

Addressing the unmet needs of patients with persistent negative symptoms of schizophrenia: emerging pharmacological treatment options

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<http://dx.doi.org/10.2147/NDT.S43404>

Abstract: The negative symptoms of schizophrenia represent an impairment of normal emotional responses, thought processes and behaviors, and include blunting or flattening of affect, alogia/aprosody, avolition/apathy, anhedonia, and asociality. Negative symptoms contribute to a reduced quality of life, increased functional disability, increased burden of illness, and poorer long-term outcomes, to a greater degree than positive symptoms. Primary negative symptoms are prominent and persistent in up to 26% of patients with schizophrenia, and they are estimated to occur in up to 58% of outpatients at any given time. Negative symptoms respond less well to medications than positive symptoms, and to date treatment options for negative symptoms have been limited, with no accepted standard treatment. Modest benefits have been reported with a variety of different agents, including second-generation antipsychotics and add-on therapy with antidepressants and other pharmacological classes. Recent clinical research focusing on negative symptoms target novel biological systems, such as glutamatergic neurotransmission. Different approaches include: enhancing N-methyl-D-aspartate receptor function with agents that bind directly to the glycine ligand site or with glycine reuptake inhibitors; influencing the metabotropic glutamate receptor (mGluR2/3) with positive allosteric modulators; and stimulating nicotinic acetylcholine receptors. In conclusion, the lack of clearly efficacious pharmacological treatments for the management of negative symptoms represents a significant unmet need, especially considering the importance of these symptoms on patient outcomes. Hence, further research to identify and characterize novel pharmacological treatments for negative symptoms is greatly needed.

Keywords: negative symptoms, schizophrenia, NMDA receptor, glycine reuptake inhibitors, metabotropic glutamate receptor-2 (mGluR2), 7- α nicotinic acetylcholine receptor agonists

Introduction

Negative symptoms of schizophrenia represent a deficit or impairment of normal emotional responses, thought processes, and behaviors affecting communication and social interaction.¹ Negative symptoms range from expressive deficits such as blunting or flattening of affect and alogia/aprosody, to motivational deficits characterized by avolition/apathy, anticipatory anhedonia, and asociality.²⁻⁵ In contrast to positive symptoms, negative symptoms are relatively enduring, constant, and more predictive of psychosocial impairment.^{6,7} Persistent negative symptoms are present in more than a quarter of patients with a first episode of psychosis⁸ and are associated with lower premorbid functioning, male sex, longer duration of untreated psychosis, and poorer insight.^{6,9} Thus, negative symptoms lead to poorer outcome, particularly if present in early psychosis, and contribute to a greater degree than positive symptoms to poorer quality of

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life, greater functional disability, and increased burden of illness. Furthermore, negative symptoms respond less well to antipsychotic medications than positive symptoms.

To date, treatment options for negative symptoms have been limited, and there is no widely accepted standard treatment. Randomized, controlled trials (RCTs) have been designed to show a specific effect on the negative symptoms of schizophrenia by recruiting patients with prominent negative symptoms and systematically minimizing confounding factors (eg, positive and depressive symptoms, extrapyramidal symptoms [EPS]). In addition, several studies have been conducted in varied patient populations without specifically recruiting patients with a negative symptom profile; these studies used different scales for assessing negative symptoms, which makes it difficult to interpret the results and translate improvements in symptom scores into clinically meaningful outcomes.

This review summarizes the published clinical trial data for emerging pharmacological treatments for negative symptoms in schizophrenic patients. A nonsystematic literature search was performed in two parts. Firstly, we performed an electronic search using MEDLINE and Embase to identify articles published up to October 2013 that evaluated emerging treatments for negative symptoms in schizophrenia. The primary search terms were “treatments”, “medications”, “negative symptoms”, and “schizophrenia”. Meta-analyses and systematic reviews were included and preferentially retained where available, based on the premise that they best captured the most robust data available; otherwise, original research articles and other articles of interest were included in this review. Secondly, we performed a search for abstracts and posters describing emerging treatments for negative symptoms presented at congresses, as well as company press releases, up to January 2014.

Prevalence of negative symptoms

There is great variability in the reported prevalence rates of negative symptoms. Discrepancies are due to differences across studies – in particular, the use of different definitions for negative symptoms. For example, if the definition used is the presence of one or more negative symptoms at any given time, regardless of etiology, severity, or duration, then the reported prevalence rates of negative symptoms in first-episode patients range from 41% to 54%, and up to 58% in patients with chronic schizophrenia.^{10–12} In contrast, the estimated prevalence of negative symptoms ranges from 23% to 26% when using a definition of primary persistent negative symptoms, which specifies a minimum severity of symptoms, excludes comorbidities such as anxiety, depression, or EPS, and stipulates a duration of at least 12 months.^{9,10,12,13}

Primary versus secondary negative symptoms

Key guidelines recommend distinguishing between primary and secondary negative symptoms. According to the 2004 American Psychiatric Association (APA) guidelines for schizophrenia, “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 cause, eg, antipsychotics for primary positive symptoms, antidepressants for depression, anxiolytics for anxiety disorders, or antiparkinsonian agents or antipsychotic dose reduction for extrapyramidal side effects.”¹⁴

Although guidelines advocate the distinction between primary and secondary negative symptoms, they can be difficult to distinguish in clinical practice;^{3,15–18} indeed, primary and secondary negative symptoms may coexist. More recently, the identification of primary negative symptoms in clinical research has shifted to a symptom dimension-based approach, which is meant to simplify the heterogeneity of negative symptoms and perhaps better inform the underlying neurobiology. Several factor analyses of negative symptoms scales have shown two subdomains to be important: diminished expression and amotivation.^{4,19} The first study to confirm the longitudinal stability of the dimension-based approach also showed it to be more predictive of psychosocial outcomes than older categorical definitions (such as deficit syndrome).¹⁹ Another recent study showed the important contribution of the amotivation domain to poor functioning in patients early in the disease course.²⁰

Neurobiology of negative symptoms

The neurobiological underpinnings of negative symptoms are complex and continue to be the subject of discussion and research.²¹ While the basis of positive symptoms may be explained by dopaminergic models, the explanatory hypotheses of negative symptoms encompass a broader array of candidate neurotransmitters and associated pathways. There is no shared common understanding of the neurobiology of negative symptoms, which may eventually be revealed as too heterogeneous a concept to unite around a single biological hypothesis, as there is for positive symptoms. Although the cellular, molecular, and circuit alterations underlying these symptoms are not clear, studies focusing on motivation, reward, working memory, and goal-oriented behavior may help shed light on the circuitry that is altered in negative symptoms,^{22,23} especially as these physiological functions correspond to the clinical dimension elucidated by factor analyses of negative symptoms discussed later.

The biology of motivation has been extensively studied across species and in humans, and some key brain regions involved are the prefrontal cortex (ventromedial, orbitofrontal, and dorsolateral), the anterior cingulate, and the striatum;²² all structures are modulated by mesocortical/mesoaccumbens dopaminergic systems and cortico-striatal-thalamo-cortical loops. There is both clinical and preclinical evidence suggesting that abnormalities in information processing in these networks play an important role in the etiology of negative symptoms.^{22–26}

These neurocircuits implicate dopamine dysregulation, as opposed to an excess of dopamine, associated with psychotic symptoms; it would appear that there is too little dopamine or sensitivity to change of dopamine input in the reward circuitry. In addition, gamma-amino butyric acid (GABA) and glutamate are key in regulating neural loops between the striatum and prefrontal cortex, as well as impacting the modulation of dopaminergic release. Specifically, hypofunction of N-methyl-D-aspartate (NMDA) receptor transmission may be responsible for functional alterations in the prefrontal cortex,²⁷ striato-ventro tegmental loops,^{28–30} and thalamocortical projections that may be associated with negative symptoms.^{31–33}

Assessment of negative symptoms

Assessing negative symptoms provides several benefits, including helping to tailor treatments for individual patients, and educating health care professionals, caregivers, and patients. Following the recommendations of the National Institute of Mental Health-Measurement and Treatment Research to Improve Cognition in Schizophrenia (NIMH-MATRICES) report,³⁴ new scales have been developed that attempt to incorporate an updated understanding of negative symptoms, especially the patient's inner experience and various aspects of motivation. In particular, work groups are actively field testing and refining two new measures: the Clinical Assessment Interview for Negative Symptoms (CAINS)³⁵ and the Brief Negative Symptom Scale (BNSS).³⁶ Although more than 18 instruments for assessing negative symptoms exist, drug development clinical trials to date have primarily used the Positive and Negative Syndrome Scale (PANSS) negative symptoms factor score (NSFS),^{37,38} the Negative Symptom Assessment (NSA) scale,³⁹ and the Schedule for the Assessment of Negative Symptoms (SANS).^{34,40}

The management of negative symptoms is a relatively new therapeutic area, and thus many questions remain regarding the optimal trial design to evaluate these symptoms. A recent report from an international workshop describes

a general consensus that in such clinical trials, ratings for negative symptoms should include a single global score.⁴¹ Moreover, these ratings should include global scores for major domains such as expressiveness and apathy/asociality.⁴¹ To achieve consistent and reliable ratings of negative symptoms over time, both the clinical setting in which the patient is managed and the medication regimen should remain stable. Functional measures should be included as key secondary end points in these clinical trials given their strong association with negative symptoms.

Impact of negative symptoms on functionality

Many patients with schizophrenia experience significant functional impairments. There is a consistent and strong correlation between both the presence and severity of negative symptoms and deleterious effects on employment, financial status, living situation, and social interaction, as well as on subjective variables such as self-esteem, distress, and satisfaction with life.^{42–46} Recent analyses of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) data demonstrate that, although both positive and negative symptoms contribute independently to functional decline, negative symptoms have a greater impact overall.^{47,48} Indeed, greater declines in functionality and health-related quality of life, and more lost caregiver work-days, are associated with patients with the greatest negative symptomatology.⁴⁸ The magnitude of the problem is amplified by the high prevalence of negative symptoms (up to 58%)¹² in routine clinical practice, as described previously.

Impact of negative symptoms on global psychosocial functioning

The presence of negative symptoms has been found to be related to poorer functioning, unemployment, single relationship status, greater severity of illness, and higher antipsychotic dose.¹² While the overall severity of negative symptoms is the most powerful predictor of global psychosocial functioning,^{19,47,49} correlations between specific symptoms (for example, motivational deficits) and functional outcome have been observed.^{20,50} It also has been reported that blunted affect and social withdrawal impact on social outcome, while lack of spontaneity affects daily functioning.⁵¹ Recent research also highlights the relevance of insight in influencing the motivational factor of self-efficacy, defined as “the confidence one has in the ability to perform a behavior or specific task,” when performing social and daily living skills.⁵² Impaired functionality cannot be attributed

exclusively to negative symptoms, as there may be overlap with the cognitive deficits of schizophrenia; however, this discussion is beyond the scope of the present paper.⁴³

Impact of negative symptoms on subjective variables

Although the patient's subjective experience is difficult to evaluate in schizophrenia,⁵³ it has been shown that negative symptoms correlate with subjective experiences of lower self-esteem, poorer satisfaction with life, and distress. These subjective variables, and self-esteem in particular, in turn impact on the functionality variables of employment, social functioning, and living situation.⁵⁴ Negative symptom severity and impaired insight were significantly associated with poor work performance, and this relationship persisted over time. In contrast, positive symptom severity was not significantly associated with work performance.⁵⁵ Individuals with prominent negative symptoms demonstrated worse performance than other patients on task orientation, social skills, and personal presentation,⁵⁶ and they actually experienced a greater decline in social functioning over time when employed in community settings compared with unemployment or employment in specialty mental health settings.⁵⁷

Impact of negative symptoms on quality of life

Negative symptoms predict lower psychological wellbeing (such as, domains of autonomy, environmental mastery, personal growth, positive relations with others, purpose in life, self-acceptance)⁵⁸ and difficulty in social competency (such as, theory of mind, attribution, empathy, self-esteem, and interpersonal self-concepts).⁵⁹ The presence of negative symptoms, psychological discomfort, and resistance are powerful predictors of impaired quality of life.⁶⁰ In addition, negative symptoms correlate with caregiver burden and distress.^{61–63}

Impact of negative symptoms on remission

The achievement of full symptomatic remission is an outcome measure in schizophrenia, and patients who achieve full remission demonstrate a level of executive function comparable to healthy controls. However, patients who achieve only positive symptomatic remission or negative symptomatic remission continue to have working memory deficits.⁶⁴ Furthermore, patients with negative symptoms show global neuropsychological impairment and deficits in a number of specific domains, including social cognition, global cognition, language, and olfaction.¹

Of 6,642 patients assessed in the Schizophrenia Outpatients Health Outcomes (SOHO) study, 33% achieved long-lasting symptomatic remission, 13% achieved long-lasting functional remission, 27% achieved long-lasting adequate quality of life, and only 4% achieved recovery during the 3-year follow-up period. Greater negative symptom severity at baseline was associated with a lower likelihood of achieving recovery.⁶⁵ Moreover, remission rates for negative symptoms are low, with only 6.4% of patients achieving and maintaining 6-month remission criteria.⁶⁶ Thus, the goal must be effective treatment of both positive and negative symptoms together.

Existing pharmacological treatment of negative symptoms

There is no standard treatment for negative symptoms, which remain a challenge for clinicians, patients, and caregivers. The British Association for Psychopharmacology (BAP), in their 2011 guidelines for the treatment of schizophrenia, recommends addressing the secondary causes of negative symptoms first, followed by a trial of an antidepressant.⁶⁷ We include here a review of the collective evidence for the use of antidepressants and antipsychotics, as these therapeutic modalities are frequently used in schizophrenia. We focus only on meta-analyses (versus individual studies), given their inclusion of greater patient numbers and the resulting increased robustness of the data.

Antidepressants

The most comprehensive meta-analysis reviewed 23 studies (eight positive and 15 negative) of antidepressants added to antipsychotics and found overall evidence of efficacy for the treatment of negative symptoms.⁶⁸ Another rigorous Cochrane systematic review reached a similar conclusion, but cautioned that given only five of 139 studies met the required standards to evaluate the effect on potential confounding symptoms (for example, depressive and positive symptoms), treatment response may have been misattributed to another cause for the symptoms. This methodological concern was addressed earlier and remains problematic for many published studies in negative symptoms.⁶⁹ Nonetheless, other meta-analyses of agents with antidepressant properties – alpha-2 receptor antagonists (mianserin, mirtazapine) and *Ginkgo biloba* (thought to increase synaptic serotonin) – also showed potential as adjunctive therapy for schizophrenia.^{68,70} In addition, selegiline, a monoamine oxidase (MAO) inhibitor with greater affinity for MAO-B than MAO-A, has been shown to be

efficacious in two small trials in patients with negative symptoms.^{71,72}

Antipsychotics

There is a lack of robust evidence for the use of antipsychotic agents as an effective approach to treating persistent negative symptoms, beyond acute inpatient hospitalization. The only exception has been amisulpride: meta-analyses of up to five double-blind, placebo-controlled studies of amisulpride in patients with predominant negative symptoms of schizophrenia found a positive correlation between the severity based on the mean SANS score at baseline and mean improvement at end point.^{73,74} Although these data are promising, they should be interpreted in the context of both the limitations of the trials and the possibility that the benefits of amisulpride may result from effects on secondary negative symptoms.⁷⁵ Trials of antipsychotics agents for acute treatment are not appropriate for determining their effects on negative symptoms,⁷⁴ but a few studies have been conducted comparing effects of monotherapy with different antipsychotics on persistent negative symptoms, with no differences among agents reported.⁷⁶ Similarly, a carefully designed trial of asenapine versus olanzapine found that neither drug significantly differed from the other after 26 weeks, but long-term follow-up suggested a modest advantage for asenapine at 52 weeks.^{77,78} A systematic review of the efficacy of clozapine monotherapy identified six studies using the SANS negative symptom scale. Although this review favored clozapine, the findings were confounded by the difficulty of interpreting the results in the context of prominent positive symptoms because the population was largely treatment refractory and had ongoing psychotic symptoms.⁷⁹

Emerging pharmacological treatment of negative symptoms

Based on the previous discussion, there is clearly a need for more efficacious agents for the treatment of negative symptoms. Table 1 summarizes published data for several investigational pharmacological agents for the treatment of negative symptoms that have shown efficacy in preliminary studies.^{17,80–115}

NMDA receptor function enhancers

Several studies have provided preliminary evidence that increasing NMDA receptor activation through glycine-site agonists (such as, glycine, D-serine, D-cycloserine, D-alanine) improves negative symptoms in schizophrenia.^{88–92} Sarcosine is a naturally occurring, nonselective glycine

reuptake inhibitor (GRI) used as a clinical research tool in some countries, and it has been found to improve negative symptoms in several studies.^{83–87} Although these results were not replicated in the largest study to date comparing glycine and D-cycloserine to placebo,¹⁷ two meta-analyses have reported a benefit with D-serine and sarcosine for the treatment of negative symptoms,^{81,82} and one meta-analysis has reported a benefit with glycine.⁸¹ Another therapeutic approach hypothesized to enhance NMDA receptor function involves increasing synaptic D-serine levels by diminishing its catabolism through administration of a D-amino acid oxidase (DAAO) inhibitor, such as sodium benzoate.¹¹⁶ Sodium benzoate was recently shown in a proof-of-concept study to improve negative symptoms when used in patients receiving a stable antipsychotic regimen.⁹³

A recent therapeutic approach in clinical development for negative symptoms involves targeting the glycine binding site of the NMDA receptor.¹¹⁷ Bitopertin, a GRI, is currently in Phase III trials. Its mechanism of action is premised on boosting the synaptic availability of glycine, a coagonist of the receptor with glutamate.^{118,119} In a Phase II study in patients with predominantly negative symptoms, the addition of bitopertin 10 mg or 30 mg once daily to a stable regimen of antipsychotic therapy significantly improved the PANSS-NSFS after 8 weeks of treatment (per protocol population) with a trend toward significance in the ITT (intent-to-treat) population.⁸⁰ The SearchLyte Phase III program studying adjunctive bitopertin for the treatment of symptoms of schizophrenia is composed of six trials; three in patients with predominant negative symptoms (NCT01192906,¹²⁰ NCT01192880,¹²¹ NCT01192867¹²²) and three in patients with suboptimally controlled symptoms (NCT01235559,¹²³ NCT01235585,¹²⁴ NCT01235520¹²⁵). The first two studies in negative symptoms did not meet their primary endpoints (reduction on the NSFS versus placebo at 6 months).^{126–128} Bitopertin was well tolerated, and the overall safety profile in these studies was similar to that seen in the previously reported Phase II trial. Results from other studies in the SearchLyte program are awaited.

Metabotropic glutamatergic receptor activation

Glutamatergic transmission can also be targeted by modifying activity of metabotropic glutamatergic receptors, specifically, subtype 2 (mGluR2). Agonism of this presynaptic autoreceptor decreases the amount of glutamate released in the synapse in an attempt to normalize putative excessive downstream glutamatergic tone resulting from hypofunctioning NMDA

Table 1 Emerging pharmacological agents for the treatment of negative symptoms in patients with schizophrenia

Class/agent	Mechanism of action	Meta-analysis?	Number of studies and major findings	Number of patients evaluated
NMDA receptor function enhancers				
Glycine-site agonists				
Glycine, D-cycloserine, D-serine, D-alanine	Increase in NMDA receptor activation through glycine-site binding	No	Five studies: improvement in negative symptoms ⁸⁸⁻⁹²	N=74
		Yes	CONSIST: no clinical benefit conferred by glycine or D-cycloserine ¹⁷ Two meta-analyses: benefit with D-serine and sarcosine for the treatment of negative symptoms ^{81,82} One meta-analysis: benefit with glycine ⁸¹	N=157 N=181 ⁸¹ ; N=145 ⁸² N=133
D-amino acid oxidase (DAAO) inhibitors Sodium benzoate	Increase D-serine by diminishing its catabolism and increase NMDA receptor activation at the glycine-binding site	No	Proof-of-concept study: improvement in negative symptoms ⁹³	N=53
Glycine reuptake inhibitors (GRIs)				
Sarcosine	Naturally occurring, nonselective GRI used as a clinical research tool	Yes	Two meta-analyses: benefit with D-serine and sarcosine for the treatment of negative symptoms ^{81,82}	N=181 ⁸¹ ; N=145 ⁸²
		No	Four studies: improvement of negative symptoms with sarcosine ⁸³⁻⁸⁷	N=203 total across four studies
Bitopertin	Corrects or compensates for potential NMDA receptor hypofunction by boosting synaptic availability of glycine (NMDA receptor coagonist with glutamate)	No	Phase II study: bitopertin (10 mg or 30 mg once daily) added to stable antipsychotic regimen significantly improved the PANSS negative symptoms factor score in patients completing the trial according to protocol ⁸⁰	N=323
Metabotropic glutamatergic receptor 2 (mGluR2)				
Pomaglumedad methionil (LY2140023)	Agonism of mGluR2/3; decreases amount of glutamate released in the synapse	No	Adjunctive therapy trial: negative results; development program terminated ⁹⁴	N=167
JNJ-40411813/ADX-71149	Positive allosteric modulator (PAM) of mGluR2	No	Phase IIa adjunctive therapy trial: trend toward separation from placebo after 1 month at moderate doses ⁹⁵	N=92
Nicotinic acetylcholine receptors				
EVP-6124	Alpha-7 nicotinic receptor agonism	No	Phase IIb study: demonstrated improvement of negative symptoms (secondary end point) ⁹⁶	N=319
TC-5619	Alpha-7 nicotinic receptor agonism	No	Phase IIb study: negative results; development program terminated ¹³³	N=477
		Yes	Proof-of-concept study: promising results on cognitive end points and negative symptoms ⁹⁷	N=185
Galantamine	Dual alpha-7 nicotinic receptor PAM and cholinesterase inhibitor	No	Small study: galantamine failed to show any benefit on negative symptoms or cognition but demonstrated significant treatment effects for global functioning and free verbal recall ⁹⁸	N=43
Donepezil	Cholinesterase inhibitor	Yes	Meta-analysis of five adjunctive therapy studies (two studies with galantamine; three studies with donepezil): greater effect on negative symptoms than cognition ⁹⁹	N=103
Psychostimulants				
Lisdexamfetamine dimesylate	Prodrug of dextroamphetamine with CNS stimulant activity; blocks the reuptake of norepinephrine and dopamine into the presynaptic neuron and increases their release into the extraneuronal space ¹⁰⁰	No	Open-label trial: potential benefit for negative symptoms without aggravating positive symptoms ^{101,102}	N=69

(Continued)

Table 1 (Continued)

Class/agent	Mechanism of action	Meta-analysis?	Number of studies and major findings	Number of patients evaluated
Modafinil, armodafinil	CNS stimulants with wake-promoting actions similar to amphetamine; both also bind in vitro to the dopamine transporter and inhibit dopamine reuptake	No	Available study data do not conclusively support use of modafinil/armodafinil as add-on treatment ^{102,103}	N=970
Other drugs				
N-acetyl cysteine (NAC)	Putative anti-inflammatory agent in schizophrenia	No	Placebo-controlled trial: NAC added to routine care for 6 months improved negative symptoms and akathisia ¹⁰⁴	N=140
Minocycline	Putative anti-inflammatory agent in schizophrenia	No	Two placebo-controlled studies: benefit in early-phase schizophrenia, especially on negative symptoms, but no benefit on overall psychopathology ^{105,106}	N=54 ¹⁰⁶ ; N=144 ¹⁰⁵
Ondansetron, granisetron, tropisetron	Serotonin 5-HT ₃ receptor antagonism; may be active in schizophrenia through their affinity for nicotinic and GABA receptors	Yes	Systematic review and meta-analysis: greater benefit for improvement of negative symptoms than positive symptoms when used as add-on therapy ¹⁰⁷	N=311
Lamotrigine	Anticonvulsant; inhibition of voltage-sensitive sodium channels, thereby stabilizing neuronal membranes and modulating presynaptic transmitter release of excitatory amino acids (eg, glutamate, aspartate)	Yes	Meta-analysis of five trials: superiority in overall symptom improvement and improvement in positive and negative symptoms ¹⁰⁸	N=161
Memantine	NMDA receptor antagonism	Yes	Meta-analysis: adjunctive therapy may improve overall symptoms and negative symptoms ¹⁰⁹	N=186
		No	Randomized, placebo-controlled trial: no benefit conferred ¹¹⁰	N=138
Pregnenolone	Neurosteroid	No	Proof-of-concept trial: significantly greater improvement in negative symptoms as adjunctive therapy (500 mg/day) ¹¹¹	N=21
			Two small studies: benefit in schizophrenia ¹¹²	
Sildenafil	Phosphodiesterase 5 (PDE5) inhibition	No	Small study: no benefits on any symptom domains ¹¹³	N=17
			Trial in patients with prominent negative symptoms: significant separation from placebo ¹¹⁴	N=40
Folic acid/vitamin B ₁₂	Increase blood folate levels, particularly in patients homozygous for the 484T allele of <i>FOLH1</i> (rs202676)	No	Randomized, placebo-controlled study: effective in a subgroup of patients homozygous for the 484T allele; response influenced by genetic variation in folate absorption ¹¹⁵	N=140

Abbreviations: CNS, central nervous system; CONSIST, cognitive and negative symptoms in schizophrenia trial; NMDA, N-methyl-D-aspartate; PANSS, Positive and Negative Syndrome Scale; GABA, gamma-amino butyric acid.

receptors. Pomaglutetad methionil (LY2140023) is an mGluR2/3 full agonist that initially appeared promising but ultimately provided disappointing results as a monotherapy in acute psychosis and as an adjunctive agent for patients with prominent negative symptoms; as a result, the development program has been terminated.⁹⁴ A similar mechanism of action is being investigated with JNJ-40411813/ADX-71149, a mGluR2 positive allosteric modulator (PAM) (NCT01323205).¹²⁹ The

preliminary Phase IIa results suggest potential in the treatment of negative symptoms, as a trend toward separation from placebo was observed after 1 month at moderate doses of the investigational drug used as an adjunct to antipsychotics.⁹⁵

Nicotinic acetylcholine receptor agonists

Agents active at alpha-7 nicotinic receptors are currently being developed as add-on therapies. It has been postulated

that targeting cognitive functions with nicotinic receptor agonists may impact negative symptoms, as working memory is a component of reward-driven, goal-directed behavior. EVP-6124 is in Phase III development for cognitive impairment associated with schizophrenia (CIAS) (NCT01714661,¹³⁰ NCT01714713¹³¹). In an earlier Phase IIb study, EVP-6124 met the primary end point on a cognition battery and demonstrated improvement of negative symptoms (a secondary end point).⁹⁶

In an exploratory proof-of-concept trial, TC-5619 showed promising results based on cognitive end points and negative symptoms.⁹⁷ TC-5619 was recently evaluated in a Phase IIb trial (NCT01488929¹³²), with a primary end point of improvement in negative symptoms (change from baseline after 24 weeks versus placebo). In this trial, TC-5619 did not meet the primary endpoint and did not demonstrate improvement on secondary measures of cognitive function.¹³³ Consequently, the development program for TC-5619 as a treatment for schizophrenia has been terminated.¹³³

A small study with galantamine, a dual PAM at the alpha-7 nicotinic receptor and a cholinesterase inhibitor, failed to show any benefit of this approach on negative symptoms or cognition but demonstrated significant treatment effects for global functioning and free verbal recall.⁹⁸

A meta-analysis of adjunctive pharmacotherapies in schizophrenia found that five studies of acetylcholinesterase inhibitors (two earlier studies with galantamine and three with donepezil) demonstrated a greater effect on negative symptoms than cognition.⁹⁹

Psychostimulants

The use of psychostimulants (such as methylphenidate, amphetamine, modafinil, armodafinil) in single acute experimental use and clinical trials has been reviewed recently.¹⁰² Study data do not conclusively support the use of modafinil/armodafinil as add-on treatment in schizophrenia for negative symptoms or for other attention or sleep-related symptoms.^{102,103} In addition, a recent open-label clinical trial with lisdexamfetamine dimesylate showed potential benefit for negative symptoms without aggravating positive symptoms. Larger placebo-controlled trials of psychostimulants are warranted to fully characterize their efficacy and safety in patients with schizophrenia.^{101,102}

Other drugs

A systematic review of anti-inflammatory drugs for schizophrenia, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, and also of agents that possess

additional anti-inflammatory properties, such as N-acetyl cysteine (NAC), estrogens, melatonin, davunetide, and fatty acids, concluded that only aspirin and NAC showed significant effects.¹³⁴ This analysis, however, assessed only general psychopathology and cognition. A placebo-controlled trial of NAC 1 g twice daily added to routine care for 6 months found improvements in negative symptoms and akathisia.¹⁰⁴ A qualitative review of the results supported the effects of NAC on negative symptom domains such as avolition.^{135,136} Although minocycline did not improve overall psychopathology, two placebo-controlled studies showed a benefit in early-phase schizophrenia, especially on negative symptoms.^{105,106}

A systematic review and meta-analysis of selective serotonin-3 (5-HT₃) receptor antagonists, including ondansetron, granisetron, and tropisetron, found that when used as add-on therapy, they conferred greater benefit for negative symptoms than positive symptoms.¹⁰⁷ It has been hypothesized that these compounds may be active in schizophrenia based on their affinity for other receptors beyond 5-HT₃, such as nicotinic and GABA receptors, but it is questionable if such activity is relevant at the concentrations achieved in clinical practice.

The efficacy of lamotrigine in clozapine-resistant schizophrenia has been evaluated in a meta-analysis of five trials, with demonstration of superiority over placebo in overall symptom improvement and improvement in positive and negative symptoms.¹⁰⁸

The data for memantine, an NMDA receptor antagonist, are mixed. A recent meta-analysis cautiously concluded that adjunctive therapy with memantine may improve overall symptoms and negative symptoms in patients with schizophrenia. However, the authors of the analysis noted that the findings from two trials in particular, in which memantine was added to clozapine or risperidone, may have influenced the results.¹⁰⁹ Another study with a targeted patient population experiencing residual, persistent negative symptoms showed no benefit conferred by memantine.¹¹⁰

A proof-of-concept trial evaluating adjunctive therapy with pregnenolone (a neurosteroid) 500 mg/day demonstrated significantly greater improvement in negative symptoms.¹¹¹ Two subsequent, small studies also supported the benefit of pregnenolone in schizophrenia.¹¹²

Trials of sildenafil, a phosphodiesterase 5 (PDE5) inhibitor, have yielded conflicting results. The first placebo-controlled augmentation study failed to show any benefits of sildenafil on any symptom domains of schizophrenia.¹¹³ However, a subsequent trial in patients with prominent negative symptoms demonstrated a significant separation from placebo for sildenafil.¹¹⁴

Another investigational approach, inspired by the correlation of low serum folate levels with the manifestation of negative symptoms, evaluated the efficacy of adjunctive daily oral folic acid plus vitamin B12 or placebo. The overall results were negative; however, for a subgroup of patients, the treatment was effective, and response was influenced by genetic variation in folate absorption.¹¹⁵

Future research

The unmet need in the treatment of negative symptoms of schizophrenia is unequivocal. The neurobiological mechanisms underpinning negative symptoms are complex and remain to be clearly elucidated. Despite the considerable investment of time and money, progress in developing agents with robust efficacy for negative symptoms has been limited. The most recent findings from studies with TC-5619 and bitopertin clearly highlight this difficulty. Furthermore, even if effective agents are identified, their place in therapy (such as single primary agent or adjunctive agent) and timing/scheduling in individual patients add multiple layers of complexity.¹¹⁷

Conclusion

Negative symptoms represent a core symptom domain in schizophrenia. Despite progress in pharmacological treatments for the positive symptoms of schizophrenia, no standard treatment exists for negative symptoms. This review attempts to summarize the evolving landscape of emerging treatments in development and new findings from available drugs that could benefit patients with prominent negative symptoms. Barriers to studying negative symptoms and interpreting results are discussed, including the difficulties in designing clinical trials. A review of nonpharmacological interventions was out of scope in this paper, but such interventions do merit a separate assessment, as these modalities are likely to further improve outcomes of any pharmacological treatment. Additionally, assessing and treating all aspects of schizophrenia early with an empirical and individualized approach, taking into account psychosocial and environmental factors, is clearly important given the limitations of the current pharmacotherapeutic armamentarium. Novel compounds in advanced clinical development focus on modulation of glutamatergic and cholinergic systems via the targeting of NMDA, mGluR2, and nicotinic receptors, respectively. Other therapeutic options with varying degrees of supportive evidence are also outlined. There is a need for better pharmacological agents for managing the negative symptoms of schizophrenia, which have been shown to contribute significantly to poor functioning and detrimentally impact clinical outcomes.

Acknowledgments

Editorial assistance was provided by ApotheCom and was financially supported by F Hoffmann-La Roche Ltd.

Disclosure

Pierre Chue has received research grants and honoraria from Janssen, Pfizer, Eli Lilly, Astra Zeneca, GlaxoSmithKline, Lundbeck, Bristol-Myers Squibb, F Hoffmann-La Roche Ltd, Sunovion, Mylan, Otsuka, and Novartis. Justine Lalonde is an employee of F Hoffmann-La Roche Ltd.

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