

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800

Open access books available

122,000

International authors and editors

135M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.

For more information visit www.intechopen.com



Negative Symptoms of Schizophrenia: Constructs, Burden, and Management

Agota Barabassy, Balázs Szatmári,
István Laszlovszky and György Németh

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/intechopen.73300>

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

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

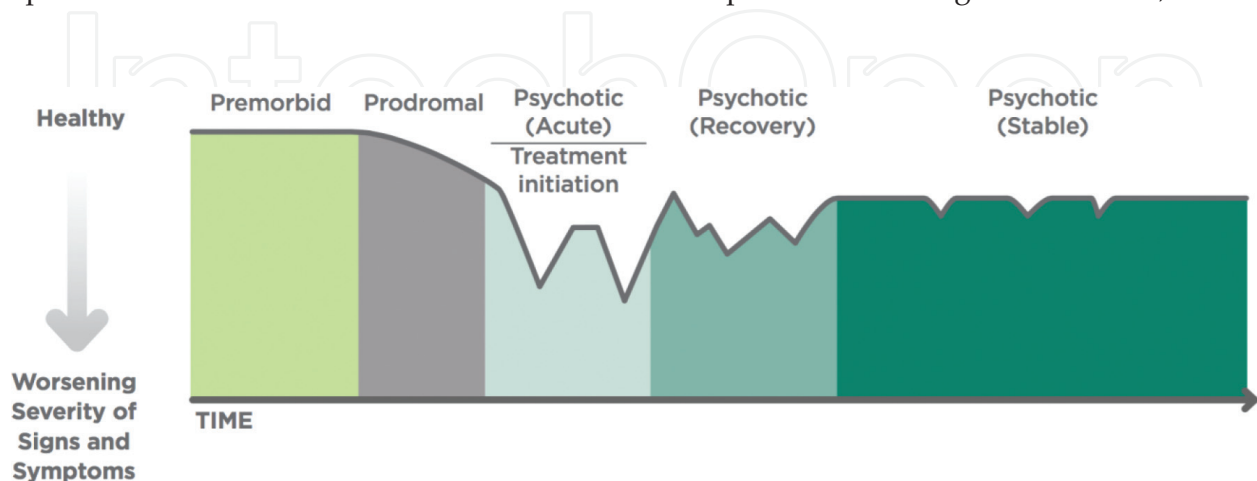


Figure 1. Individual clinical course of schizophrenia (adapted from American Psychiatric Association [32]).

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.

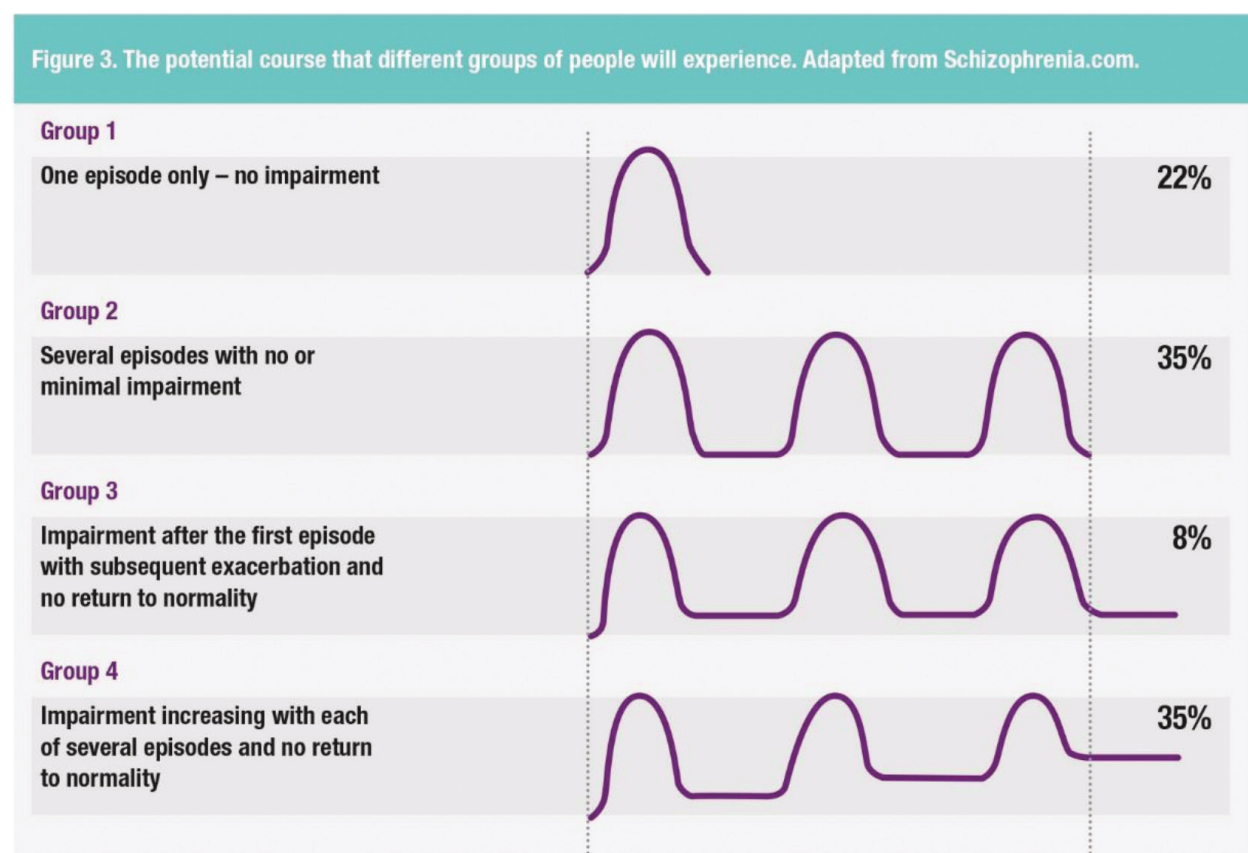


Figure 2. Overall clinical course of schizophrenia (adapted from Schizophrenia.com).

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.

Author details

Agota Barabassy*, Balázs Szatmári, István Laszlovszky and György Németh

*Address all correspondence to: barabassya@richter.hu

Gedeon Richter Plc., Budapest, Hungary

References

- [1] National Institute of Mental Health. Schizophrenia; 2017. <https://www.nimh.nih.gov/health/publications/schizophrenia-booklet/index.shtml>
- [2] Fischer BA, Buchanan RW. Schizophrenia: Clinical Manifestations, Course, Assessment, and Diagnosis; 2017. www.up-to-date.com/schizophrenia
- [3] Hales RE, Yudofsky SC. The American Psychiatric Publishing Textbook of Psychiatry. 5th ed. Washington DC, London: American Psychiatric Publishing; 2008
- [4] Marder S, Galderisi S. The current conceptualization of negative symptoms in schizophrenia. *World Psychiatry*. 2017;**16**:14-24
- [5] Merck Manual-Second Home Edition. Schizophrenia; 2017. <http://www.merckmanuals.com/en-ca/home/mental-health-disorders/schizophrenia-and-delusional-disorder/schizophrenia>
- [6] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5). 5th ed. Arlington, VA: American Psychiatric Publishing; 2013
- [7] Kirkpatrick B, Strauss GP, Nguyen L, Fischer BA, Daniel DG, Cienfuegos A, Marder SR. The brief negative symptom scale: Psychometric properties. *Schizophr Bull*. 2011 Mar;**37**(2): 300-305
- [8] Kring AM, Gur RE, et al. The Clinical Assessment Interview for Negative Symptoms (CAINS): Final development and validation. *American Journal of Psychiatry*. 2013;**170**: 165-172
- [9] Mucci A, Merlotti E, Üçok A, Aleman A, Galderisi S. Primary and persistent negative symptoms: Concepts, assessments and neurobiological bases. *Schizophrenia Research*. 2017 Aug;**186**:19-28

- [10] Carpenter WT Jr, Heinrichs DW, Alphas LD. Treatment of negative symptoms. *Schizophrenia Bulletin*. 1985;**11**:440-452
- [11] WFSBP Task Force on Treatment Guidelines for Schizophrenia. Hasan A, Falkai P, Wobrock T, Lieberman J, Glenthøj B, Gattaz WF, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia, part 1: Update 2012 on the acute treatment of schizophrenia and the management of treatment resistance. *The World Journal of Biological Psychiatry*. 2012;**13**:318-378
- [12] Carpenter WT Jr, Heinrichs DW, Wagman AM. Deficit and nondeficit forms of schizophrenia: The concept. *The American Journal of Psychiatry*. 1988 May;**145**(5):578-583
- [13] Kirkpatrick B, Buchanan RW, McKenney PD, Alphas LD, Carpenter WT Jr. The schedule for the deficit syndrome: An instrument for research in schizophrenia. *Psychiatry Research*. 1989 Nov;**30**(2):119-123
- [14] Kirkpatrick B, Buchanan RW, Ross DE, et al. A separate disease within the syndrome of schizophrenia. *Archives of General Psychiatry*. 2001;**58**:165-171
- [15] European Medicines Agency. Guideline on Clinical Investigation of Medicinal Products, Including Depot Preparations in the Treatment of Schizophrenia. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). London; 2012
- [16] Rabinowitz J, Werbeloff N, Caers I, Mandel FS, Stauffer V, Menard F, Kinon BJ, Kapur S. Negative symptoms in schizophrenia – The remarkable impact of inclusion definitions in clinical trials and their consequences. *Schizophrenia Research*. 2013;**150**:334-338
- [17] Galderisi S, Mucci A, Bitter I, Libiger J, Bucci P, Fleischhacker WW, Kahn RS; EUFEST Study Group. Persistent negative symptoms in first episode patients with schizophrenia: Results from the European First Episode Schizophrenia Trial. *European Neuropsychopharmacology*. 2013 Mar;**23**(3):196-204
- [18] Liemburg E, Castelein S, Stewart R, van der Gaag M, Aleman A, Kneegting H; Genetic Risk and Outcome of Psychosis (GROUP) Investigators. Two subdomains of negative symptoms in psychotic disorders: Established and confirmed in two large cohorts. *Journal of Psychiatric Research*. 2013 Jun;**47**(6):718-725
- [19] Fatemi SH, Clayton PJ. *The Medical Basis of Psychiatry*. 4th ed. New York: Springer; 2016. pp. 104-105
- [20] World Health Organization. International Statistical Classification of Diseases. Online version; 2010. <http://apps.who.int/classifications/icd10/browse/2016/en#/F20-F29>
- [21] Farahani A, Correll CU. Are antipsychotics or antidepressants needed for psychotic depression? A systematic review and meta-analysis of trials comparing antidepressant or antipsychotic monotherapy with combination treatment. *The Journal of Clinical Psychiatry*. 2012 Apr;**73**(4):486-496. DOI: 10.4088/JCP.11r07324
- [22] van Os J, Kapur S. Schizophrenia. *Lancet*. 2009 Aug 22;**374**(9690):635-645

- [23] Kashdan TB, Elhai JD, Christopher Frueh B. Anhedonia, emotional numbing, and symptom overreporting in male veterans with PTSD. *Personality and Individual Differences*. 2007 Sep;**43**(4):725-735. DOI: 10.1016/j.paid.2007.01.013
- [24] Chen RY, Chen EY, Chan CK, Lam LC, Lieh-Mak F. Verbal fluency in schizophrenia: Reduction in semantic store. *The Australian and New Zealand Journal of Psychiatry*. 2000 Feb;**34**(1):43-48
- [25] Chaturvedi SK, Prasad Rao G, John Mathai P, Sarmukaddam S, Gopinath PS. Negative symptoms in schizophrenia and depression. *Indian Journal of Psychiatry*. 1985 Jul-Sep; **27**(3):237-241
- [26] Larson MK, Walker EF, Compton MT. Early signs, diagnosis and therapeutic of the prodromal phase of schizophrenia and related psychotic disorders. *Expert Review of Neurotherapeutics*. 2010;**10**:1347-1359
- [27] Buchanan RW. Persistent negative symptoms in schizophrenia: An overview. *Schizophrenia Bulletin*. 2007;**33**:1013-1022
- [28] Tandon R, Gaebel W, Barch DM, Bustillo J, Gur RE, Heckers S, et al. Definition and description of schizophrenia in the DSM-5. *Schizophrenia Research*. 2013 Oct;**150**(1):3-10
- [29] Bobes J, Arango C, Garcia-Garcia M, Rejas J; CLAMORS Study Collaborative Group. Prevalence of negative symptoms in outpatients with schizophrenia spectrum disorders treated with antipsychotics in routine clinical practice: Findings from the CLAMORS study. *The Journal of Clinical Psychiatry*. 2010 Mar;**71**(3):280-286
- [30] Sicras-Mainar et al. Impact of negative symptoms on healthcare resource utilization and associated costs in adult outpatients with schizophrenia: A population-based study. *BMC Psychiatry*. 2014;**14**:225
- [31] Sicras-Mainar et al. Prevalence of metabolic syndrome according to the presence of negative symptoms in patients with schizophrenia. *Neuropsychiatric Disease and Treatment*. 2015;**11**:51-57
- [32] American Psychiatric Association. *Practice Guideline for the Treatment of Patients with Schizophrenia*. 2nd ed. Arlington, VA: American Psychiatric Publishing; 2010
- [33] Rector NA, Beck AT, Stolar N. The negative symptoms of schizophrenia: A cognitive perspective. *Canadian Journal of Psychiatry*. 2005;**50**:247-257
- [34] Milev P, Ho B-C, Arndt S, Andreasen NC. Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: A longitudinal first-episode study with 7-year follow-up. *The American Journal of Psychiatry*. 2005;**162**(3):495-506
- [35] Kurtz MM, Moberg PJ, Ragland JD, Gur RC, Gur RE. Symptoms versus neurocognitive test performance as predictors of psychosocial status in schizophrenia: A 1- and 4-year prospective study. *Schizophrenia Bulletin*. 2005 Jan;**31**(1):167-174

- [36] Alonso J, Croudace T, Brown J, Gasquet I, Knapp MR, Suárez D, Novick D. Health-related quality of life (HRQL) and continuous antipsychotic treatment: 3-year results from the Schizophrenia Health Outcomes (SOHO) study. *Value in Health*. 2009 Jun;**12**(4):536-543
- [37] Harvey PD, Heaton RK, Carpenter WT Jr, Green MF, Gold JM, Schoenbaum M. Functional impairment in people with schizophrenia: Focus on employability and eligibility for disability compensation. *Schizophrenia Research*. 2012 Sep;**140**(1–3):1-8
- [38] Rabinowitz J, Levine SZ, Garibaldi G, Bugarski-Kirola D, Berardo CG, Kapur S. Negative symptoms have greater impact on functioning than positive symptoms in schizophrenia: Analysis of CATIE data. *Schizophrenia Research*. 2012 May;**137**(1–3):147-150
- [39] Kirkpatrick B, Buchanan RW. Anhedonia and the deficit syndrome of schizophrenia. *Psychiatry Research*. 1990 Jan;**31**(1):25-30
- [40] Fenton WS, McGlashan TH. Natural history of schizophrenia subtypes. II. Positive and negative symptoms and long-term course. *Archives of General Psychiatry*. 1991 Nov;**48**(11):978-986
- [41] Kirkpatrick B, Fenton WS, Carpenter WT Jr, Marder SR. The NIMH-MATRICES consensus statement on negative symptoms. *Schizophrenia Bulletin*. 2006;**32**(2):214-219
- [42] Rudnick A, Kravetz S. The relation of social support-seeking to quality of life in schizophrenia. *The Journal of Nervous and Mental Disease*. 2001 Apr;**189**(4):258-262
- [43] Tandon R, Jibson M. Negative symptoms of schizophrenia: How to treat them most effectively. *Current Psychiatry*. 2002;**1**(9):36-42
- [44] Kane JM, Zukin S, Wang Y, Lu K, Ruth A, Nagy K, Laszlovszky I, Durgam S. Efficacy and safety of cariprazine in acute exacerbation of schizophrenia: Results from an international, phase III clinical trial. *Journal of Clinical Psychopharmacology*. 2015 Aug;**35**(4):367-373
- [45] Mohr PE, Cheng CM, Claxton K, Conley RR, Feldman JJ, Hargreaves WA, Lehman AF, Lenert LA, Mahmoud R, Marder SR, Neumann PJ. The heterogeneity of schizophrenia in disease states. *Schizophrenia Research*. 2004 Nov 1;**71**(1):83-95
- [46] Arsova S, Kopacheva Barsova G. Patients with schizophrenia and social contacts. *Open Access Macedonian Journal of Medical Sciences*. 2016 Sep 15;**4**(3):388-391
- [47] Luther L, Fukui S, Firmin RL, McGuire AB, White DA, Minor KS, Salyers MP. Expectancies of success as a predictor of negative symptoms reduction over 18 months in individuals with schizophrenia. *Psychiatry Research*. 2015 Sep 30;**229**(1–2):505-510
- [48] Tandon R, Nasrallah HA, Keshavan MS. Schizophrenia, “just the facts” 5. Treatment and prevention. Past, present, and future. *Schizophrenia Research*. 2010 Sep;**122**(1–3):1-23
- [49] Millier A, Horváth M, Ma F, Kóczyán K, Götze A, Toumi M. Healthcare resource use in schizophrenia, EuroSC findings. *Journal of Market Access & Health Policy*. 2017;**5**(1):1372027. DOI: 10.1080/20016689.2017.1372027

- [50] Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: A meta-analysis. *Lancet*. 2009 Jan 3; **373**(9657):31-41
- [51] Jones PB, Barnes TR, Davies L, Dunn G, Lloyd H, Hayhurst KP, Murray RM, Markwick A, Lewis SW. Randomized controlled trial of the effect on Quality of Life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). *Archives of General Psychiatry*. 2006;**63**(10):1079-1087
- [52] Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *The New England Journal of Medicine*. 2005 Sep 22; **353**(12):1209-1223
- [53] Millan MJ, Fone K, Steckler T, et al. Negative symptoms of schizophrenia: Clinical characteristics, pathophysiological substrates, experimental models and prospects for improved treatment. *European Neuropsychopharmacology*. 2014;**24**:645-692
- [54] Arango C, Garibaldi G, Marder SR. Pharmacological approaches to treating negative symptoms: A review of clinical trials. *Schizophrenia Research*. 2013 Nov;**150**(2-3):346-352. DOI: 10.1016/j.schres.2013.07.026. Epub 2013 Aug 9
- [55] Fusar-Poli P, Rocchetti M, Sardella A, Avila A, Brandizzi M, Caverzasi E, Politi P, Ruhrmann S, McGuire P. Disorder, not just state of risk: Meta-analysis of functioning and quality of life in people at high risk of psychosis. *The British Journal of Psychiatry*. 2015 Sep;**207**(3):198-206
- [56] Danion JM, Rein W, Fleurot O. Improvement of schizophrenic patients with primary negative symptoms treated with amisulpride. Amisulpride Study Group. *The American Journal of Psychiatry*. 1999;**156**:610-616
- [57] Loo H, Poirier-Littre MF, Theron M, Rein W, Fleurot O. Amisulpride versus placebo in the medium-term treatment of the negative symptoms of schizophrenia. *The British Journal of Psychiatry*. 1997;**170**:18-22
- [58] Boyer P, Lecrubier Y, Puech AJ, Dewailly J, Aubin F. Treatment of negative symptoms in schizophrenia with amisulpride. *The British Journal of Psychiatry*. 1995;**166**:68-72
- [59] Paillere-Martinot ML, Lecrubier Y, Martinot JL, Aubin F. Improvement of some schizophrenic deficit symptoms with low doses of amisulpride. *The American Journal of Psychiatry*. 1995;**152**:130-134
- [60] Németh G, Laszlovszky I, Czobor P, Szalai E, Szatmári B, Harsányi J, Barabássy Á, Debelle M, Durgam S, Bitter I, Marder S, Fleischhacker WW. Cariprazine versus risperidone monotherapy for treatment of predominant negative symptoms in patients with schizophrenia: A randomised, double-blind, controlled trial. *Lancet*. 2017 Mar 18;**389**(10074):1103-1113

- [61] Lecrubier Y, Quintin P, Bouhassira M, Perrin E, Lancrenon S. The treatment of negative symptoms and deficit states of chronic schizophrenia: Olanzapine compared to amisulpride and placebo in a 6-month double-blind controlled clinical trial. *Acta Psychiatrica Scandinavica*. 2006;**114**:319-327
- [62] Olie JP, Spina E, Murray S, Yang R. Ziprasidone and amisulpride effectively treat negative symptoms of schizophrenia: Results of a 12-week, double-blind study. *International Clinical Psychopharmacology*. 2006;**21**:143-151
- [63] Möller HJ, Czobor P. Pharmacological treatment of negative symptoms in schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience*. 2015 Oct;**265**(7):567-578
- [64] Veerman SRT, Schulte PFJ, de Haan L. Treatment for negative symptoms in schizophrenia: A comprehensive review. *Drugs*. 2017 Sep;**77**(13):1423-1459
- [65] Davidson M, Saoud J, Staner C, Noel N, Luthringer E, Werner S, Reilly J, Schaffhauser JY, Rabinowitz J, Weiser M, Luthringer R. Efficacy and safety of MIN-101: A 12-week randomized, double-blind, placebo-controlled trial of a new drug in development for the treatment of negative symptoms in schizophrenia. *The American Journal of Psychiatry*. 2017 Dec 1;**174**(12):1195-1202. DOI: 10.1176/appi.ajp.2017.17010122. Epub 2017 Jul 28
- [66] Stahl SM. Mechanism of action of cariprazine. *CNS Spectrums*. 2016;**21**:123-127
- [67] Maramai S, Gemma S, Brogi S, Campiani G, Butini S, Stark H, Brindisi M. Dopamine D3 receptor antagonists as potential therapeutics for the treatment of neurological diseases. *Frontiers in Neuroscience*. 2016;**10**:451
- [68] Buchanan RW, Panagides J, Zhao J, Phiri P, den Hollander W, Ha X, Kouassi A, Alphs L, Schooler N, Szegedi A, Cazorla P. Asenapine versus olanzapine in people with persistent negative symptoms of schizophrenia. *Journal of Clinical Psychopharmacology*. 2012 Feb;**32**(1):36-45
- [69] Durgam S, Starace A, Li D, Migliore R, Ruth A, Nemeth G, Laszlovszky I. An evaluation of the safety and efficacy of cariprazine in patients with acute exacerbation of schizophrenia: A phase II, randomized clinical trial. *Schizophrenia Research*. 2014;**152**:450-457
- [70] Durgam S, Cutler AJ, Lu K, Migliore R, Ruth A, Laszlovszky I, Németh G, Meltzer HY. Cariprazine in acute exacerbation of schizophrenia: A fixed-dose, phase 3, randomized, double-blind, placebo- and active-controlled trial. *The Journal of Clinical Psychiatry*. 2015; **76**(12):1574-1582
- [71] Durgam S, Earley W, Li R, Li D, Lu K, Laszlovszky I, Fleischhacker WW, Nasrallah HA. Long-term cariprazine treatment for the prevention of relapse in patients with schizophrenia: A randomized, double-blind, placebo-controlled trial. *Schizophrenia Research*. 2016 Oct;**176**(2-3):264-271
- [72] Leucht S, Leucht C, Huhn M, Chaimani A, Mavridis D, Helfer B, Samara M, Rabaioli M, Bächter S, Cipriani A, Geddes JR, Salanti G, Davis JM. Sixty years of placebo-controlled antipsychotic drug trials in acute schizophrenia: Systematic review, Bayesian meta-analysis, and meta-regression of efficacy predictors. *The American Journal of Psychiatry*. 2017 Oct 1;**174**(10):927-942