

Persistent Negative Symptoms in Schizophrenia: An Overview

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Persistent negative symptoms represent an alternative approach for assessing negative symptoms in the context of clinical trials. Persistent negative symptoms are designed to capture those symptoms that lead to functional impairment but are currently understudied and for which there are no currently available effective treatments. Persistent negative symptoms differ from the 2 most commonly used approaches: primary, enduring negative symptoms or deficit symptoms and negative symptoms broadly defined to include negative symptoms, regardless of their etiology or duration. In contrast to deficit symptoms, persistent negative symptoms may include secondary negative symptoms. However, in contrast to negative symptoms broadly defined, the secondary negative symptoms included in the assessment of persistent negative symptoms only include those that have failed to respond to usual treatments for secondary negative symptoms. In consequence, the presence of persistent negative symptoms identifies a patient population with clinically relevant symptomatology, which is larger than the one with the deficit syndrome but less heterogeneous than that captured through the use of a non-restrictive definition of negative symptoms. This may facilitate the selection of subjects for inclusion into research and efforts to develop new pharmacological treatments and enhance our understanding of a relevant clinical problem. Ultimately, the investigation of the different entities characterized by negative symptoms, such as persistent negative symptoms, and the enhanced understanding of their biological and clinical characteristics may help to unravel the psychopathological and biological heterogeneity of schizophrenia.

Key words: persistent negative symptoms/deficit syndrome/negative symptoms/schizophrenia/pharmacological treatment

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Introduction

The negative symptoms of schizophrenia, defined as the absence or diminution of normal behaviors and functions, have been recognized since Kraepelin¹ and Bleuler.² Kraepelin's description of the "avolitional syndrome,¹" manifested as a "weakening of those emotional activities which permanently form the mainsprings of volition," and resulting in "emotional dullness, failure of mental activities, loss of mastery over volition, of endeavor, and of ability for independent action," represents one of the most elegant descriptions of negative symptoms. The work of Strauss and colleagues,³ separating schizophrenia symptoms into 3 specific complexes (ie, positive symptoms, negative symptoms, and disorders of relating) rekindled interest in the positive/negative classification of symptoms. Other models using the positive/negative symptom dichotomy ensued, such as, type I and type II schizophrenia^{4,5} and positive and negative schizophrenia.^{6,7} All these constructs were attempts to explain the heterogeneity of schizophrenia.

Negative symptoms account for much of the long-term morbidity and poor functional outcome of patients with schizophrenia.^{8–10} The development of a negative symptom treatment is a major challenge for the field. Negative symptoms, as broadly defined by such measures as the Brief Psychiatric Rating Scale (BPRS)¹¹ anergia factor, Scale for the Assessment of Negative Symptoms (SANS),¹² or Positive and Negative Symptom Scale (PANSS),¹³ improve during conventional and second generation antipsychotic drug treatment.^{14–18} However, in most of these studies, this effect has been observed in the context of, and correlated with, concurrent improvement of positive, depressive, and/or extrapyramidal symptoms.^{14–20} These are the major sources of secondary negative symptoms, and other sources of secondary symptoms are usually not even assessed. Thus, the use of negative symptoms broadly defined is unlikely to lead to the development of effective treatments for those negative symptoms, which persist during clinical stability and are associated with impaired role function performance.²¹

There are 2 alternative approaches for defining negative symptoms in the context of clinical trials. The first approach is to restrict negative symptoms to primary, enduring negative symptoms or deficit symptoms.²² Deficit symptoms are highly correlated with impaired role

function.⁸ The second approach is to include both primary negative symptoms and those secondary negative symptoms, which have not responded to appropriate treatments.²³ Both these approaches have advantages over negative symptoms broadly defined for isolating those negative symptoms that are the most relevant treatment target.

In this article, we will review negative symptom definitions and terminology. We will contrast persistent negative symptoms with deficit symptoms and propose the use of persistent negative symptoms in pharmacological studies of negative symptoms. We will define persistent negative symptoms and propose study design guidelines for clinical trials. Finally, we will propose future areas of research for persistent negative symptoms. The ultimate goal is to facilitate the development of new drugs for this component of the illness.

Terminology

There is a substantial terminological conundrum in the area of negative symptoms. Therefore, prior to focusing on persistent negative symptoms, an overview of terms and definitions is presented. Carpenter and colleagues²⁴ noted that negative symptoms do not represent a homogenous entity and suggested their division into primary and secondary symptoms. The term *negative symptoms* was suggested as a descriptive term without considering their cause, longitudinal stability, or duration. *Primary* and *secondary negative symptoms*, by contrast, would refer to distinct subgroups of negative symptoms differing in their cause, longitudinal stability, or duration and differentiated through longitudinal observation rather than cross-sectional assessment.²² *Primary and enduring negative symptoms* or *deficit symptoms* refer to the symptoms that are intrinsic to schizophrenia, while *secondary negative symptoms* refer to negative symptoms occurring in association with, or presumably caused by, positive symptoms, affective symptoms, medication side effects, environmental deprivation, or other treatment- and illness-related factors.^{24,25} The term deficit symptoms is used to refer to those negative symptoms that are present as enduring symptoms, present during and between episodes of positive symptom exacerbation, and observable regardless of the patient's medication status (see full definition²²). By contrast, secondary negative symptoms present with a greater fluctuation, a lack of persistence and a temporal association with a possible underlying cause (eg, depressive or extrapyramidal symptoms). It is also suggested that secondary negative symptoms are usually responsive to treatment of the underlying cause, while primary negative symptoms or deficit symptoms, due to their different pathophysiological mechanism, may require different treatment options.²⁴ Subjects with deficit symptoms may also present with superimposed secondary symptoms. Some authors suggest an ad-

ditional group of primary negative symptoms, ie, *primary nonenduring* or *psychotic phasic primary negative symptoms*.²⁶ It is proposed that these symptoms occur only in association with positive symptoms, with presence restricted to the period around a psychotic exacerbation of schizophrenia. They are hypothesized to have an etiopathophysiological mechanism separate from the one underlying primary enduring negative symptoms.²⁷ It should be noted that in the literature, the term primary (or idiopathic) enduring negative symptoms is used interchangeably with other terms such as deficit symptoms, deficit primary symptoms, primary negative symptoms, idiopathic trait negative symptoms, primary enduring negative symptoms, or enduring or persistent negative symptoms.

Defining the Deficit Syndrome and Persistent Negative Symptoms

Kraepelin's "avolitional syndrome" is the foundation for the concept of the deficit syndrome in schizophrenia.¹ In 1988, Carpenter and colleagues proposed a schizophrenia subtype defined by negative symptoms primary (or idiopathic) to the illness and not secondary to other manifestations of the illness or its treatment.²² The term deficit symptoms was suggested to specifically refer to those negative symptoms that are present as primary, enduring traits and that are present during as well as between episodes of positive symptom exacerbation.²² Carpenter and colleagues went on to propose that deficit symptoms may define a separate disease entity, ie, the deficit syndrome, which is characterized by a distinct etiopathophysiology.²⁸ Deficit psychopathology defined a group of patients with schizophrenia presenting with specific signs and symptoms, course, biological correlates, treatment response and etiology, thus differing from patients without deficit symptoms.⁸ Furthermore, the development of deficit syndrome criteria^{22,29} allowed for the clear identification of subjects with deficit schizophrenia. Thus, the deficit syndrome represented an important advancement in comparison to other negative symptom constructs as it facilitated research in homogenous patient samples and instigated a large body of research specifically addressing this patient population.

The deficit form of schizophrenia, an illness different from schizophrenia without deficit features, is defined by the following criteria^{22,29}:

1. At least 2 of the following 6 features must be present and of a clinically significant severity: (1) restricted affect, (2) diminished emotional range, (3) poverty of speech, (4) curbing of interest, (5) diminished sense of purpose, and (6) diminished social drive.
2. Two or more of these features must have been present for the preceding 12 months and must have always been present during periods of clinical stability

- (including chronic psychotic states). These symptoms may or may not be detectable during transient episodes of acute psychotic disorganization or decompensation.
- Two or more of these enduring features are also idiopathic, ie, not secondary to factors other than the disease process. Such factors include: (1) anxiety, (2) drug effects (especially, extrapyramidal side effects), (3) suspiciousness, (4) formal thought disorder, (5) hallucinations or delusions, (6) mental retardation, and (7) depression.
 - The patient meets *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria for schizophrenia.

Although the deficit/nondeficit categorization can be made reliably,²⁹ the categorization of subjects into deficit and nondeficit forms of schizophrenia may be difficult in the clinical trial context. The most challenging issue is that information about the longitudinal course of the symptoms required to make the primary/secondary distinction may not always be readily available. In addition, the differentiation of primary and secondary negative symptoms requires a level of clinical sophistication above and beyond what is usually available in clinical raters.

The concept of persistent negative symptoms represents a broader concept than the deficit syndrome. Persistent negative symptoms include the negative symptoms of schizophrenia that:

- are primary to the illness
- are secondary, but have not responded to the usual treatments for these symptoms
- interfere with the ability of the patient to perform normal role functions
- persist during periods of clinical stability
- represent an unmet therapeutic need.³⁰

Persistent negative symptoms differ from negative symptoms broadly defined by the requirement for persistence of the symptoms. The requirement for persistence is designed to maximize the likelihood that patients who are included in clinical trials are characterized by the presence of primary negative symptoms and those secondary negative symptoms, which are not associated with the onset or recovery from an acute exacerbation of the illness. In addition, persistent negative symptoms exclude those secondary negative symptoms for which there are currently available treatments.

Persistent negative symptoms differ from deficit symptoms in several aspects:

- The definition of duration: deficit symptoms need to be present for at least 12 months, whereas persistent negative symptoms may be present for any predefined time period, though usually a minimum of 6 months.

- Their severity is defined by a clinical need for therapeutic intervention.
- They are defined through a number of temporal and scalar criteria easily applicable within the clinical trial context.

In consequence, persistent negative symptoms identify a patient population substantially larger than the one with the deficit syndrome. The use of persistent negative symptoms can define a patient population with a clinically relevant symptomatology large enough to be targeted, selected, and studied, thereby facilitating research efforts into a clinical problem of a substantial magnitude and importance.

Prevalence

Epidemiological data support the notion that patients with the deficit syndrome represent a distinct subgroup within schizophrenia. In clinical samples, patients with the deficit form of schizophrenia or primary negative symptoms represent about 20%–30% of patients, whereas in population-based samples approximating incidence samples, patients with the deficit form of schizophrenia comprise 14%–17% of patients with schizophrenia.³⁰ Carpenter and colleagues examined the prevalence of the deficit syndrome within an outpatient clinical population.²² They reported a 19% prevalence rate in a nonrandom population of patients. Bottlender and colleagues reported a similar prevalence (26%) in patients who were evaluated 15 years after their first hospitalization.³¹ The prevalence of the deficit syndrome was substantially higher (37%) in a sample of patients with schizophrenia who were 45 years or older.³² However, in a sample of patients with first-episode schizophrenia and followed up through their recovery for at least 6 months, only 4% met all criteria for deficit syndrome, while 19% had deficit symptoms.³³ In a retrospective study of 660 consecutively admitted psychiatric inpatients that presented with at least one psychotic symptom and severe negative symptoms, a modified version of the Schedule for the Deficit Syndrome (SDS)²⁹ was used to identify subjects with persistent primary negative symptoms.³⁴ The symptoms were required to have persisted over the last year, and their association with putative sources of secondary negative symptoms was examined. The subjects were not required to have a diagnosis of schizophrenia. Using the above criteria, the authors identified the presence of persistent primary negative symptoms in 15.5% of all subjects irrespective of the diagnosis, whereas the prevalence was 25.7% in subjects with schizophrenia, 8.1% in those with schizoaffective disorder, 2.3% in mood disorders, and 15.6% in psychotic disorders not otherwise specified.

Population-based studies have the advantage of random selection of subjects and may provide more unbiased estimates of deficit syndrome prevalence. In a study

looking at subjects who met criteria for schizophrenia or simple schizophrenia in a population-based psychiatric registry in County Roscommon, Ireland, the lifetime prevalence of the deficit syndrome was 16.5%.³⁵ In the Irish Study of High-Density Schizophrenia Families in subjects who were members of the full sibling pairs concordant for schizophrenia, schizoaffective disorder with poor outcome or simple schizophrenia,³⁶ the prevalence of the deficit syndrome was 13.9%. Although there is clearly a need for more studies, the available results suggest a prevalence of the deficit syndrome of approximately 15%–20%.

There is little epidemiological data pertaining to persistent negative symptoms. In light of the estimated 15%–20% prevalence of the deficit syndrome, the prevalence of persistent negative symptoms is probably higher because persistent negative symptoms also include unresponsive secondary negative symptoms. The lack of reliable information regarding the prevalence of negative symptoms warranting therapeutic intervention is acknowledged in the recently published NIMH-MATRICES Consensus Statement on Negative Symptoms, and longitudinal studies providing information on the persistence of negative symptoms have been identified as one of the areas for future research.³⁰

Assessment

Classification of patients into those with and those without the deficit syndrome can be achieved through the SDS.²⁹ The SDS is a semi-structured interview that provides specific criteria for assessing the presence of negative symptoms, as well as information about the duration of these symptoms and whether they are primary or secondary. Additional information is obtained from clinicians with long-standing contact with the patient and from family members. The SDS has good interrater reliability, but its successful application requires familiarity of the rater with the longitudinal clinical course of the patient, including periods of relapse and of relative remission, interview of the patient during the baseline period, and longitudinal information about the patient from sources other than an interview.²⁹

The clinical assessment of persistent negative symptoms is based on cross-sectional and longitudinal evaluation of negative symptoms, in conjunction with the use of other symptom criteria designed to minimize the inclusion of secondary negative symptoms. Restricted affect, diminished emotional range, and poverty of speech are mainly evaluated by observation, while curbing of interest, diminished sense of purpose, and diminished social drive by interview.³⁷ Longitudinal stability of persistent negative symptoms may be assessed retrospectively through interviews with a reliable source, reviewing clinical charts, and prospectively through regular follow-up of patients.

Table 1. Criteria for Persistent Negative Symptoms

At least moderate severity of negative symptoms, defined on an accepted and validated rating scale
A defined threshold level of positive symptoms on an accepted and validated rating scale
No (or low level of) depressive symptoms on an accepted and validated rating scale
No (or low level of) extrapyramidal symptoms on an accepted and validated rating scale
Demonstrated clinical stability for an extended period of time prior to the start of the study

In the context of a clinical trial in schizophrenia, subjects with persistent negative symptoms would be defined as having at least moderate severity of negative symptoms, defined on an accepted and validated rating scale (eg, the PANSS negative subscale score,¹³ the SANS total score,¹² or the Negative Symptom Assessment Scale [NSA-16] total score³⁸); a defined threshold level of positive symptoms on an accepted and validated rating scale (eg, BPRS four positive symptoms score [conceptual disorganization, hallucinations, suspiciousness and unusual thought content],¹¹ PANSS positive subscale score, or the Scale for Assessment of Positive Symptoms [SAPS])³⁹; no (or low level of) depressive symptoms on an accepted and validated rating scale (eg, Calgary Depression Scale⁴⁰ or BPRS anxiety/depression factor [items somatic concern, anxiety, guilt, depression]); no (or low level of) extrapyramidal symptoms on an accepted and validated rating scale (eg, Simpson-Angus Extrapyramidal Rating Scale [SAS]⁴¹ or Extrapyramidal Symptom Rating Scale⁴²) and demonstrated clinical stability for an extended period of time prior to the start of the study, eg, 4 weeks. Proposed persistent negative symptom criteria are summarized in table 1.

The SANS and PANSS are currently the standard scales used to assess negative symptoms, but they have a number of limitations including insufficient number of items to assess the full range of negative symptoms, inclusion of nonspecific items that can be found in other psychiatric disorders, inadequately defined anchors, lack of standardized scoring methods or lack of sensitivity to change over brief periods of time.⁴³ In addition, the PANSS defines several aspects of schizophrenia that appear to be cognitive in nature (eg, deficit in abstract thinking, stereotyped thinking, and poor attention) as negative symptoms.⁴⁴ There has also been growing agreement, supported by several factor analyses, that the SANS items—inappropriate affect, attentional impairment, and poverty of content of speech—should not be grouped under the negative symptom construct, as they appear not to be uniquely related to negative symptoms.^{45–48}

The NSA⁴³ was developed to overcome some of above-mentioned limitations. It covers a wide range of negative symptoms, has well-defined items, anchor points for

rating symptom severity, a semi-structured interview for eliciting information for making ratings, and sensitivity to changes over a brief period of time such as weeks.⁴⁹ However, the NSA has not been extensively used in clinical trials to date.

The *NIMH Initiative Regarding Treatment for Negative Symptoms* is currently developing a new scale that will incorporate features from previous scales but will be specifically designed to be applicable in both inpatient and outpatient settings, with clearly defined items and anchors, and will be sensitive to change during pharmacological treatment.⁵⁰

Toward an Innovative Clinical Trial Design for Psychopharmacological Studies in Persistent Negative Symptoms

A number of factors have contributed to the difficulty of conducting psychopharmacological research on the deficit syndrome and persistent negative symptoms. In addition to problems in recruiting adequate numbers of patients into clinical trials, the development of the optimal clinical trial design is challenging because it has to address issues such as temporal stability of symptoms while controlling for as many sources of secondary negative symptoms as possible and selecting appropriate negative symptom rating instruments sensitive to change during pharmacological treatment. In long-term clinical trials (ie, >6 months duration), the high attrition rates typically seen in clinical studies in schizophrenia may further reduce the sample size.

The first step in developing an innovative clinical trial design is defining a population with persistent negative symptoms (see above). The definition should include a minimal severity level of negative symptoms and restrict the severity of other symptoms that may contribute to secondary negative symptoms or whose change during the course of a clinical trial could compromise the interpretation of any observed effect on negative symptoms.⁵¹ This definition has been used in 2 recent studies.^{52,53} In addition:

1. Subjects should be clinically stable patients in the residual phase of their illness, and their negative symptoms should persist despite adequate antipsychotic treatment.^{30,54}
2. Proof of concept studies may be of 4–12 week duration, while registration studies should be of a longer duration (eg, 6 months) to confirm persistent efficacy.³⁰
3. The experimental treatment should be administered as a comedication with a second generation antipsychotic.³⁰ Concomitant medications may be allowed depending on the mechanism of action of the agent.
4. The PANSS, SANS, and perhaps other instruments (eg, NSA) are appropriate for application in current clinical trials.³⁰
5. Procedures should be used for dosing and titration that minimize expression of side effects.⁵⁵

These study design guidelines are intended to provide an approach to managing the various complications associated with conducting negative symptom clinical trials and facilitate the development of new treatments for negative symptoms.

Treatments

Currently available psychopharmacological research involving patients with the deficit syndrome is scarce, accompanied by a striking paucity of data from large-scale clinical trials that focus on patients selected on the basis of severe and persistent negative symptoms.⁵⁶ In the following section, we will review the evidence for an effective pharmacological treatment for deficit symptoms or persistent negative symptoms and the extent to which these studies have used a trial design similar to the one we propose above.

Deficit Syndrome Clinical Trials

Antipsychotics. Only 3 studies have compared the efficacy and tolerability of antipsychotics in deficit and nondeficit subjects. Two studies have been double blind and placebo controlled. In the first study, the comparative efficacy of clozapine (200–600 mg/day) and haloperidol (10–30 mg/day) was evaluated in partially responsive outpatients with schizophrenia, who were categorized into deficit and nondeficit groups.⁵⁷ The subjects had a total score of ≥ 8 on the BPRS items for conceptual disorganization, hallucinatory behavior, unusual thought content, and suspiciousness or a score of ≥ 4 on any one of the items; a total score of ≥ 20 on the SANS or a score of ≥ 2 on at least one SANS global item. Clozapine was superior to haloperidol in treating positive symptoms, but there was no evidence for clozapine to have superior efficacy or significant long-term effects for primary or secondary negative symptoms. In the second study, 63 outpatients with schizophrenia who met retrospective and prospective criteria for either residual positive or negative symptoms, with or without the deficit syndrome, were treated for 16 weeks with either olanzapine (10–30 mg/day) or haloperidol (10–30 mg/day).⁵³ There were no significant group differences or group interactions between deficit/nondeficit categorization and treatment assignment for any of the efficacy or social functioning measures, which suggested that olanzapine does not exhibit superior efficacy for positive or negative symptoms in outpatients with partially responsive schizophrenia. In a single-blind, non-placebo-controlled study, 39 outpatients with schizophrenia, severe negative symptoms (SANS global subscale total score ≥ 18), and deficit symptoms were treated in a 12-week open-label treatment study with olanzapine 5–30 mg/day.⁵⁸ The nondeficit patients improved significantly in all symptom domains except quality of life, while the deficit group showed no improvement.

In summary, the above studies used various procedures to identify a cohort of subjects with deficit symptoms and examine their response to clozapine and olanzapine. The study designs allowed for the assessment of the efficacy of these drugs for both primary and secondary negative symptoms (ie, the negative symptoms present in the non-deficit patients). Neither deficit nor secondary negative symptoms improved with treatment.

Glutamatergic Agents. Efficacy of add-on therapy with d-cycloserine, a partial agonist acting at the glycine modulatory site of the glutamatergic N-methyl-d-aspartate receptor, was examined in 3 double-blind trials in patients with deficit syndrome. In the first study, Goff and colleagues⁵⁹ compared the addition of 50 mg/day of d-cycloserine ($n = 23$) or placebo ($n = 24$) with their conventional antipsychotic. Subjects were required to have a high level of negative symptoms, and low levels of depressive or EPS symptoms. The presence of the deficit syndrome was determined by the SDS. After 8 weeks of treatment, the mean reduction in negative symptoms was significantly greater with d-cycloserine than with placebo (23% vs 7%), as calculated by slopes representing SANS total scores, without changes in other symptom domains. Evins and colleagues⁶⁰ enrolled 15 outpatients who were treated with a stable dose of risperidone for at least 4 months into a single-blind, consecutive 2-week treatment with placebo and 5, 15, 50, and 250 mg/day add-on d-cycloserine. The subjects met SDS criteria for the deficit syndrome, had moderate to severe negative symptoms at baseline as assessed by SANS, low EPS symptoms on the SAS, and no current diagnosis of major depression. The only effective dose was 50 mg/day, which produced a 10% improvement in negative symptoms. The third study enrolled 22 male subjects with the presence of the deficit syndrome assessed by the SDS, prominent negative symptoms assessed by the SANS, and treated with a stable dose of a conventional antipsychotic for ≥ 60 days prior to baseline.⁶¹ However, no baseline assessments of depressive or EPS symptoms were performed. After 4 weeks of double-blind treatment with 50 mg/day add-on d-cycloserine or placebo, there were no significant between-group differences. Although 2 of the 3 studies suggest add-on d-cycloserine 50 mg/day may have some effect on negative symptoms in patients with deficit syndrome, small sample sizes, different study designs and duration, and inconsistencies in assessments of depressive and EPS symptoms make the interpretation of the results challenging.

Persistent Negative Symptom Clinical Trials

A number of clinical trials have been performed in subjects with prominent negative symptoms. However, few of the studies have used inclusion criteria to define persistent negative symptom or used designs that allowed for

the evaluation of a change in negative symptoms in isolation from change in other symptoms.

Amisulpride. Amisulpride, a substituted benzamide antipsychotic, is licensed in several European countries for the treatment of negative symptoms in schizophrenia. The efficacy of low-dose amisulpride in patients with predominant negative symptoms was assessed in 3 placebo-controlled and 1 haloperidol-controlled studies. Efficacy of 50 mg/day amisulpride was examined in a 6-week placebo-controlled study in 21 young subjects with schizophrenia and 6 with schizotypal personality disorder.⁶² Subjects were required to have SANS global item ratings of 3 on 2 or more SANS subscales, a short disease course and were neuroleptic naïve or their lifetime neuroleptic treatment was shorter than 1 month. Both treatment groups had similar, low baseline levels of depressive symptoms assessed by Montgomery-Åsberg depression Rating Scale (MADRS).⁶³ Amisulpride-treated subjects showed statistically significant larger endpoint improvement in negative symptoms vs placebo (32% vs 8%, $P = 0.05$) but not in depressive symptoms (42% vs 5%, $P = 0.17$) or positive symptoms (25% vs 23%, $P = 0.49$). Although the results suggest a negative symptom effect, the magnitude of the concurrent change in depressive symptoms raises questions about whether the observed effect on negative symptoms was a direct effect. In a 6-month trial, Loo and colleagues⁶⁴ assessed the efficacy of amisulpride, 100 mg/day, or placebo in 141 subjects with subchronic or chronic schizophrenia, with SANS global item ratings of 3 on 2 or more SANS subscales, a SANS total score ≥ 60 , and a SAPS total score ≤ 50 . Amisulpride had a significantly greater endpoint improvement in negative symptoms (41% vs 20%, $P < 0.0002$). Both positive and extrapyramidal symptoms were low at baseline and did not change substantially during treatment. However, lack of depressive symptom assessments, of information demonstrating a stable disease period prior to the start of the study, and of predefined depressive and extrapyramidal symptom entry criteria represent important study limitations. The third placebo-controlled study compared the efficacy of amisulpride 50 mg/day and 100 mg/day administered for 12 weeks in 242 patients with residual type schizophrenia of ≤ 20 years duration, and predominant negative symptoms defined as a SANS total score ≥ 60 and a SAPS total score ≤ 50 .⁶⁵ Both amisulpride doses produced significantly larger improvements on the SANS, SAPS, and MADRS compared with placebo. Although this study was performed in subjects with residual schizophrenia, there is no information available to support a stable disease course prior to inclusion into the trial, and predefined depressive and extrapyramidal symptom entry criteria were not utilized. More importantly, the concurrent change in positive and depressive symptoms raises questions about whether amisulpride was having a direct

effect on negative symptoms. Speller and colleagues⁶⁶ conducted a 1-year double-blind comparison between amisulpride and haloperidol in 60 inpatients with chronic schizophrenia. The subjects had at least moderate negative symptoms (a combined score of ≥ 4 on the flatness of affect and poverty of speech items on the Manchester Scale),⁶⁷ and the dose of each patient was progressively reduced toward the minimum effective dose to allow comparison of 2 clinically equivalent regimens. Amisulpride was well tolerated, but both drugs failed to produce any significant improvement in negative symptoms. The juxtaposition of these 4 studies helps to underscore the importance of the methodological issues raised in the discussion of the placebo-controlled studies. The failure to adequately control for potential sources of secondary negative symptoms led to the conclusion that amisulpride was effective for negative symptoms; a conclusion that was clearly refuted by the failure to demonstrate increased negative symptom efficacy compared with haloperidol.

Glutamatergic Agents. Glycine and d-cycloserine have shown inconsistent results on persistent negative symptom improvement when studied as add-on therapies. Twenty-two treatment-resistant patients with schizophrenia with persistent negative symptoms (defined as prestudy PANSS positive and negative scores in the 70th percentile or higher, based on normative data for inpatients with chronic schizophrenia) were treated with 0.8 g/kg per day of glycine added to their ongoing antipsychotic medication in a double-blind, placebo-controlled, 6-week, crossover trial.⁶⁸ Glycine administration resulted in a significant $30\% \pm 16\%$ reduction ($P < 0.001$) in negative symptoms, as measured by the PANSS, and a significant $30\% \pm 18\%$ improvement ($P < 0.001$) in the BPRS total scores, unrelated to changes in extrapyramidal or depressive symptoms. However, glycine also resulted in significant positive symptom improvement, which may have contributed to the observed negative symptom effect (not evaluated in the study) and underscores the importance of limiting the severity of positive symptoms. To overcome potentially confounding results from small sample sizes used in previous trials with glycine and d-cycloserine and concurrent changes in secondary sources of negative symptoms, the CONSIST study compared the efficacy of coadministration of glycine, d-cycloserine or placebo in 171 patients with persistent negative symptoms, identified using clearly defined scalar criteria on the SANS for negative symptoms, on the BPRS for positive and depressive symptoms, and on the SAS for the EPS, and stratified according to the SDS criteria.⁶⁹ The study results were not in the public domain at the time of preparation of this article.

Selective Monoamine Oxidase B Inhibitors. Add-on therapy with 5mg/day selective monoamine oxidase B inhibitors selegiline was studied in a 12-week placebo-

controlled trial in 67 patients with schizophrenia and persistent negative symptoms.⁵² The subjects were on a stable antipsychotic dose, their baseline severity of negative symptoms was assessed by the SANS, they had no prominent positive symptoms as assessed by BPRS thinking disturbance items and no current diagnosis of a mood disorder. Changes significantly favoring selegiline over placebo were evident in the SANS total and avolition-apathy and anhedonia global scores, BPRS total score, and Clinical Global Impression severity and improvement scores. There were no significant group differences in positive, depressive, or extrapyramidal symptoms. These results provide preliminary evidence that selegiline may have a beneficial effect for persistent negative symptoms.

In summary, few studies have used clinical trial designs that would allow unequivocal interpretation of results. In addition, the paucity of studies precludes any definitive statement about effective treatments and underscores the pressing need for more concerted research efforts in this area.

Future Directions

The development of new drugs for the treatment of deficit symptoms and persistent negative symptoms will be facilitated by further investigation of the pathophysiology and clinical significance of these symptoms. In particular, research efforts should be aimed at addressing those areas currently lacking adequate data, such as etiology, functional outcomes, burden of disease, quality of life, and costs associated with deficit symptoms and persistent negative symptoms, as well as to assess potential therapeutic benefits of novel compounds using innovative clinical trial designs.

A major area of research is the relationship between deficit symptoms and persistent negative symptoms and functional outcomes in schizophrenia because the role that negative symptoms play in functional outcomes has not been fully clarified.⁷⁰ Although negative symptoms and cognitive deficits in schizophrenia share many characteristics and are both associated with poor community functioning,^{21,71} insights into the nature of their relationship have only started to evolve.⁴⁴ Currently, it is cognitive dysfunction that is the focus of pharmacological research efforts, recently channeled and consolidated through development of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) process.⁷² It is hoped that similar advancements will commence in the area of negative symptoms in general and deficit symptoms and persistent negative symptoms in particular.³⁰

Conclusions

The Food and Drug Administration has recently stated that they may consider negative symptoms as a target for

a drug indication.⁵³ The identification of negative symptoms as a suitable target should stimulate a new generation of drug development. The use of persistent negative symptoms and the study design guidelines defined and described herein should greatly facilitate the conduct of negative symptom clinical trials. Persistent negative symptoms are thought to affect more patients and are, in particular, easier to define within a research context. Hopefully, the investigation of the different entities characterized by negative symptoms, such as persistent negative symptoms, and the enhanced understanding of their biological and clinical characteristics may ultimately help to unravel the psychopathological and biological heterogeneity of schizophrenia and lead to the development of more effective and better tolerated treatments with enhanced specificity for particular symptoms domains.²¹

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