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Editorial

Negative symptoms in schizophrenia: reconsidering evidence and focus in clinical trials

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Negative symptoms of schizophrenia have been documented in the literature for over a century. Nevertheless, research has not convincingly produced effective interventions for their treatment. We propose to re-analyse currently published evidence on treatment of negative symptoms, using narrower definitions for symptom dimensions, to better understand what works for whom.

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Until the 1950s, negative symptoms have been central to the definition of schizophrenia. Since then, interest has shifted toward positive symptoms, for several reasons: mainly because of their higher interrater reliability, positive symptoms were thought to be more pathognomonic for schizophrenia, and positive symptoms respond to antipsychotic drug treatment.[1,2] However, toward the end of the 20th century, negative symptoms began to regain importance, particularly because of their strong association with functional outcomes.[1] At that time, Andreasen expressed the hope for increased research into treatment options for negative symptoms.[1] Unfortunately, to date, progress in the field remains limited. Aleman et al reviewed the literature on the biological and psychosocial treatment options for negative symptoms, and concluded that little progress has been made since Andreasen's work.[2] More recent meta-analyses have yielded promising findings for certain pharmacological (e.g. antidepressant add-on) and psychosocial (e.g. social skills training[3]) interventions. Nevertheless, clinical trials specifically aimed at reducing negative symptoms remain scarce, and the trials that use negative symptoms as a primary outcome measure have often not yielded promising results. Given these results and the strong impact on functional outcome, negative symptoms may well be the most important unmet need in schizophrenia.

Differentiating negative symptoms

The limited effectivity of interventions for negative symptom raises the question of whether we have to reconsider the paradigms employed. The heterogeneity of the negative symptoms construct may represent an important reason for the lack of clinically significant treatment effects on negative symptoms.[4] Investigating the effectiveness of new interventions targeting negative symptoms must demonstrate improvement in a very diverse set of items that, together, make up the heterogeneous symptom domain of negative symptoms. As a consequence, there will be a high risk of false negatives, and thus dismissing clinically significant effects on subsets of symptoms.

Converging evidence consistently suggests the necessity of separating negative symptoms both from positive symptoms and from symptoms of disorganisation. Recent work has been devoted to disentangling the construct of negative symptoms. A body of evidence suggests that the negative symptom domain can likely be subdivided by two or more multidimensional constructs,[4] which is consistent with the subdomain structure that is now distinguished in the DSM-V. Bucci and Galderisi[4] present an overview of the literature concerning the categorisation and assessment of negative symptoms. They confirm that, based upon factor-analytical studies with the Scale to Assess Negative Symptoms (SANS) and the Positive and Negative Syndrome Scale (PANSS), converging evidence points toward an underlying two-factor structure of negative symptoms construct into the domains 'diminished expression/expressive deficits' and '(social) amotivation (including anhedonia, asociality and avolition)'. Importantly, these two domains demonstrate a differential relationship with the outcome of patients with a severe mental illness. Particularly, the domain (social) amotivation seems to be related to functional outcomes such as instrumental role performance, (re) gaining employment and the number of hospital admissions, whereas the domain diminished expression has been related to neurocognitive deficits and level of independency (see Strauss et al[5] for an overview). More recently, it has been suggested that a five-factor model may better reflect the latent structure than the two-factor model employed here.[5] Although there certainly is good psychometric evidence for this, it remains an open issue whether this even more fine-grained approach provides added value in reducing heterogeneity of findings on pathophysiology and treatment.

Differential effects of treatments on symptom dimensions are not the only potential source of heterogeneity in negative symptom research. Another body of literature proposes that the negative symptom construct may be divided into primary and secondary negative symptoms.[5] This work suggests that primary and persistent negative symptoms represent a core symptom of the disorder, whereas secondary negative symptoms can be attributed to other factors (e.g. depression, medication side-effects).

Specifying negative symptom outcomes in clinical trials

Despite increasing evidence for the importance of assessing heterogeneity of negative symptoms in schizophrenia, clinical trials have generally defined global negative symptoms as an outcome instead of using one of the available solutions to account for this heterogeneity (see Strauss et al[5] for possible assessment tools). This is an important concern. Failing to recognise this heterogeneity in outcomes of clinical trials may result in dismissing treatment options because they were not found to be effective on a total score of a global negative symptom outcome measure. We believe that a re-evaluation of present and available data is an important avenue for reducing heterogeneity in negative symptom research. The two-domain structure of negative symptoms in diminished expression and (social) amotivation provides an excellent opportunity to be more specific in assessing current and new interventions. The main advantage of choosing this approach and this domain structure is that the trials assessing the effectivity of treatment can be re-evaluated retrospectively, since most of these studies have either used the PANSS or the SANS as an outcome measure. Although, it would be interesting and informative to pursue a similar effort for the five-factor structure of negative symptoms, this is more difficult in a retrospective manner because the PANSS, as the most commonly used scale in schizophrenia research, does not allow a distinction of five factors. By choosing this approach, we may be able to expose underlying effects of treatments that have been dismissed as non-effective when they may, in fact, be effective in reducing negative symptoms in specific subgroups of patients. This way, we can set an important step toward the treatment of negative symptoms.

We call upon the authors of the various studies assessing the effectiveness of psychosocial treatments targeting negative symptoms as primary or secondary outcome measures to re-analyse their data with the proposed negative symptoms subdomains. In doing so, we hope we can jointly reconsider the evidence, focus and the effectivity for negative symptoms treatment in schizophrenia.

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