

Treating negative symptoms of schizophrenia

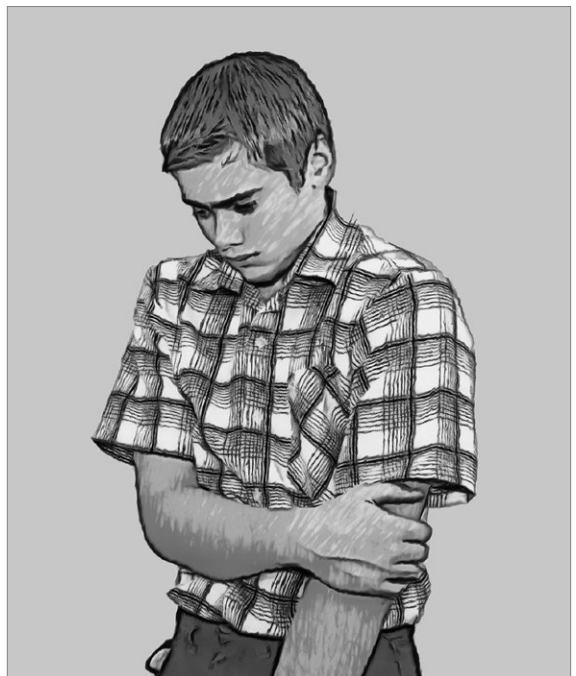
Few pharmacologic options, but evidence supports combining psychosocial interventions

In schizophrenia, negative symptoms such as social withdrawal, avoidance, lack of spontaneity and flow of conversation, reduced initiative, anhedonia, and blunted affect are among the most challenging to treat. These symptoms commonly persist after positive symptoms such as hallucinations, delusions, and paranoia have subsided. In an analysis of 20 pivotal placebo-controlled trials of second-generation antipsychotics (SGAs), almost 45% of patients who completed 6 weeks of treatment still had at least 1 residual negative symptom of at least moderate severity, and approximately 25% had 2 or more.¹ Negative symptoms are viewed as being intrinsic to schizophrenia, and also as the result of extrapyramidal symptoms, depression, and psychosis.

Nearly a decade ago, the Schizophrenia Patient Outcomes Research Team (PORT) published its recommendations for psychopharmacologic and psychosocial treatments of schizophrenia. Unfortunately, due to insufficient evidence, there is still no proven treatment for negative symptoms.²⁻⁴ This is particularly problematic because negative symptoms are a major determinant of the poor social and vocational abilities of patients with schizophrenia.

This review focuses on treatments for negative symptoms of schizophrenia that have been evaluated since the PORT treatment recommendations were published and highlights those approaches that show promise.

continued



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Negative symptoms of schizophrenia

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D2-blocking antipsychotics may produce negative symptoms that can be hard to distinguish from primary negative symptoms



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Box

Treatments for negative symptoms: 5 Drugs that didn't pan out

Since the Schizophrenia Patient Outcomes Research Team (PORT) treatment recommendations were published in 2010, many compounds have been investigated for treating negative symptoms of schizophrenia. Based on the findings of early research, further development of 5 of these has been abandoned.

Encenicline and TC-5619⁹ were both α -7 nicotinic acetylcholine receptor agonists¹⁰; bitopertin and AMG 747¹¹ were glycine reuptake inhibitors¹²; and pomaglumetad methionil¹³ was an amino acid analog drug that acts as a highly selective agonist for the metabotropic glutamate receptor.

Encenicline showed a treatment effect on negative symptoms in an add-on phase

II study,¹⁴ but not in 2 subsequent phase III trials (NCT01716975, NCT01714661). TC-5619 showed a treatment effect in a 12-week phase II study of participants with persistent negative symptoms,¹⁵ but then failed in a subsequent study.⁹ Bitopertin showed a treatment effect on negative symptoms in 1 clinical trial,¹⁶ but the results were not replicated in a subsequent large multi-center trial.¹⁷ The AMG 747 development program was halted due to safety concerns.¹¹ Finally, pomaglumetad methionil failed to meet its primary endpoint in a study of prominent negative symptoms and to show a treatment effect on psychotic symptoms in 2 pivotal phase III trials.¹³

The limitations of antipsychotics

Antipsychotics can both worsen and alleviate negative symptoms by reducing psychotic symptoms. Double-blind, placebo-controlled trials have found that most, if not all, antipsychotics are superior to placebo for treating negative symptoms in patients with acute psychosis.⁴ However, because these improvements occur in the early stages of treatment, concomitantly with improvement of psychotic symptoms, antipsychotics generally are not viewed as being very effective in the treatment of primary negative symptoms.⁴ Indeed, an examination of patients with prominent negative symptoms *without* prominent positive symptoms in the NEWMEDS cohort, which was extracted from 20 pivotal placebo-controlled trials of SGAs, revealed no clinically meaningful treatment effect on negative symptoms.¹

There is evidence that antipsychotics can contribute to the development of apathy, flat affect, and other negative symptoms.⁵ Dopamine (D2)-blocking antipsychotics produce secondary negative symptoms that are not always easy to distinguish from primary negative symptoms.⁶ In a double-blind, placebo-controlled trial of single doses of risperidone, haloperidol, or placebo in healthy participants, the antipsychotics increased negative symptoms, particularly avolition/apathy.⁷ Another study found that chronic treatment with

antipsychotics did not necessarily affect motivation in patients with schizophrenia.⁸

Adverse effects, such as anhedonia, often produce and enhance negative symptoms and therefore can limit the use of pharmacologic treatment options. Other adverse effects associated with specific antipsychotics include extrapyramidal symptoms, sedation, increased prolactin secretion, weight gain, and other metabolic abnormalities.

Seeking new pharmacologic options

The years since the PORT review have been filled with initial promise, a series of bitter disappointments, and a renewed spark of hope in the quest to treat negative symptoms in schizophrenia.

Compounds that have been abandoned.

Since PORT, researchers have evaluated 5 major compounds that mainly targeted cognition and negative symptoms in patients with schizophrenia (*Box*⁹⁻¹⁷). Unfortunately, 4 of them failed to provide significant superiority over placebo, and 1 was withdrawn due to safety concerns.

Initial favorable results. Registered, robust trials of other compounds have had some initial favorable results that need to be replicated. These agents include:

- **MIN-101** is a novel cyclic amide derivative.¹⁸ In a phase IIb 12-week study of MIN-101 monotherapy (32 mg, n = 78; 64 mg, n = 83) vs placebo (n = 83), both dose groups had significantly more improvement on the Positive and Negative Syndrome Scale (PANSS) negative factor score, which was the primary outcome measure, than placebo (32 mg/d; effect size = .45, $P < .02$, 64 mg/d; effect size = .57, $P < .004$) as well as on PANSS negative symptom score and other measures of negative symptoms.¹⁸

- **Cariprazine** is a D2 and D3 receptor partial agonist with high selectivity towards the D3 receptor.¹⁹

- **Minocycline** is a broad-spectrum tetracyclic antibiotic displaying neuroprotective properties.^{18,20,21}

- **Raloxifene** is a selective estrogen receptor modulator for postmenopausal women.^{22,23}

- **Pimavanserin**, which was FDA-approved in 2016 for the treatment of Parkinson's disease psychosis, is being tested in a large trial for adjunctive treatment of patients with negative symptoms of schizophrenia. This medication is a nondopaminergic antipsychotic that acts as a selective serotonin inverse agonist that preferentially targets 5-HT_{2A} receptors while avoiding activity at common targets such as dopamine.²⁴

All of these compounds except MIN-101 are currently available in the U.S. but have not been approved for the treatment of negative symptoms in patients with schizophrenia. MIN-101 is in phase III testing (NCT03397134).

Nonpharmacologic treatments

Recent studies of nonpharmacologic treatments for negative symptoms, including psychosocial approaches and noninvasive electromagnetic neurostimulation, have also been performed. The major psychosocial approaches that have been studied include social skills training (SST), cognitive-behavioral therapy (CBT) for psychosis, cognitive remediation, and family intervention. Some positive findings have been reported. A recent review of psychosocial treatments for negative symptoms in schizophrenia concluded that CBT

and SST have the most empirical support, with some evidence even suggesting that gains from CBT are maintained as long as 6 months after treatment.²⁵ Another review found that CBT was significantly more efficacious for reducing positive symptoms and SST in reducing negative symptoms.²⁶

It remains unclear if a combined treatment approach provides improvements above and beyond those associated with each individual treatment modality. Motivation and Enhancement therapy (MOVE) is a potentially promising approach that combines environmental support, CBT, skills training, and other components in an attempt to address all domains of negative symptoms.²⁷ Preliminary results from a randomized controlled trial examining 51 patients with clinically meaningful negative symptoms suggested that MOVE improves negative symptoms. However, the group differences were not significant until after 9 months of treatment and not for all negative symptom scales. A follow-up study has been completed, but the results are not yet available.²⁸

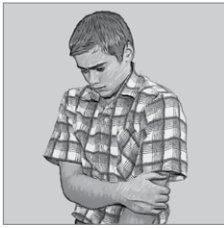
Some small studies have suggested improvement of negative symptoms after noninvasive electromagnetic neurostimulation,²⁹⁻³¹ but this has not been replicated in larger studies.³² In the last few years, there were several studies underway that could help clarify if there is a role for noninvasive electromagnetic neurostimulation in the treatment of negative symptoms in schizophrenia; however, results have not been reported at this time.³³⁻³⁵

Social skills training and combined interventions

Taken together, the data suggest that treating negative symptoms in schizophrenia remains a major challenge. Patients with negative symptoms are difficult to engage and motivate for treatment and there are no well-supported treatment options. Given the lack of evidence, it is not possible to synthesize this data into clear treatment recommendations. Because many of the negative symptoms are social in nature, it is perhaps not surprising that some evidence has emerged supporting the role of psychosocial approaches. Studies have pointed

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Many negative symptoms are social in nature, and some evidence supports the role of psychosocial approaches



Negative symptoms of schizophrenia

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Treatment packages that combine several psychosocial interventions may achieve better outcomes

Related Resource

- Tandon R, Jibson M. Negative symptoms of schizophrenia: How to treat them most effectively. *Current Psychiatry*. 2002;1(9):36-42.

Drug Brand Names

Cariprazine • Vraylar	Pimavanserin • Nuplazid
Haloperidol • Haldol	Raloxifene • Evista
Minocycline • Dynacin, Minocin	Risperidone • Risperdal

to the potential role of SST. It is believed to be beneficial as it targets participants' social functioning by training verbal and nonverbal communication alongside perception and responses to social cues.³⁶ Some evidence suggests that treatment packages that combine several psychosocial interventions (eg, family psychoeducation and skill training) achieve better outcomes than standalone interventions.³⁷ Thus, psychosocial approaches appear to be potentially effective for the treatment of negative symptoms in patients with schizophrenia. In addition, because some antipsychotics has been shown to be associated with fewer negative symptoms than others, another treatment strategy could be to attempt the use of a different antipsychotic, or to revisit whether continued antipsychotic treatment is needed in the absence of positive symptoms.

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Bottom Line

Treating negative symptoms in schizophrenia remains a major challenge. There is a lack of evidence for pharmacologic treatments; psychosocial approaches may be beneficial due to the social nature of many negative symptoms. Further, some evidence suggests that treatment packages that combine several psychosocial interventions may achieve better outcomes than standalone interventions.

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