Overview

Developing Drugs for Negative Symptoms of Schizophrenia

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Negative symptoms in schizophrenia represent a clinically important target for drug development due to their profound effect on an individual’s ability to function normally. The lack of effective medications for this domain of psychopathology is a major unmet medical need in schizophrenia. Earlier clinical trials for negative symptoms have been criticized mixing primary and secondary negative symptoms as treatment target and lack of standard protocols for clinical trial design. In the first part, The author is reviewing the methodological issues on defining and measuring negative symptoms and on developing the consensus for clinical trial design for negative symptoms. Deficit symptoms and persistent negative symptoms, instead of broadly defined negative symptoms, have been advocated as the treatment target of clinical trial. There were five commonly used interview-based negative symptom scales with satisfactory psychometric profiles. The consensus has been achieved for the design of clinical trials for negative symptoms. In the second part, the treatment efficacy of different class of drugs on negative symptoms is reviewed. Some second-generation antipsychotics, antidepressants, psychostimulants, glutamate pathway molecules, serotonin receptor antagonists, and anti-inflammatory agents have modest effects on improving negative symptoms than placebo. Although some statistically significant effects on negative symptoms are evident, none has reached the threshold for clinically significant. Several new molecules with potentials in treating negative symptoms are still in development.

Key words: schizophrenia, negative symptoms, medication, clinical trials

Introduction

The negative symptoms of schizophrenia have been receiving much clinical attention for a long time because of its significant correlation with poor functional and long-term outcomes [1]. Negative symptoms are substantially more resistant to current pharmacological treatments than positive symptoms [2]. With the exception of amisulpride [3] in some European countries, no pharmacological agents have been approved for the treatment of negative symptoms. The National Institute of Mental Health (NIMH) Measurement
and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) has turned its attention to negative symptoms [4]. The United States Food and Drug Administration (FDA) has endorsed negative symptoms of schizophrenia as a legitimate drug target for a labeling indication and has offered guidelines for development [5]. The European Medicines Agency has also offered guidelines for claiming effects on negative symptoms.

**Methodological Issues**

**Definition of negative symptoms**

Negative symptoms of schizophrenia contain the following features: affective flattening, alogia, avolition, asociality, and anhedonia [4]. Factor analyses have isolated two separate but related subdomains, diminished expression (e.g., affective flattening), and amotivation (e.g., avolition/apathy) [6].

Heterogeneous clinical manifestations exist with different causes and longitudinal stability. Considering their causes and longitudinal stability, secondary negative symptoms are referred to negative symptoms occurring presumably caused by positive symptoms, affective symptoms, medication side effects, environmental deprivation, or other treatment- and illness-related factors [7], while primary enduring negative symptoms referring to the ones, from which other secondary causes have been ruled out, persistently presenting for a long duration and with a stable degree of severity. The term broadly defined negative symptoms are negative symptoms without considering their causes, longitudinal stability, or duration. Earlier studies showed negative symptoms improve during first- and second-generation antipsychotic drug treatment [8, 9]. But in most of these studies, this effect has been correlated with con-current improvement of positive, depressive, and/or extrapyramidal symptoms. These are the major sources of secondary negative symptoms, and other sources of secondary symptoms are usually not even assessed. Thus, the use of broadly defined negative symptoms as treatment target is unlikely to lead to the development of effective treatments for those negative symptoms, which persist during clinical stability and are associated with impaired rôle function performance [10].

There are two alternative approaches for defining negative symptoms in the context of clinical trials. The first approach is termed as “deficit symptoms,” which restrict negative symptoms to primary enduring negative symptoms, which required clinicians to rule out any secondary causes of negative symptoms and confirm the persistence of these symptoms during clinical stable period [11]. The second approach is termed as “persistent negative symptoms” to include both primary negative symptoms and those secondary negative symptoms, which are persistent presented during clinical stable period and have not responded to appropriate treatments [12]. Both those approaches have advantages over negative symptoms broadly defined for isolating those negative symptoms that are the most relevant treatment target.

Researchers proposed that primary enduring negative symptoms, named as deficit symptoms, may define a separate disease entity, i.e., the deficit syndrome, which is characterized by a distinct etiopathophysiology [13]. The deficit form of schizophrenia is defined by the following criteria [11]:

- At least 2 of the following 6 features must be present and of a clinically significant severity: (A) restricted affect, (B) diminished emotional range, (C) poverty of speech, (D) curbing of interest, (E) diminished sense of purpose, and (F) diminished social drive.
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).

Two or more of these enduring features are also idiopathic, i.e., not secondary to factors other than the disease process. Such factors include (A) anxiety, (B) drug effects (especially, extrapyramidal side effects), (C) suspiciousness, (D) formal thought disorder, (E) hallucinations or delusion, (F) mental retardation, and (G) depression.

The patient meets the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for schizophrenia.

The most challenging issue for the deficit syndrome 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. Also, the prevalence of deficit syndrome of schizophrenia has been estimated only 15% - 20% of patients [4, 14], which cause difficulty recruiting adequate number of patients for clinical trial and limited the generalizability of the drugs.

The concept of persistent negative symptoms represents a broader concept than the deficit syndrome. The criteria of persistent negative symptoms [12] are described:

- 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.

Persistent negative symptoms differ from broadly defined negative symptoms by the requirement for persistence of the symptoms. 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 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 [12].

**Measurement of negative symptoms**

Instruments for measuring negative symptoms suitable for use in the clinical trial should have the following characteristics: (A) the scale should measure all of the domains of negative symptoms and not be contaminated by other domains; (B) it should be sensitive to change; (C) the instrument should demonstrate good reliability in the settings where the trials will be carried out; (D) it should be relatively brief; and (E) it should be an instrument that can measure negative symptoms in international trials that include diverse languages and cultures [15].

An NIMH consensus statement has characterized the domains of negative symptoms as
blunted affect, alogia, asociality, anhedonia, and avolition [4]. A recent review of factor analysis studies of the SANS found that roughly the same two factors had been found with rather good consistency [16]. Those two factors consisted of (A) internal experience, which includes apathy, amotivation, asociality, and anhedonia; this factor is often termed avolition/ apathy; and (B) behaviors related to the expression of emotion, specifically blunted affect and alogia (poverty of speech); this factor is often termed expressivity. Subsequent studies have replicated the existence of these factors when negative symptoms are rated by other scales as well [17, 18]. Such a finding would suggest that in the analysis of future treatment trials, these two factors should routinely be examined separately.

Recent studies of negative symptom patients have suggested that it may be useful to separate the anticipatory component of anhedonia (or the wanting) from the consumatory (or the liking) component [19, 20]. Studies suggest that schizophrenia patients have impairments in the anticipatory aspect, but have a relatively normal ability to experience consumatory pleasure.

There are five instruments suitable for use in clinical trials for negative symptoms, including the Schedule for the Assessment of Negative Symptoms (SANS) [21], the Positive and Negative Syndrome Scale (PANSS) [22], the Negative Symptom Assessment Scale (NSA) [23], the Brief Negative Symptom Scale (BNSS) [17] and the Clinical Assessment Interview for Negative Symptoms (CAINS) [24]. All of them are considered to be reliable and valid measures for negative symptom trials but differ with respect to their domain coverage, use of informants, integration of global scores, administration time and comprehensiveness of their structured interviews. Table 1 summarizes the items of these instruments corresponding to the five domains of negative symptoms [15]. All of them are corresponding to the five domains of negative symptoms, except the PANSS without items corresponding to anhedonia. The BNSS and CAINS has separated anhedonia into two parts: the anticipatory component and the consumatory component [15]. When using SANS, it was suggested to remove the items in the Attention subscale, as well as the Inappropriate Affect item from the Affective Flattening subscale [15, 25]. When using PANSS, it was suggested to use the PANSS negative factors derived from factor analyses, instead of the original PANSS negative subscale [25].

**Consensus on clinical trial design for negative symptoms**

- Definition of negative symptoms: consensus-based definitions of negative symptoms currently include the following five sub-domains: blunted affect, alogia, anhedonia, asociality, and avolition [4].
- Assessment: negative symptoms should be assessed with a validated interview-based measure [26]. Information from informants should be included for ratings when available [27].
- Study subjects should be under the age of 65 years [27].
- Severity of negative symptoms: subjects should have no fewer than two negative symptoms and at least one should be rated as moderate or greater [27].
- Negative symptoms should be stable and persistent: this may be operationally defined using criteria for persistent negative symptoms [12] or the deficit form of schizophrenia [11]. Before entering into a negative symptom study, subjects should demonstrate clinical stability for a period of 4 to 6 months by collection of retrospective information; and prior to entry, the sta-
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<th>Symptom domains</th>
<th>SANS</th>
<th>PANSS</th>
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<td>Blunted affect</td>
<td>Unchanging facial expression</td>
<td>Blunted affect</td>
<td>Affect: reduced modulation</td>
<td>Facial expression</td>
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<td>Decreased spontaneous movements</td>
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<td>Affect: reduced display</td>
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<td>Paucity of expressive gestures</td>
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<td>Poor eye contact</td>
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<td>Affective non responsivity</td>
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<td>Lack of vocal inflections</td>
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<td>Alogia</td>
<td>Poverty of speech</td>
<td>Lack of spontaneity and flow of conversation</td>
<td>Restricted speech quantity</td>
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<td>Asociality</td>
<td>Sexual interest and activity</td>
<td>Poor rapport</td>
<td>Reduced social drive</td>
<td>Asociality: behavior</td>
<td>Motivation for close family/ spouse relationships</td>
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<td>Ability to feel intimacy and closeness</td>
<td>Passive/apathetic expression</td>
<td>Poor rapport with interviewer</td>
<td>Asociality: internal experience</td>
<td>Motivation for close friendships and romantic relationships</td>
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<td>Relationship with friends and peers</td>
<td>Social withdrawal</td>
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<td>Avolition</td>
<td>Grooming and hygiene</td>
<td>Emotional withdrawal</td>
<td>Poor grooming and hygiene</td>
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<td>Motivation for work and school and work activities</td>
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<td>Impersistence at work of school</td>
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<td>Reduced sense of purpose</td>
<td>Avolition: internal experience</td>
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<td>Physical anergia</td>
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<td>Anhedonia</td>
<td>Recreational interests and activities</td>
<td>Reduced hobbies and interests</td>
<td>Intensity of pleasure during activities</td>
<td>Frequency of pleasurable recreational activities – past week</td>
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<td>Other</td>
<td>Social inattentiveness</td>
<td>Difficulty in abstract thinking</td>
<td>Prolonged time to respond</td>
<td>Lack of normal distress</td>
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<td>Inattentiveness during mental status testing</td>
<td>Stereotyped thinking</td>
<td>Inarticulate speech</td>
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SANS, the Schedule for the Assessment of Negative Symptoms; PANSS, the Positive and Negative Syndrome Scale; NSA, the Negative Symptom Assessment Scale; BNSS, the Brief Negative Symptom Scale; CAINS, the Clinical Assessment Interview for Negative Symptoms
bility of negative symptoms should be confirmed prospectively for four weeks or longer [27].

- Secondary negative symptoms: Subjects with notable extrapyramidal side effects from antipsychotic medications should be excluded. Scales measuring the extrapyramidal syndromes should be included in negative symptom trials. Subjects should be excluded for symptoms of depression that do not overlap with negative symptoms. For those subjects with positive symptoms, the positive symptoms should not be so severe to hinder the assessment of negative symptoms and should be confirmed persistently stable for a period and not responsive to current treatment [26, 27].

- Cognitive function assessment: Negative symptom trials should include an assessment battery to measure cognition [27].

- Functional measures should not be required as a co-primary in negative symptom trials [27].

- Subjects currently treated with clozapine should not be excluded in negative symptom trials of co-medication [27].

- Trial duration: clinical trials evaluating treatments for negative symptoms should be of longer duration than those targeting positive symptoms. The extra time is necessary because negative symptoms do not improve at the same rate as do positive symptoms [28]. Preregistration trials should be at least 6 months in duration, not including prospective assessment of clinical stability. A briefer duration of treatment is acceptable for proof-of-concept trials. Phase 2 negative symptom trials should be 12 weeks and 26 weeks is preferred for Phase 3 trials [27].

- Adjunctive agents in clinical trials: In trials addressing the use of co-medications to treat negative symptoms, all antipsychotics, may be allowed except when the antipsychotic has a potential pharmacokinetic or pharmacodynamic interaction with the experimental medication [26].

- Monotherapy trials: an experimental medication being considered for broad spectrum antipsychotic efficacy (e.g., improving both positive and negative symptoms) should initially be demonstrated as effective in treating positive symptoms. It can then be tested in a comparator trial against another antipsychotic that does not have effects on negative symptoms, while carefully assessing potential confounders (e.g., depression, EPS, etc.) to show improvements are specific for primary negative symptoms [26].

Overview of the Effects of Different Classes of Drugs on Negative Symptoms

There have been several meta-analyses and systematic reviews about the treatment effects of various classes of drugs on the negative symptoms. Some of those studies have included the clinical trials in which negative symptoms were not the primary target and all of them have included those clinical trials which did not strictly define negative symptoms as deficit syndrome or persistent negative symptoms. Therefore, the medication effects upon negative symptoms revealed by these meta-analyses and reviews should be viewed as treatment effects upon broadly defined negative symptoms, not deficit syndrome or persistent negative symptoms. Because the consensus of methodological issue about clinical trial on negative symptoms has been achieved several years ago, there may not be enough data accumulating for meta-analysis of treatment effects upon persistent negative symptoms using data of clinical trials meeting the standard consensus. Therefore, I will
present the treatment effects of medication on broadly defined negative symptoms according to these meta-analyses and systemic reviews and highlight some recent clinical trials of which target is persistent negative symptoms and which meet the standard consensus in different class of drugs.

**Antipsychotics**

A systematic meta-analysis of 168 unique and independent placebo-controlled trials for negative symptoms, including 6,503 patients in the treatment arm and 5,815 patients in the placebo arm revealed second-generation antipsychotics had significant effect on negative symptoms, while the effect of first-generation antipsychotics is non-significant [29]. But, the effects of second-generation antipsychotics are modest and not to the level of clinical meaningfulness. A novel antipsychotics, cariprazine, a dopamine D\(_3\) and D\(_2\) receptor partial agonist with preferential binding to D\(_3\) receptors, have shown superior effects over risperidone on treating the schizophrenia with predominant negative symptoms in a double-blind randomized controlled trial containing a relative large sample (230 patients for cariprazine and 231 patients for risperidone) [30].

**Antidepressants**

Antidepressants have been used in treating negative symptoms for a long time. Two earlier meta-analyses provided equivocal evidence [31] and a lack of support [32], respectively, while the two recent reports have supported some evidence of benefits that differs between agents [29, 33]. One recent double-blind randomized controlled trial using duloxetine add-on risperidone revealed significant effect of duloxetine in improving negative symptoms of schizophrenia [34], while another similar clinical trial using citalopram add-on antipsychotics has shown no significant treatment effect [35]. A commentary on the collective work concluded that the evidence is not strong enough to support their use [36].

**Psychostimulants**

An earlier systematic review of psychostimulants for negative symptoms has revealed improvement of negative symptom scores with various agents such as methylphenidate, amphetamine, and modafinil or armodafinil. The literature points to evidence that, used adjunctively, DA agonists may improve negative symptoms without worsening of positive symptoms in selected patients who are stable and treated with effective antipsychotic medications [37]. A recent meta-analysis has reported significant differences with modafinil or armodafinil in treating negative symptoms, but the effect size was small, and the advantage disappears when chronically ill patients or those with high negative symptom burden are treated [38].

**Glutamate pathway related molecules**

Evidence continues to grow supporting a rôle for glutamate in processes critical to schizophrenia [39]. Two meta-analyses, not specific to negative symptoms, have suggested a favorable, albeit small, signal supporting the efficacy of drugs enhancing NMDA receptor function (e.g., d-serine, sarcosine, N-acetylcysteine, D-cycloserine), although the effect was different between agents [40, 41]. A relative large scale double-blind randomized placebo controlled proof-of-concept trial of bitopertin, a glycine transporter 1 inhibitor, has successfully demonstrated treatment effects on persistent negative symptoms of schizophrenia [42]. But a larger scale international phase III trial for bitopertin has been discontinued due to lack of efficacy [43]. The development of molecules with mGluR2/3- positive allosteric modulation (e.g.,
LY2140023) has also failed eventually [44]. A double-blind randomized placebo controlled trial using another novel molecule, AMG 747, also a glycine transporter 1 inhibitor, has been found to have significant treatment effects of 15 mg AMG 747, but not higher or lower doses, on the improvement of PANSS negative symptom factor score [45]. But the trial was terminated because one patient using 40 mg AMG 747 had Stevens-Johnson syndrome/toxic epidermal necrolysis.

For NMDA receptor antagonists, a meta-analysis examining amantadine and memantine has not supported significant effect in treating negative symptoms, although they seemed to have small effects on cognitive improvement [46].

Acetylcholine pathway related molecules

Most of the clinical trials about the related drugs of this pathway have focused on cognitive symptoms as the primary endpoint, instead of negative symptoms. Many newer α7 nicotinic acetylcholine receptor (α7 nAChR) agonists/partial agonists as well as positive allosteric modulators have been developed. A recent phase II trial with the α7 nAChR agonist, TC-5619 failed to demonstrate any significant effects in treating negative symptoms [47].

Serotonin receptor antagonists

The notion that serotonin antagonism may prove useful in treating negative symptoms came from the early claims that second-generation antipsychotics are superior to first-generation antipsychotics in treating negative symptoms [48]. A selective 5-HT3 antagonist, ritanserin, has been reported to have treatment efficacy for the negative symptoms in two randomized controlled trials [49, 50]. The more recent focus has turned to selective 5-HT3 antagonists (e.g., ondansetron, tropisetron, granisetron). A meta-analysis of clinical trials using 5-HT3 antagonists, including six studies (total N = 311). Those study drugs included one granisetron plus risperidone study, one ondansetron plus risperidone study, one ondansetron plus haloperidol, and three tropisetron plus risperidone studies. The results showed 5-HT3 antagonists add-on therapy is more beneficial on the psychopathology (especially negative symptoms) than controls in patients with schizophrenia [51].

Sex hormones

Pregnenolone, a neurosteroid, has been reported to have treatment effects on negative symptoms of schizophrenia in two randomized controlled trials [52, 53]. Recently, a combination of pregnenolone and L-theanine over 8 weeks can decrease both negative and anxiety symptoms of schizophrenia [54]. Raloxifene, an estrogen receptor modulator, has been reported to improve negative symptoms over 6 months in post-menopausal female patients with schizophrenia with prominent negative symptoms [55].

Anti-inflammatory agents

Minocycline, a broad-spectrum tetracycline antibiotic with neuroprotective properties mediated through anti-inflammatory, anti-apoptotic, and antioxidant effects [56], has received the greatest attention. A meta-analysis, including 4 randomized controlled trials with 330 patients, revealed that minocycline is superior to placebo for decreasing PANSS negative subscale scores, showing its value on improving the psychopathology of schizophrenia, especially the negative symptoms [57]. A 16-week, double-blind, randomized, placebo-controlled clinical trial of minocycline recruited 92 patients with early stage schizophrenia treated with risperidone has demonstrated that the addition of minocycline to second-generation antipsychotic drugs in early schizophrenia has sig-
significant efficacy on negative symptoms [58]. Pioglitazone, an antidiabetic agent with anti-inflammatory and antioxidant properties, has shown to have efficacy as an augmentation therapy in reducing the negative symptoms of schizophrenia in a clinical trial [59].

**Conclusion**

There have been a number of important advances in search of pharmacological treatments for negative symptoms over the past decade. For methodological issue, consensus-based guidelines have been established for defining and measuring negative symptoms, sample inclusion/exclusion criteria, trial design, and duration. Controlling for symptom stability and ruling out possible secondary sources of negative symptoms are the most important for determining whether new medications can treat primary negative symptoms.

There are some evidences that second-generation antipsychotics have modest benefits for overall negative symptoms over first-generation antipsychotics. Those apparent benefits are likely largely due to improvements in secondary, rather than primary, negative symptoms. A novel antipsychotic, cariprazine, has recently shown significantly more improvement than risperidone in schizophrenia with predominant negative symptoms. It is worth noting that further development and real experiences are needed in clinical practice. There is also evidence that some available medications, including antidepressants, NMDA glutamatergic modulators, serotonin receptor antagonists, and some anti-inflammation agents may offer modest benefits as adjunctive treatments for negative symptoms. Despite all the above significant findings, there are still no drugs, achieving the level of significant clinical efficacy and indicating for the treatment of primary negative symptoms. It is partly because heterogeneity of negative symptoms and our limited understanding regarding negative symptoms underlying etiology and pathophysiology. Another reason is the onset of negative symptoms, which can precede the first psychotic break, also means that treatments are delayed.

Based on those evidences in this overview, I hope that improved assessment tools, the development of performance-based measures for negative symptoms, the discovery of biomarkers to use as proxies for efficacy, and improved animal models will help further the development of new therapeutics. Studies intervening at particular stages of the illness (i.e., prodromal or early in course) may also be warranted. Investigations combining specific pharmacotherapies in combination with specific psychosocial or psychotherapeutic interventions may also be future possibilities. With advances in these areas, We hope to have effective treatments in alleviating negative symptoms, and in improving real world functioning and quality of life.

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