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Chapter 4

Negative Symptoms of Schizophrenia: Constructs, Burden, and Management

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Abstract

The aim of the chapter is to raise awareness about recent constructs of negative symptoms, their burden on patients, caregivers and society, and about their management. Schizophrenia consists of positive, negative, and cognitive symptoms. However, treating physicians are not necessarily aware about recent constructs of negative symptoms, their presence at prodromal stage, and the distinction among primary, secondary, persistent, prominent, or predominant negative symptoms. Negative symptoms have a substantial impact on the day-to-day functioning of patients with schizophrenia and contribute more to impaired quality of life and poor functioning than positive symptoms do. Additionally, they are associated with high costs for society and a substantial burden for caregivers. Negative symptoms are not adequately treated by available antipsychotic therapies. Publications have shown that no antipsychotic has a beneficial effect when compared to another. Cariprazine is the only antipsychotic that has proven superiority over another antipsychotic (risperidone) in one clinical study.

Keywords: primary, secondary, prominent, predominant, negative symptoms, deficit syndrome, alogia, affect blunted, avolition, anhedonia, asociality, antipsychotic treatment

1. Introduction

It is well known and established in the scientific community that schizophrenia symptoms can be categorized as positive, negative, and cognitive. While positive symptoms are easy to recognize, negative symptoms are often more difficult to distinguish, as they can be mistaken for depressive symptoms [1, 2]. For the treatment of schizophrenia symptoms, several antipsychotics were discovered, developed, and registered from the 1950s. These drugs are efficiently

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improving the positive symptoms of schizophrenia but have slight or no effect on the negative and cognitive symptoms. Since no real treatment was available for negative symptoms, little focus has been laid on this particular field of the disease so far. With very recent development approaches and the new potential treatments on the horizon, discussions on how to define, distinguish, and treat negative symptoms are increasing day by day.

Negative symptoms are a key element of schizophrenia including symptoms such as blunt affect, lack of motivation, asociality, and impoverished speech. They are associated with disruptions and/or lack of normal emotions and behavior [1, 3]. These symptoms may occur with or without positive symptoms and can, at times, be difficult to recognize as part of the disorder.

Recently, a consensus has been reached on how to describe negative symptoms [4]:

Five constructs (the 5 "A") were identified as negative symptoms namely affect (blunted), alogia, anhedonia, asociality, and avolition and were clustered into two factors: one including blunted affect and alogia and the other consisting of anhedonia, avolition, and asociality (**Table 1**). For each construct, symptoms due to identifiable factors, such as medication effects,

Blunted affect and alogia cluster
 Affect blunted/flat affect Blunted affect refers to a decrease in emotions and expressions. Patients may appear immobile, lifeless, and have a wooden expression [5]. They may make little to no eye contact and speak in a dull monotone voice [1]. Absence of emotions is called flat affect [3]
 Alogia Patients with schizophrenia often have reduced speech and may give short answers to questions. Many questions may be required in order to receive sufficiently detailed information from the patient [3, 6]
Anhedonia, avolition and asociality cluster
 Avolition Avolition refers to lack of motivation, sense of purpose, or ability to follow through on plans. For example, the patient may have a desire or interest to grow a garden but never act on the plan [6]
 Anhedonia Anhedonia refers to lack of pleasure. Patients suffering from schizophrenia may not take interest in activities they previously enjoyed. For example, a patient who was an avid gardener before may have a complete lack of interest in gardening when suffering from schizophrenia [5]
 Asociality/Social withdrawal Patients with schizophrenia may exhibit social withdrawal, show diminished interest and pleasure in social interactions, and often neglect activities of daily living (such as personal hygiene) [1, 3]. Asociality should not be defined in purely behavioral terms (whether the subject has social interactions and close relationships), but mainly as a reduction in motivation for social contacts (whether the subject values and desires social interactions and close social bonds) [7, 8]

Table 1. Characteristics of the most important negative symptoms.

Primary	Considered a core symptom of schizophrenia which persist during clinical stability [9]
Secondary	A consequence of positive symptoms, neurological side effects, depressive symptoms, or environmental factors [10, 11]
Deficit syndrome	Presence of at least two out of the following six negative symptoms in patients meeting criteria for schizophrenia: 1. restricted affect (referring to observed behavior), 2. diminished emotional range (i.e., reduced range of the patient's subjective emotional experience), 3. poverty of speech, 4. curbing of interests, 5. diminished sense of purpose, 6. diminished social drive for at least 12 months including periods of clinical stability. The above symptoms are primary, i.e., not secondary to factors such as anxiety, drug effect, psychotic symptoms, intellectual disability or depression [12–14]
Prominent	Prominent negative symptoms were defined as: 1. Baseline score ≥4 on at least 3, or ≥5 on at least 2 negative PANSS subscale items; or 2. PANSS negative score >3 on item 1 and item 6 and at least one third item with a score >3 and a maximum of two items with a score >3 from the positive subscale [15, 16]
Predominant	Predominant negative symptoms were defined as: 1. Baseline score ≥4 on at least 3 or ≥5 on at least 2 of the 7 negative subscale items and a PANSS positive score of <19; 2. PANSS negative score ≥6 points over PANSS positive score; 3. PANSS negative score of at least 21 and at least 1 point greater than the PANSS positive score and 4. A common sense definition, negative subscale greater than positive subscale [15, 16]
Persistent	Persistent negative symptoms are defined as the presence of at least one negative symptom of moderate or higher severity, not confounded by depression or parkinsonism, at baseline and after 1 year of treatment [17]
Liemburg—core negative symptoms	Avolition, anhedonia (Intensity of expected pleasure from activities diminished, asocial behavior) [18]
Liemburg—expressive deficit	Blunted affect, alogia (Facial expression, expressive gestures, vocal expression, spontaneous elaboration, quantity of speech diminished) [18]

Table 2. List and characteristics of frequently used negative symptom definitions.

psychotic symptoms or depression, should be distinguished from those regarded as core symptoms of the disease.

Besides this new adaptation, negative symptoms can also be characterized as primary, secondary, prominent, predominant or persistent, as deficit syndrome, or clustered as Liemburg "core negative symptoms" and "expressive deficit" clusters. **Table 2** gives an overview of frequently used negative symptom definitions.

2. Differential diagnosis

Negative symptoms can be part of various conditions/diseases and must be distinguished from those related to schizophrenia. The most important differentiation for clinical practice is between primary and secondary negative symptoms. While primary negative symptoms are considered a core symptom of schizophrenia, which persist during clinical stability [9], secondary negative symptoms are believed to be a consequence of other factors such as:

- positive symptoms (for example, social withdrawal because of paranoid ideas),
- neurological side effects of antipsychotic treatment (Parkinson like symptoms),
- depressive symptoms
- or environmental factors (social under stimulation due to hospitalization) [10, 11].

The importance of distinguishing primary from secondary negative symptoms lies in its therapeutic implication; while secondary negative symptoms can be improved by removing the underlying cause, primary negative symptoms are likely to persist despite treatment [9].

Additionally, negative symptoms, especially symptoms of **anhedonia, avolition, and asociality** can also occur in a number of other psychiatric diseases including depressive episodes, substance abuse, and internal or neurological disorders [19]. Schizoaffective disorder, depressive type (ICD-10 F25.1), and severe major depressive disorder with psychotic symptoms (ICD-10 F32.3) are two diseases that are particularly difficult to distinguish from schizophrenia with negative symptoms. Schizoaffective disorder, depressive type is "a disorder in which both schizophrenic and depressive symptoms are prominent, so that the episode of illness does not justify a diagnosis of either schizophrenia or depressive episode" [20]. The patient experiences a combination of schizophrenia symptoms, such as hallucinations or delusions, and mood symptoms, such as potentially anhedonia, avolition, and asociality. Severe major depressive disorder with psychotic symptoms is a disease where "the patient suffers from lowering of mood, reduction of energy, and decrease in activity. Capacity for enjoyment, interest, and concentration is reduced, and marked tiredness after even minimum effort is common. The lowered mood varies little from day to day, is unresponsive to circumstances, and may be accompanied by so-called 'somatic' symptoms, such as loss of interest and pleasurable feelings, marked psychomotor retardation, agitation, loss of appetite, weight loss, and loss of libido. Hallucinations, delusions, psychomotor retardation, or stupor so severe that ordinary social activities are impossible" might be present [20]. A correct diagnosis and distinction from schizophrenia with negative symptoms has a great impact on therapy in these diseases: while for schizoaffective disorder and major depressive disorder the therapy includes antidepressants next to antipsychotics [21], for negative symptoms of schizophrenia, this has not been shown as effective [22].

The differential diagnosis of **blunted affect** includes next to schizophrenia, post-traumatic stress disorder (PTSD). PTSD is a mental disorder that is triggered by a terrifying event (war, torture, sexual assault). Symptoms include flashbacks, nightmares, inability to feel positive emotions, dissociative symptoms, severe anxiety, and avoidance of triggers [19]. Blunted affect, anhedonia, and feelings of detachment are also core symptoms of PTSD, which cause diminished interest in activities that produce pleasure, and reduced tendency of emotional expressions [23].

Alogia is caused by a dysfunction in the fronto-striatal area of the brain and can therefore also occur in several neurological diseases (such as Huntington's and Parkinson's diseases, dementia, etc.) [24]. However, physical symptoms that accompany such diseases make the differentiation from schizophrenia not so difficult.

Overall, it can be concluded that while symptoms of anhedonia, avolition, and asociality also occur in the course of several other diseases (especially those with depressive episodes), blunted affect and alogia seem to be more inherent to schizophrenia with negative symptoms [25].

3. Course

Schizophrenia typically begins with a prodromal period, which precedes first episode psychosis and can last from a few days to around 18 months. The prodromal period and the very early phases of the disease are characterized by negative symptoms [26]. In contrast, early stages and acute exacerbations are more characterized by positive symptoms. Over time, the positive symptoms diminish due to treatment or due to the natural course of the illness and are replaced by more prominent negative symptoms. Finally, during the residual phase of the illness, negative symptoms are most prevalent [27]. **Figure 1** shows a typical course of the disease.

Although this is a common pattern for schizophrenia, the course can vary considerably. Some patients have psychotic episodes lasting weeks or months with full remission of their symptoms between each episode; others have a fluctuating course in which symptoms are continuous but rise and fall in intensity; yet others have relatively little variation in the symptoms of their illness over time.

In order to define clinically relevant course variants, a healthcare professional needs to be able to characterize both the current state as well as the longitudinal pattern of the illness in the individual patient [28]. For this, ICD-10 provides the following course specifiers [20] (**Table 3**).

At one end of the spectrum, the person has a single psychotic episode of schizophrenia followed by complete recovery; at the other end of the spectrum is a course in which the illness never abates and debilitating effects increase (**Figure 2**).

Negative symptoms are common in the prodromal phase of the disease, in between psychotic episodes and at the end of the disease in the residual phases. According to the ICD-10, which

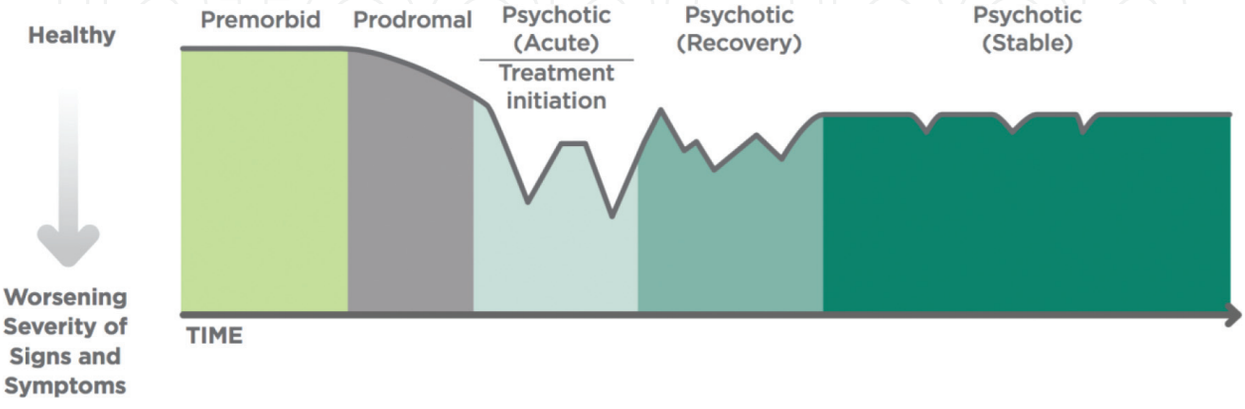

Figure 1. Individual clinical course of schizophrenia (adapted from American Psychiatric Association [32]).

Class	Course
F20.x0	Continuous; no remission of psychotic symptoms throughout the period of observation
F20.x1	Episodic; with a progressive development of "negative" symptoms in the intervals between psychotic episodes
F20.x2	Episodic; with persistent but nonprogressive "negative" symptoms in the intervals between psychotic episodes
F20.x3	Episodic (remittent); with complete or virtually complete remissions between psychotic episodes
F20.x4	Incomplete remission
F20.x5	Complete or virtually complete remission
F20.x8	Other pattern of course
F20.x9	Course uncertain, period of observation too short

Table 3. ICD-10 course specifiers.

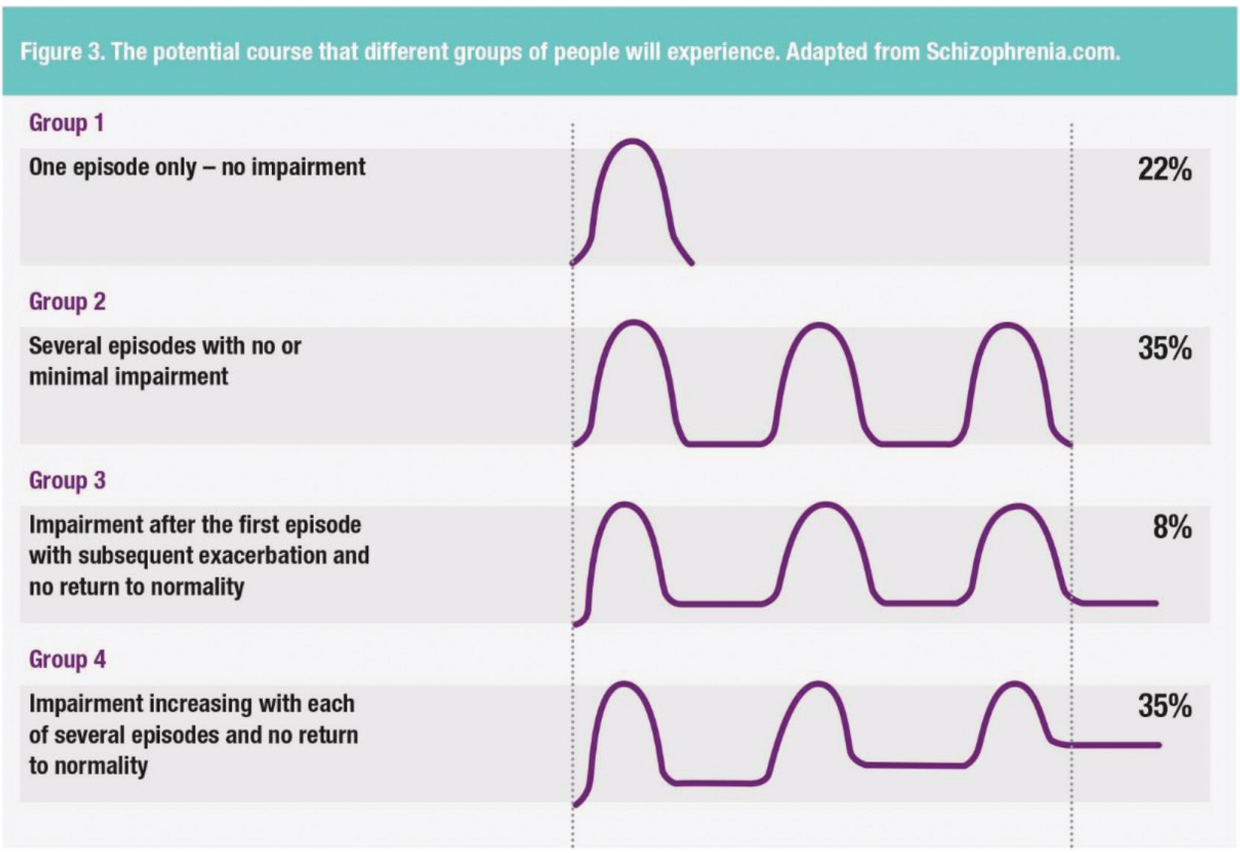

Figure 2. Overall clinical course of schizophrenia (adapted from Schizophrenia.com).

classifies schizophrenia into different subtypes (**Table 4**), negative symptoms prominently occur in hebephrenic, simple, and residual schizophrenia.

Hebephrenic schizophrenia is "a form of schizophrenia in which affective changes are prominent, delusions and hallucinations fleeting and fragmentary, behavior irresponsible and unpredictable,

F20.0	Paranoid schizophrenia
F20.1	Hebephrenic schizophrenia
F20.2	Catatonic schizophrenia
F20.3	Undifferentiated schizophrenia
F20.4	Post-schizophrenic depression
F20.5	Residual schizophrenia
F20.6	Simple schizophrenia
F20.8	Other schizophrenia
F20.9	Schizophrenia, unspecified

Table 4. Subtypes of schizophrenia according to ICD-10.

and mannerisms common. The mood is shallow and inappropriate, thought is disorganized, and speech is incoherent. There is a tendency to social isolation. Usually, the prognosis is poor because of the rapid development of 'negative' symptoms, particularly flattening of affect and loss of volition. Hebephrenia should normally be diagnosed only in adolescents or young adults" [20].

"Simple schizophrenia is a disorder in which there is an insidious but progressive development of oddities of conduct, inability to meet the demands of society, and decline in total performance. The characteristic negative features of residual schizophrenia (e.g., blunting of affect and loss of volition) develop without being preceded by any overt psychotic symptoms" [20].

"Residual schizophrenia is a chronic stage in the development of a schizophrenic illness in which there has been a clear progression from an early stage to a later stage characterized by long-term, though not necessarily irreversible, 'negative' symptoms, e.g., psychomotor slowing; underactivity; blunting of affect; passivity and lack of initiative; poverty of quantity or content of speech; poor nonverbal communication by facial expression, eye contact, voice modulation and posture; poor self-care and social performance" [20].

In summary, negative symptoms constitute a core element of the disease. They dominate the clinical picture at the beginning and at the end of the disease but are also found in between psychotic episodes.

4. Epidemiology

Historically, applying different diagnostic criteria for patients with negative symptoms has affected the incidence and prevalence numbers of such patients. Depending on the diagnostic criteria applied, negative symptoms may comprise 5–60% of patients with schizophrenia, as shown by Rabinowitz et al., who found that in a large sample of negative symptom patients, 8.1–62.3% met criteria for prominent negative symptoms and 10.2–50.2% met criteria for

predominant negative symptoms [16]. Bobes reported that approximately 60% of individuals with schizophrenia-spectrum disorders experience one or more negative symptoms [29] and about 13% of the schizophrenic patients could be described as having primary negative symptoms [29]. Buchanan claimed 15–20% experience enduring negative symptoms that are primary to the disorder [27]. In a further study by Sicras-Mainar, it was reported that 52% of the patients presented one or more negative symptoms, the most common being passive/apathetic social withdrawal and emotional withdrawal [30, 31]. Furthermore, the prevalence of negative (deficit) states has been estimated to be 15% in first episode patients, 25–30% in clinical samples and 14–17% in population studies [9].

In conclusion, it is evident that negative symptoms are highly prevalent in the schizophrenic population.

5. Risk factors

Brain imaging, electrophysiological, and oculomotor data, showing either less or different abnormalities in negative symptom patients (here defined as deficit syndrome), suggest that deficit syndrome represents a separate disease entity with respect to other forms of schizophrenia, and not just the extreme end of a severity continuum. This is further supported by evidence that deficit syndrome has different risk factors than general schizophrenia [9].

These are

- male gender—while in general schizophrenia, there is no difference in gender [9, 32]
- summer births, compared to a winter birth in general schizophrenia [9]
- serum antibodies to cytomegalovirus [9]
- low serum folate concentration [9]
- higher genetic contribution in negative symptoms than to positive symptoms [27]
- obstetric complications [33]
- structural abnormalities, such as enlarged ventricles [33]
- dysfunctional beliefs about performance (increased defeatist performance beliefs), acceptance, likelihood of success, and resources, which reduce motivation [33]

6. Burden

Negative symptoms account for much of the long-term morbidity, poor functional outcomes, and high rates of disability in patients with schizophrenia [14, 34, 35]. They have a substantial impact on the day-to-day functioning of patients affecting the ability to live independently, to perform activities of daily living, to be socially active, to maintain personal relationships, and

to work and study [16, 36–40]. Research evidence suggests that the negative symptoms of schizophrenia contribute more to impaired quality of life and poor functioning than positive symptoms do [35, 38, 41] and that their severity is associated with a lower quality of life [42].

The three major challenges of schizophrenia's negative symptoms are their modest therapeutic response, pervasiveness, and diminution of patients' quality of life and functioning [43].

Evidence suggests that even after significant improvements in psychotic symptoms, patients with schizophrenia continue to experience poor quality of life due to residual negative symptoms, depression/anxiety, or cognitive impairment [44].

Mohr et al. (using their own definition of disease states based on the PANSS, as described above) found that patients who began therapy in disease state four (high negative symptoms but low to moderate other symptoms) seemed relatively intractable to treatment, with lower odds ratios than patients starting in disease states five (cognitive impairment predominant) and seven (positive predominant) [45].

Negative symptoms are major contributors to low function levels and deterioration in most patients with schizophrenia, because poorly motivated patients cannot function at school or work, cannot maintain relationships with family and friends in the face of unresponsive affect, and do not develop personal interests when experiencing anhedonia, apathy, and inattention [43].

One longitudinal study showed that negative symptoms predicted long-term impairment in global psychosocial functioning and work performance, with negative symptom severity being a significant individual predictor of the degree of impairment in relationships [34]. Additionally, the degree of impairment in participation and enjoyment of recreational activities was significantly correlated with the severity of negative symptoms [34].

Negative symptoms affect patients' ability to cope with daily activities and have a negative impact on their quality of life. Negative symptoms are relatively common and account for much of the long-term morbidity and poor functional outcome of patients with schizophrenia.

Patients with schizophrenia have severe problems with personal and social relations, which affect their quality of life (QoL) [46]. Negative symptoms, in particular, are often enduring and lead to poor functional outcomes in individuals with schizophrenia [47]. Increased risk of suicide, an unhealthy lifestyle, poor physical health, and CV disease (which is a leading cause of death) are main reasons associated with excess early mortality in schizophrenia [31].

Negative symptoms are recognized by both the Food and Drug Administration (FDA) and European Medicines Association (EMA) as features of schizophrenia that are not adequately treated by available antipsychotic therapies and are considered a valid target for drug development [16]. Negative symptoms can often persist despite psychosocial treatments and antipsychotic medication [47, 48].

As previously discussed, increased costs are positively correlated with lower functioning and negative symptoms are the major contributor to low function levels in patients with schizophrenia. Patients with negative symptoms have been shown to use more healthcare resources (including primary care, emergency care, and specialized care visits, laboratory tests, radiology

tests, and pharmaceutical prescriptions), especially with regard to primary care visits [30]. The highest direct costs are due to a high frequency of hospital admissions in negative symptom patients [49]. In addition to this direct cost, negative symptoms represent a burden for patients, caregivers, and society and therefore constitute a relevant economic burden [30].

7. Treatment

With the development of second-generation antipsychotics, there was initially hope within the medical community of targeting the negative and cognitive symptoms, as well as the positive symptoms of schizophrenia. Indeed, various therapeutic guidelines suggest second-generation antipsychotics (SGAs) over first-generation antipsychotics (FGAs); however, this suggestion is controversial.

The second-generation antipsychotics demonstrated efficacy in treating positive symptoms with less motor side effects than first-generation antipsychotics (with accompanied improvement in secondary negative symptoms), but the treatment goal of also improving the primary, negative, and cognitive symptoms was not achieved with these medications [22].

To explore any differential efficacy against negative symptoms, Leucht et al. [50] conducted a meta-analysis of 150 RCTs that directly compared an FGA with an SGA and included data from more than 21,000 patients. They found that four SGAs (clozapine, olanzapine, amisulpride, and risperidone) were most effective overall, but also specifically with respect to negative symptoms, when compared to FGAs. The magnitude of this difference, however, was small, with the largest effect size reported being 0.32 for olanzapine. With respect to EPS side effects, these four drugs were better than high dose FGAs but not when compared to low doses. The findings of pragmatic studies comparing the clinical effectiveness of SGAs and FGAs in schizophrenia [51, 52] are consistent with the findings of Leucht et al. meta-analysis.

More recent publications have shown that no drug has a beneficial effect on negative symptoms when compared to another [53–55]. In the only meta-analysis assessing available treatments for negative symptoms versus placebo, some statistically significant differences were found for various treatments (e.g., second-generation antipsychotics, antidepressants, glutamatergic agents, psychological interventions), but no effect reached the level of clinically significant improvement [55].

The results of the Cutlass1 study showed no advantage of second-generation drugs in terms of quality of life or symptoms over 1 year in patients with schizophrenia. In fact, those participants receiving a first-generation antipsychotic did rather better. In addition, there were no significant differences in rates of objectively assessed extrapyramidal side effects [51].

Amisulpride, the most widely studied antipsychotic in patients with negative symptoms, is indicated for negative symptoms in several European countries. However, most of the evidence showing efficacy is versus placebo and was obtained from clinical trials that were conducted in the 1990s (before the introduction of the current EMA recommendations) [56–59]. When amisulpride was evaluated in two recent studies conducted in patient populations

specifically selected for predominant negative symptoms, the findings for amisulpride were equivocal [60]. A 6-month trial comparing olanzapine (5 or 20 mg/d) and amisulpride 150 mg/d with placebo only found significant improvement for low-dose olanzapine versus placebo, but not for amisulpride [61]. Additionally, in a 12-week double-blind trial comparing amisulpride and ziprasidone, equivalent improvement in negative symptoms was demonstrated for both drugs [62]. Improvement in patient functioning in conjunction with negative symptom improvement was not investigated in any of these studies [54], and pseudospecificity parameters were also not well controlled for.

Scant information is currently available to guide clinicians on the treatment of negative symptoms. This leads to

- **Treatment guidelines** rarely mentioning treatment of negative symptoms specifically, and if they do, they suggest second-generation antipsychotics. **Table 5** gives a few examples of treatment guideline suggestions. It is agreed that these antipsychotics are to be used for the treatment of negative symptoms, because so far no effective therapies were available. The scientific community agrees, however, that current antipsychotics do not adequately address negative symptoms. Therefore, it is to be shown, how therapeutic guidelines will change once an agent is available that shows better efficacy on negative symptoms than other antipsychotics.
- **Physicians prescribing** various medications including anxiolytics, antidepressants, and anticonvulsants, which sometimes add little value and create unnecessary polypharmacy [22]. Antidepressants are a common treatment choice given the overlap between predominant negative symptoms and depressive symptoms, but supporting evidence is limited [63].

In the light of these facts, it is paramount to find efficacious therapies for negative symptoms, as there is a huge unmet medical need. Extensive research is ongoing, and there are some promising agents in development that could potentially be used for negative symptom treatment later on [60, 64, 65]. However, at the moment, only one antipsychotic exists, which has shown superiority over another antipsychotic in the treatment of negative symptoms in a well-designed study examining treatment effects on primary, persistent negative symptoms and that agent is cariprazine [60].

Cariprazine is a new D3/D2 partial agonist antipsychotic with preferential binding to D3 receptors. Cariprazine differs from all available antipsychotics due to its higher affinity for D3 receptors, which is higher than that of any other antipsychotic or in fact than dopamine itself. Cariprazine can therefore affect a D3 receptor blockade [66] that no other antipsychotic can. Since the blockade of D3 receptors has been shown to be related to improvement of negative and cognitive symptoms [67], it is assumed that cariprazine's blockade of D3 receptors is responsible for its effects on negative symptoms.

This was demonstrated in a randomized, double-blind, risperidone-referenced clinical trial [60]. The study enrolled schizophrenic patients with persistent (at least 6 month), predominant (high level on negative symptoms low level of positive symptom), primary (extrapyramidal symptoms (EPS), high positive symptoms and depression were exclusionary) negative symptoms. After the 26 week treatment period, cariprazine-treated patients showed significant

Organization	Terminology	Recommendation
World Federation of Societies of Biological Psychiatry (2012)	Negative symptoms	"For primary negative symptoms, treatment with certain SGAs (amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, ziprasidone), but not with FGAs, is recommended with inconsistent evidence and with the need for more studies to prove the efficacy."
British Association for Psychopharmacology (2011)	Recommendations for the pharmacological management of negative symptoms	"Psychotic illness should be identified and treated as early as possible as this may offer some protection against the development of negative symptoms. For any given patient, the antipsychotic that gives the best balance between overall efficacy and side effects should be used."
British Association for Psychopharmacology (2011)	Where negative symptoms persist beyond an acute episode of psychosis	"To ensure EPS (specifically bradykinesia) and depression are detected and treated if present, and consider the contribution of the environment to negative symptoms (e.g., institutionalization, lack of stimulation). Consider augmentation of antipsychotic treatment with an antidepressant such as an SSRI, ensuring that choice is based on minimizing the potential for compounding side effects through pharmacokinetic or pharmacodynamic drug interactions. If clozapine is prescribed, consider augmenting with lamotrigine or a suitable second antipsychotic."
American Psychiatric Association (2010)	Negative symptoms	"Treatment of negative symptoms begins with assessing the patient for syndromes that can cause the appearance of secondary negative symptoms. The treatment of such secondary negative symptoms consists of treating their causes, e.g., antipsychotics for primary positive symptoms, antidepressants for depression, anxiolytics for anxiety disorders, or antiparkinsonian agents or antipsychotic dose reduction for extrapyramidal side effects. If negative symptoms persist, they are presumed to be primary negative symptoms of the deficit state. There are no treatments with proven efficacy for primary negative symptoms."

Table 5. Treatment guideline suggestions for negative symptoms treatment.

improvement in negative symptoms (measured by PANSS-Factor Score for Negative Symptoms /PANSS-FSNS/) and patient functionality (Personal and Social Performance /PSP/) alike compared to risperidone. Subanalyses of individual negative symptom items and PSP subdomains measuring day-to-day functioning showed that this effect was global and not only driven by selected items [60].

Responder analyses have a primary position in defining the clinical relevance of study results. In this study, these analyses with a 20 and 30% cut-off were both in favor of cariprazine over risperidone. One of the strongest methods to evaluate clinical relevance of PANSS results is the combined rate of CGI (improved/very much improved) with responder rates at 30 and 20% reduction level. Also here, cariprazine showed a clear, significant superiority of over risperidone.

The results are clinically relevant, especially bearing in mind that a significant difference over a comparator is much more difficult to achieve than over placebo, since the active comparator would be assumed to also have some activity [60].

Differences in PANSS total score, positive subscale score, general psychopathology, depression scale, or EPS scales were minimal and not statistically significant, substantiating that the change seen on negative symptoms was not due to improvement in secondary negative symptoms [60] but a true improvement on primary negative symptoms.

With no standard of care available for negative symptoms, the choice of risperidone in this study might be subject to potential criticism; however, it is the right choice considering the alternatives. Since the late 1990s, second-generation antipsychotics are the preferred treatment over first-generation antipsychotics. From the existing and available second-generation antipsychotics, only four are known to have somewhat better efficacy on negative symptoms, and these are clozapine, olanzapine, amisulpride, and risperidone [50]. Of these four:

- Clozapine is not considered a valid first-line treatment due to its severe side-effect profile. It is only a valid therapy if other antipsychotics have failed.
- Olanzapine is an effective antipsychotic medication and has, however, a completely different adverse event profile than cariprazine: its high weight gain and sedative properties would have unblinded the study. Therefore, it could not be used for this study. However, olanzapine was studied in a similarly designed negative symptom study and compared to asenapine. Olanzapine was not better in controlling negative symptoms of schizophrenia than asenapine [68], and its change from baseline to week 26 on the PANSS FSNS was lower (−7.1) than change from baseline to week 26 with cariprazine (−8.9).
- Amisulpride would have been a potential choice, since it is approved for the treatment of negative symptoms of schizophrenia in some European countries. However, which dose to choose is a challenging question: amisulpride is used in different doses for the treatment of positive symptoms (400–800 mg) and for the treatment of negative symptoms (50–300 mg) with no overlapping between the two dose ranges. Since the aim of the study was equally to improve negative symptoms and to keep positive symptoms well under control, no dose could be chosen as a well-established and empirically proven dose. Differences in equivalent doses and side-effect profiles further blurred the picture.
- Finally, risperidone was chosen, because it has a similar side-effect profile and a similar dose range to cariprazine. As no antipsychotic is considered truly better than another in the treatment of negative symptoms, risperidone is considered a valid choice and served as a representative for all antipsychotics. Risperidone kept the positive and depressive symptoms, as well as the level of EPS, well under control.

Other comparators for the study could have been placebo or aripiprazole. However,

- no empiric evidence is available for aripiprazole being an effective therapy for negative symptoms,
- and placebo would have been controversial from an ethical perspective (leaving patients untreated for 26 weeks). Moreover, such a study would have measured relapse rates instead of efficacy on negative symptoms and the results would have been difficult to interpret.

Additionally, cariprazine has demonstrated efficacy in the treatment of acute schizophrenic symptoms [44, 69, 70] as well as in relapse prevention and maintenance treatment [71]. It is generally safe and well tolerated and has a manageable safety profile. In a recent meta-analysis by Leucht et al. [72], several drugs were examined after 60 years of available antipsychotic treatment. Efficacy data on primary negative symptoms were not examined, but data on safety in the short-term acute schizophrenia trials were presented. Cariprazine showed a favorable safety profile concerning weight gain, QT prolongation, and prolactin increase [72] compared to the other antipsychotics.

8. Conclusions

Negative symptoms such as blunted affect, alogia, anhedonia, avolition, and asociality can be clustered into two main clusters: blunted affect and alogia cluster and anhedonia, avolition, and asociality cluster [4]. They can be further characterized as primary (key element of schizophrenia, and inherent to the disease) and secondary (due to external factors such as side effects, depression or positive symptoms). They affect patients' ability to cope with daily activities and have a negative impact on their quality of life.

Negative symptoms are relatively common (15–60%), and account for much of the long-term morbidity and poor functional outcome of patients with schizophrenia [16, 29–31, 68]. Despite the introduction of second-generation antipsychotics in the 1990s, the clinical management of these symptoms continued to be an unmet medical need [30]. Though these agents are very effective in managing positive symptoms of schizophrenia, they have relatively poor long-term efficacy for negative symptoms. Thus, many patients are left with negative symptoms after their positive symptoms have been partially or completely controlled [29].

Cariprazine is a new D3/D2 partial agonist antipsychotic with preferential binding, and subsequent blockade of D3 receptors [66]. Since the blockade of D3 receptors is assumed to be related to an improvement in negative and cognitive symptoms [67], cariprazine is assumed to be effective in the treatment of negative symptoms. This has been demonstrated in a well-designed clinical trial where cariprazine has shown a statistically significant improvement in negative symptoms and patient functioning compared to risperidone. Cariprazine has also shown to have an acceptable safety profile, with advantages in weight gain, QT prolongation and hyperprolactinemia compared to other antipsychotics [72].

In summary, with no antipsychotic therapies available for the treatment of primary negative symptoms, cariprazine is an exciting new potential. It could be the first-in-class compound and a game changer in the treatment of negative symptoms. With demonstrated efficacy on positive [44, 69–71] and negative symptoms [60], and a manageable safety profile, cariprazine monotherapy covers the full range of schizophrenic symptoms and could be a good long-term treatment choice for schizophrenia.

Conflict of interest

All authors are co-workers of Gedeon Richter Plc.

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