can reveal a reduced level of emotional response, reduced interest, hobby, the purpose of life, and the will to initiate and maintain social relationships [7].

Several conditions can resemble negative symptoms, i.e. positive symptoms, depression symptoms, environmental factors (lack of stimulation because of hospitalization), substance abuse, neurological abnormality, depressive-type schizoaffective disorder, PTSD, neurological disease, and neurological side effects from antipsychotics [4]. The mechanism involved in the development of negative symptoms is multifactorial, including structural, neurobiological, environmental, and psychosocial factors [3].

The prevalence of negative symptoms in the schizophrenia population is high. Bobes reported that 60% of schizophrenia spectrum disorder patients had experienced at least one negative symptom, and 13% of schizophrenia patients had primary negative symptoms. Further study by Sicras-Mainar revealed that the most common characteristics of negative symptoms are passive (social withdrawal) and emotional withdrawal [4].

Negative symptoms have an important role in long-term morbidity, poor functional outcome, and disability of schizophrenia patients. This further affects independency, work, and the ability to form a relationship, which will result in a poor quality of life. Those affected with negative symptoms cannot function well in school or the workplace due to a lack of motivation. Unresponsive affect also hinders the relationship between patients with their friends and families. Anhedonia, apathy, and inattention interfere with the evoking of personal interest [4].

**3. Management of negative symptoms**

The first step in preventing and improving negative symptoms is by early identification and treatment of psychotic symptoms. Caution is needed in using antipsychotics due to possible secondary negative symptoms caused by antipsychotics [3]. The conditions underlying secondary negative symptoms such as depression and substance abuse should be identified and treated adequately [8]. Several organizations issued a recommendation on the

treatment of negative symptoms of schizophrenia, as follows:

**Table of recommendation on the management of negative symptoms of schizophrenia**

Organization	Terminology	Recommendation
World Federation of Societies of Biological Psychiatry (2012)	Negative symptoms	For primary negative symptoms, a certain atypical antipsychotic regimen is recommended (amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, ziprasidone), and non-typical group. Further studies are needed to support this [4].
British Association for Psychopharmacology (2011)	Recommendation of pharmacotherapy management in negative symptoms	The psychotic condition should be identified and treated as early as possible to prevent negative symptoms. For certain patients, the choice of antipsychotics should also consider a balance between side effects and therapeutic effects [4].
British Association for Psychopharmacology (2011)	Where negative symptoms last outside an acute episode of psychotic	Ensure that no EPS (especially bradykinesia), depression, and environmental influence (institutionalization, lack of stimulation). If there is, provide therapy. Consider a combination of antipsychotics and antidepressants such as SSRI. Ensure that the medicines do not interfere with each other's work based on the pharmacokinetic and pharmacodynamic interaction

American Psychiatric Association (2010)

Negative symptoms

between two medicines. If the patient receives clozapine, choose lamotrigine or suitable secondary antipsychotic [4].

The therapy of negative symptoms starts with an assessment of other conditions that may cause secondary negative symptoms. If there is, treat the condition, such as administration of antipsychotic for primary negative symptoms, antidepressant for depression, anti-anxiety for anxiety problems, anti-Parkinson, or reduction of antipsychotic dose for EPS. If negative symptoms still exist, then we can assume that this is a primary negative symptom in deficit state [4].

negative symptoms of schizophrenia [12]. The second-generation antipsychotic is considered to overcome negative symptoms better because:

- a) Other than D<sub>2</sub> receptor, second-generation antipsychotics also bond to serotonin, glutamate, histamine, α adrenergic, and muscarinic receptors [8]. The positive effect of clozapine on the cognitive function is a result of the work of clozapine in M<sub>1</sub> receptor [14].
- b) The combination of D<sub>2</sub> receptor blockade and inhibition in 5HT<sub>2</sub> receptor increases dopamine release in the frontal lobe [8]. It is shown by aripiprazole, a partial agonist of D<sub>2</sub> receptor, where 5HT<sub>1A</sub> agonist receptor if combined with a weak receptor from D<sub>2</sub> will support the work of atypical antipsychotic, where 5HT<sub>1A</sub> agonist receptor increases dopamine in the prefrontal cortex [14].
- c) Cognitive deficit is lower, thus giving better functional outcomes, improving positive symptoms, improving negative symptoms with minimum side effects on the motor system [12] due to higher dissociation of second-generation antipsychotic on D<sub>2</sub> receptor [15].

The following antipsychotics are commonly used and are considered effective [8][4]:

### 3.1.1. Cariprazine

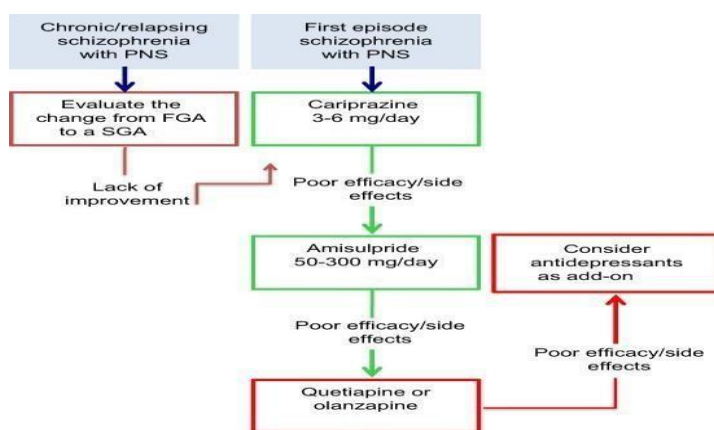
Several studies showed that cariprazine is effective to treat primary and persistent negative symptoms [16][12] and had been approved by the European Medicines Agency and Food and Drug Association [12] because:

- a) Partial agonist of D<sub>2</sub>/D<sub>3</sub>, 5HT<sub>1A</sub> [16][4] and antagonist to 5HT<sub>2B</sub> and 5HT<sub>2A</sub> and H<sub>1</sub>[12]
- b) Compared to other antipsychotics, the affinity to receptor D<sub>3</sub> is up to 10 times higher, even compared to dopamine itself [12].
- c) The side effects of weight gain, QT lengthening, or increasing prolactin hormone lowered when compared to other antipsychotics [4][16].

### 3.1.2. Amisulpride

This regime works by blocking D<sub>2</sub> and D<sub>3</sub> receptors [17]. There are two types of doses in Europe, i.e. 400-800 mg for positive symptoms and 50-300 mg for negative symptoms. Ideally, we treat negative symptoms while controlling positive symptoms. Therefore, these two types of doses will interfere with

Cerveri, Gesi, and Mencacci (2019) proposed an algorithm to the management of negative symptoms of schizophrenia [12]:



### 3.1. Effective pharmacotherapy on negative symptoms

Antipsychotic is still the primary therapy for treating

the achievement of the ideal goal of treatment [4].

### 3.1.3. Olanzapine

The effectivity of olanzapine is better than haloperidol in improving negative symptoms [12].

### 3.1.4. Risperidone

This regime is considered better than other second-generation antipsychotics because of similar dosage range and side effects to cariprazine and its ability to control positive symptoms, depression, and EPS [4].

### 3.1.5. Aripiprazole

The dose of aripiprazole approved by the Food and Drug Administration is 10-15 mg/day [16].

### 3.1.6. Clozapine

Its prescription can be considered if there is no improvement after treatment with other antipsychotics. The side effects of this medicine in the cardiovascular aspect should be a consideration when prescribing this regime [4].

## 3.2. Pharmacotherapy with its effectiveness on negative symptoms of schizophrenia overlaps with the effect of antidepressant

### 3.2.1. SSRI

The synergistic effect of SSRI and antipsychotics such as clozapine will modulate GABA-A system and receptors, which is expected to reduce the severity of negative symptoms [8]. Citalopram is the safest choice to combine with antipsychotics because it is well-tolerated, it has minimum effect on the liver metabolism enzyme and also its affinity on  $\alpha 1$  adrenergic and muscarinic receptors [8].

## 3.3. Adjuvant pharmacotherapy

### 3.3.1. N-acetyl cysteine (NAC)

In an 8-week-long RCT, the administration of 2000 mg of N-acetylcysteine in addition to risperidone to chronic schizophrenia patients with prominent negative symptoms resulted in an improvement to primary negative symptoms compared to the placebo [8].

## 3.4. Effective non psychopharmaceuticals on negative symptoms of schizophrenia

### 3.4.1. Cognitive Behavioral Therapy (CBT) and Family Therapy

Negative symptoms are closely related to low

self-esteem and negative beliefs such as low expectations on successfulness and happiness [8]. In CBT, the patient learns to manage destructive thinking which often underlies problems in growing motivation. Improvement in negative symptoms after CBT is related to the increase of gray matter volume in the left precentral gyrus and the right inferior parietal lobe [18]. To date, CBT is still the most common non psychopharmaceutical therapy to reduce negative symptoms [19].

### 3.4.2. Cognitive Remediation (CR)

CR helps reducing negative symptoms by modulating the working memory, reward sensitivity, and executive function. CR is expected to improve the patient's self-esteem by improving mindset and cognitive function which express helplessness, evasive behavior, and low motivation [8].

### 3.4.3. Cognitive Adaptation Training (CAT)

CAT is a therapy based on the living and environmental conditions of the patients by using aids such as signs, checklist, and electronic appliances to improve social function and to develop adaptive social behavior without being distracted by the reduction of cognitive ability [3].

### 3.4.4. Motivation and Engagement Training (MOVE)

MOVE is designed to break negative feedback on sequence of negative symptom. This therapy combines five components: antecedent control, changes in anticipatory pleasure, emotional processing, CBT for negative cognition, and skill building [3].

- a) Antecedent control refers to environmental modification, such as the application of signs to improve initiation to an activity, maintaining it to become automaticity in performing and completing activities or tasks [3].
- b) MOVE aims to improve the deficit in anticipatory pleasure experienced by the patients. Anticipated pleasure in this therapy is brought up before and during the activity. The patient's statement on the pleasure that he or she felt during the activity is noted,



recorded, and will be played back in the next activity. The picture capturing happy moments felt by the patient when doing the activity is displayed at home to motivate the patient to perform similar activities [3][20].

- c) The goal of emotional processing is to identify emotion and expression. The therapist will help patient in recognizing his or her feeling in various ways, including audio and video recordings. The patient will be guided in how to express emotion using the correct expression, voice, and body language. The patient will also learn expressions from other people through social cognition interaction training with the help of a computer [3][20].
- d) CBT is used to overcome negative ideas which will ruin initiation and planning in socialization [3][20].
- e) The skill building aims for patients to learn various skills related to independence and social function. The therapist helps the patient to perform simulation of the patient's daily activities [3][20].

#### 3.4.5. Music Therapy

Several meta-analyses showed a significant effect of music therapy. This therapy can be applied especially in high doses on negative symptoms because there have not been any side effects [8].

#### 3.4.6. Physical Activity

Physical activity provides a positive effect on negative symptoms of schizophrenia [21]. Although, a clear mechanism that underlies this effect is not yet revealed [8]. Moderate to vigorous physical activity for 90 minutes each week will provide a mild- moderate reduction on significant negative symptoms in schizophrenia spectrum disorder patients [22][8].

## SUMMARY

Negative symptoms experienced by schizophrenia patients are described using 5As divided into two clusters. The first cluster (reduced expression) consists of blunted affect and alogia. The second cluster (amotivation) consists of avolition, anhedonia, and asociality. Primary negative symptoms emerge intrinsically from schizophrenia, while secondary negative symptoms are caused by external factors of schizophrenia, such as EPS, depression, and substance abuse. Determining primary or secondary symptoms affect the correct choice of therapy for this condition.

There are several ways to recognize and measure the severity of negative symptoms. Beside observation and interview, clinicians in an outpatient setting can use NSA-4 to measure negative symptoms of schizophrenia.

Caution should be taken while treating negative symptoms to ensure that no comorbidity may cause these negative symptoms. Otherwise, treatment of the underlying disease should be chosen.

Along with the development in the pharmaceutical field, the use of second-generation antipsychotics as a choice of therapy for negative symptoms of schizophrenia is recommended. Psychosocial interventions such as CBT and MOVE are also recommended because their effectivity has been proven to overcome negative symptoms.

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