

Analysis

Treating negative symptoms of schizophrenia: current approaches and future perspectives

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Summary

Negative symptoms are core symptoms of schizophrenia which are common throughout the course of the illness. We outline their functional impact, before reviewing the latest research and guidelines on their assessment and treatment. Finally, we discuss conceptual issues related to measurement of negative symptoms and approaches to address these.

Keywords

Antipsychotics; psychosis; anhedonia; trial; outcome.

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Negative symptoms have been regarded as core symptoms of schizophrenia since the conception of the disorder.¹ They represent a reduction or deficit in normal functioning, and continue to form part of the diagnostic criteria for schizophrenia in both ICD-11 and DSM-5.² Current consensus recognises five negative symptoms: reduced motivation for goal directed activities (avolition or amotivation), reduced social engagement (asociality), reduced ability to experience pleasure (anhedonia), reduced verbal output and expressiveness (alogia) and reduced non-verbal expressivity and responsiveness (blunted affect).^{1,3}

These are commonly grouped into two domains, one representing reduced motivation and pleasure (comprising asociality, avolition and anhedonia) and another representing reduced expressivity (comprising blunted affect and alogia).⁴ However, this approach is based on exploratory factor analysis studies, which are hypothesis generating and not designed to specify an underlying factor structure; confirmatory factor analysis studies show that a five-factor model consisting of the five consensus symptoms of avolition, asociality, anhedonia, alogia and blunted affect represents the best fit.⁴

Prevalence and relevance

A large proportion of people with schizophrenia, around 50%, experience negative symptoms in the prodromal phase, prior to the onset of the first episode of psychosis (FEP).⁵ Negative symptoms often persist into the first episode and continue to be common throughout the course of schizophrenia.⁵ For example, a review of 47 observational studies found that approximately one-third of people in their FEP and over 70% of people who experienced multiple episodes of psychosis had at least one negative symptom at the time of assessment.⁵ This is further supported by an analysis of data from 20 clinical trials including over 7400 patients in total, which found that nearly two-thirds of patients with schizophrenia entering clinical trials (often with acute exacerbations of schizophrenia) had prominent negative symptoms (a score of at least moderate on three or more Positive and Negative Syndrome Scale (PANSS) negative subscale items, or at least moderately severe on two or more items).⁶

Although these data make clear that negative symptoms are common, they beg the question: what impact do they have? A major area of research over the past two decades has been to address this, particularly by investigating whether negative symptoms are associated with clinically important disability and poor functional outcomes. A meta-analysis of longitudinal studies of patients who received follow-up after their FEP investigated this

by combining data from 17 studies, including over 2200 patients. This showed that baseline negative symptom severity is associated with poorer overall functioning at long-term follow-up, with a small to moderate effect size ($r = -0.26$).⁷ The relationship between negative symptoms and specific domains of functioning has also been investigated.^{8–10} Greater negative symptoms were associated with poorer outcomes in domains of cognitive functioning ($k = 25$ studies, $n = 4929$, $r = -0.24$), community functioning ($k = 9$, $n = 2341$, $r = -0.42$), social network size ($k = 8$, $n = 577$, standardised mean difference s.m.d. = -0.75) and quality of life ($k = 44$, $n = 4114$, $r = -0.25$). The effect sizes for the social functioning domains are moderate to large. Negative symptoms are also associated with a substantial familial burden.¹¹ Moreover, negative symptoms are associated with a higher risk of obesity and metabolic syndrome, poorer cardiorespiratory fitness, higher overall healthcare costs and increased risk of and duration of psychiatric hospital admission.^{12–16} Finally, a meta-analysis of risk factors among individuals at clinical high risk of developing psychosis (CHR-P) found that negative symptoms were among the strongest predictors of schizophrenia onset ($k = 49$, $n = 1374$, s.m.d. = 0.39).¹⁷

Although negative symptoms pre-date the onset of positive symptoms in the early stages of the disorder, individuals with predominant negative symptoms are less likely to be detected by CHR-P or early intervention services and offered prompt interventions.¹⁸ Undetected negative symptoms are strongly associated with a prolonged duration of untreated psychosis, another strong predictor of poor outcomes in schizophrenia.¹⁹ These associations of negative symptoms with poorer outcomes are all drawn from observational studies, limiting inferences on causation, as confounding factors such as antipsychotic treatment may be responsible for the relationship between negative symptoms and the outcome variables. Additionally, the relationship between more severe negative symptoms and poorer outcomes in multiple different domains raises the question of whether this reflects more severe illness overall. However, accumulating evidence suggests that negative symptoms are more strongly associated with functional outcomes than positive symptoms in schizophrenia.^{20,21}

Primary and secondary negative symptoms and differentiation from depression

A key issue for clinical trials and practice is to distinguish primary negative symptoms from secondary negative symptoms. There are multiple factors that may lead to secondary negative symptoms. One important factor is positive psychotic symptoms. For example, patients with persecutory delusions may display asociality

to protect themselves from perceived threats, in which case the resultant negative symptoms are secondary and would improve if the delusions resolve. Another common contributor is the adverse effects of antipsychotics and other medications. Antipsychotics may cause sedation and bradykinesia, which would affect ratings of both motivation and expression.²² Dopamine receptor blockade is also thought to impair motivation and reward-related behaviour independently of these effects.²² The social sequelae of having a mental disorder may also contribute to secondary negative symptoms. For example, stigma may lead to patients losing friends and/or employment, resulting in less opportunity for socialising and other activities. Similarly, hospital admission may disrupt social networks and lead to loss of social skills.²² Comorbid conditions, such as substance misuse or major depressive episodes, can lead to negative symptoms such as anhedonia and lack of motivation.²² In clinical practice, differentiating between depression and negative symptoms can be particularly difficult in schizophrenia, because of their shared high prevalence in the disorder and overlapping symptoms.²³ In a narrative systematic review, low mood, suicidal ideation and pessimism were found to be specific to depression, whereas anhedonia and blunted affect were specific to negative symptoms.²³ Highlighting the challenge in distinguishing them, anhedonia, asociality and avolition were common to both. However, results of factor analysis studies and a meta-analysis of 56 observational studies demonstrating a small effect size in the relationship between them ($r = 0.19$) suggests that they represent different underlying constructs.^{1,24} In practice, the Calgary Depression Scale for Schizophrenia can be administered in approximately 15 min, and reliably differentiates depressive symptoms from symptoms of schizophrenia.²⁵

In contrast, primary negative symptoms are part of the presentation of schizophrenia not better accounted for by other factors, and they are putatively related to the underlying pathophysiology of the disorder.¹ Meta-analysis of observational studies published between 2010 and 2015 indicates that approximately one-third of patients with schizophrenia meet criteria for deficit schizophrenia, characterised by primary and persistent negative symptoms.²⁶ However, prior estimates from studies conducted in Europe/the USA and taxometric studies suggest that the prevalence is lower, around 15–20%.²⁷ It can be difficult to distinguish primary from secondary negative symptoms because patients commonly present with a number of factors that may cause secondary negative symptoms, and it can be a matter of judgement whether these factors have led to the symptoms. Nevertheless, the distinction is important, as they may respond to different treatments. Differentiating between them requires a careful clinical assessment for possible sources of secondary negative symptoms, which can be supported by current clinical guidelines.^{22,28} A practical example of a clinical trial which distinguished primary from secondary negative symptoms²⁹ is illustrated below.

Treatment of negative symptoms

There are no treatments specifically licensed for people with schizophrenia or individuals at CHR-P presenting with negative symptoms in Europe or the USA.^{1,30} However, there have now been over 60 randomised control trials (RCTs), including over 18 000 patients, comparing antipsychotics with placebo for acute exacerbations of schizophrenia which report effects on negative symptoms.³¹ Meta-analysis of these shows that antipsychotic treatment led to a statistically significantly greater improvement of negative symptoms compared with placebo. However, the effect size was relatively modest (s.m.d. = -0.35). Additionally, as discussed above, negative symptoms that are secondary to psychosis may improve as the

psychotic symptoms improve. Of course, this does not negate the improvement in negative symptoms, but it does mean that it is not clear from these studies whether antipsychotic treatment is specifically improving negative symptoms or whether the change is secondary to other improvements. The latter is termed pseudospecificity.

Although not specifically licensed for the treatment of negative symptoms, the summaries of product characteristics for amisulpride and cariprazine refer to potential benefit for patients with predominant negative symptoms. The product summary for amisulpride states: for the 'treatment of schizophrenia [...] including patients characterised by predominant negative symptoms'. Supporting this, amisulpride has one of the largest effect sizes among antipsychotics against negative symptoms in placebo-controlled trials involving patients with acute exacerbations (s.m.d. = -0.50), and three studies have been published demonstrating efficacy over placebo in patients with predominant negative symptoms.^{32,33} The majority of participants in these three trials were treated with low doses of amisulpride (50–100 mg daily). The summary of product characteristics for cariprazine has a section on 'efficacy in predominantly negative symptoms of schizophrenia'. This summarises the results of a 26-week RCT comparing cariprazine with risperidone which found superior efficacy of cariprazine on predominant negative symptoms in patients with stable positive symptoms.²⁹

Another approach to treat negative symptoms is to augment existing antipsychotic treatment with another agent. More than 25 different augmentation agents have been investigated.³⁴ However, most of the trials are very small, with fewer than 100 participants across all studies, limiting the conclusions that can be drawn at this stage. The largest evidence bases in terms of total sample size are for augmentation with oestrogens ($n > 800$ patients in total) or an antidepressant ($n > 1200$ patients in total).³⁴ Meta-analyses of both these approaches showed statistically significant improvements relative to no augmentation, but the effect sizes were, again, relatively modest (s.m.d. = -0.35 for oestrogens, s.m.d. = -0.29 for antidepressants). Among other treatments with an evidence base of at least 100 participants, there were statistically significant benefits for augmentation with serotonin 3A (5-HT_{3A}) receptor antagonists (s.m.d. = -1.1 , $n = 261$), minocycline (s.m.d. = -0.76 , $n = 299$), topiramate (s.m.d. = -0.58 , $n = 236$) and modafinil (s.m.d. = -0.27 , $n = 342$); but no significant benefits for augmentation with lithium, non-steroidal anti-inflammatory drugs (NSAIDs), varenicline, azapirones, adenosine modulators, dehydroepiandrosterone, oxytocin, pregnenolone or *N*-methyl-D-aspartate (NMDA) receptor antagonists. The effect size seen for modafinil is modest, and there are wide confidence intervals (CI) for the effects of augmentation with 5-HT_{3A} receptor antagonists (the 95% CI of the s.m.d. is -2.44 to -0.36), minocycline (95% CI -1.21 to -0.31) and topiramate (95% CI -0.87 to -0.29), indicating uncertainty about the potential benefit of these approaches. Moreover, topiramate, oestrogens and some antidepressants were also found to significantly improve positive symptoms, again raising the issue of pseudospecificity.

Developing well-tolerated drugs, with innovative mechanisms of action, to ameliorate negative symptoms therefore remains a priority. Two candidate molecules that are under development are pimavanserin and roluperidone. Pimavanserin does not induce clinically significant antagonism of dopaminergic, adrenergic, histaminergic or muscarinic receptors.³⁵ Although the exact mechanism of action of pimavanserin is unknown, a combination of inverse agonist and antagonist activity at the serotonin 2A (5-HT_{2A}) receptors and, to a lesser extent, at the 5-HT_{2C} receptors, is reported.³⁶ A recent 26-week phase 2 RCT conducted in patients with predominant negative symptoms of schizophrenia showed a reduction in

negative symptoms after treatment with pimavanserin, although the effect size was small (s.m.d. = -0.21).³⁷

Roluperidone is a novel cyclic amide derivative with antagonistic properties for 5-HT_{2A}, sigma-2 and α_{1A} -adrenergic receptors (and to a lesser extent, α_{1B} -adrenergic receptors).³⁵ An initial RCT demonstrated statistically significant efficacy (s.m.d. = -0.57) in reducing negative symptoms, with good tolerability in patients with stable schizophrenia selected for predominant negative symptoms; but a more recent trial showed somewhat equivocal results.^{38,39} Non-pharmacological approaches, such as social skills training or cognitive remediation, are also being developed, and might be considered in combination with drug strategies in the future.

Issues for interpretation and approaches to address them

One key issue is whether the statistically significant effect sizes seen for many of these agents are clinically meaningful. For example, an analysis found that the minimum standardised mean difference for negative symptoms that corresponded to at least a 1-point change on the Clinical Global Impression-Severity scale (CGI-S) ranged from 0.6 to almost 1.0.^{40,41} On this basis, no drug listed above shows a sufficiently large, replicated effect size to be readily observed in routine clinical practice.⁴¹ However, it should be noted that effect sizes derived from between-group placebo–drug comparisons may not be directly comparable to the measurement of within-participant improvement over time, and the CGI may not be sensitive to change in negative symptoms or capture what is important to patients/carers.⁴² Notwithstanding these issues, a major problem is the limitations of the scales typically used to measure negative symptoms, which are not optimised to assess negative symptoms. For example, the PANSS-Negative Subscale includes assessment of cognitive impairment (which is not currently conceptualised as a negative symptom) and focuses only on behaviour, failing to assess the patient's subjective experience.²⁸ This problem can be addressed by using 'second-generation' scales specifically designed for negative symptoms, such as the Brief Negative Symptom Scale (BNSS) or Clinical Assessment Interview for Negative Symptoms (CAINS), and to complement them with real-world outcome measures that directly measure functional outcomes, such as the Personal and Social Performance scale (PSP).^{28,29} Patient-assessed quality of life is another critical outcome measure which provides an overall measure of the efficacy and tolerability of a treatment; however, it is often not assessed or reported in drug trials in schizophrenia.³¹

Pseudospecificity can be addressed by focusing on primary negative symptoms. In practice, this can be a challenge, as discussed above. Nevertheless, to know that a treatment is specifically effective for negative symptoms, it is important to address pseudospecificity by attempting to ensure as much as possible that negative symptom change reflects specific improvement in negative symptoms. One approach to do this is to have recruitment criteria into trials that select for patients with predominant negative symptoms and exclude patients with substantial positive and/or negative symptoms. Another strategy is to include an active comparator arm, for example with an existing antipsychotic, to control for improvement in secondary negative symptoms. Actively addressing and minimising secondary negative symptoms (e.g. through treating depressive symptoms) prior to enrolment could also be useful. Finally, most randomised controlled treatment trials in schizophrenia are typically relatively short: 4–8 weeks in duration.³⁰ Given the slowly progressive nature of primary negative symptoms, and the anticipated time needed for treatments to lead to behavioural


change, longer trials are likely needed to elicit significant symptomatic and real-world improvements.^{43,44}

The trial of cariprazine discussed above is an example of a trial that used a combination of these strategies. To address pseudospecificity, the trial restricted inclusion to individuals with predominant negative symptoms and included risperidone as an active control.²⁹ It also made efforts to exclude secondary negative symptoms by excluding patients with comorbid depression and/or extrapyramidal symptoms. Notably, this study complemented the PANSS assessment with assessment of real-world functioning.^{28,29} Finally, the trial was 26 weeks, addressing the concern about shorter trials being inadequate in duration to observe an effect.

Conclusions

Negative symptoms are related to clinically important disability and poor functional outcomes in schizophrenia. The main strategies for their pharmacological management are antipsychotic monotherapy and augmentation of antipsychotic treatment with other agents, such as antidepressants, based on statistically significant benefits of these approaches against negative symptoms in meta-analyses of RCTs. However, the effect sizes demonstrated are modest and may not be clinically relevant. Moreover, this evidence comes from trials that used outcome measures and study designs that were not optimised to measure meaningful change in primary negative symptoms, most notably because these treatments can often improve secondary negative symptoms and most of the trials were not designed to control for this.

The treatment of primary negative symptoms therefore represents a major unmet need in schizophrenia. This unmet need can be addressed by developing new compounds but also by evaluating promising existing agents, for example amisulpride, cariprazine, pimavanserin and roluperidone. This would require further trials of such agents designed to ensure that changes in negative symptoms are specific and meaningful, through their duration, exclusion of patients with secondary negative symptoms, use of active comparators and assessment of negative symptoms using 'second-generation' scales complemented by the use of patient-centred outcome measures with real-world relevance, such as functioning or quality of life.

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Data availability

Data availability is not applicable to this article as no new data were created or analysed in this study.

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