Schizophrenia Bulletin vol. 43 no. 4 pp. 681–682, 2017
doi:10.1093/schbul/sbx054
Advance Access publication May 30, 2017

EDITORIAL

Negative Symptom Therapeutics

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This issue of the Bulletin continues the emphasis on the 5 Criteria A symptoms that have played a central role in the diagnosis of psychotic disorders. In previous 2017 issues, hallucinations, delusions and thought disorder have been viewed in the context of porous diagnostic boundaries. We seek clarity regarding critical variables that are common to several disorders and those variables that may be discriminating between disorders. Negative symptom psychopathology is the focus in this issue. The lead article[1] and commentaries[2–4] cover the concepts and science related to the negative symptom construct. This psychopathology, when viewed as a manifestation of schizophrenia, remains an unmet therapeutic challenge. Here we briefly address the shortfall in treatment development and issues that complicate the design and interpretation of therapeutic studies.

Negative symptoms have been considered a core aspect of schizophrenia since Kraepelin described the "weakening of the wellsprings of volition."[5] In his conceptualization, avolition, together with dissociative pathology and poor prognosis, formed the essence of dementia praecox psychopathology. Later, in the context of the re-conceptualization of schizophrenia as a clinical syndrome rather than a disease entity, expressive psychotic symptoms were termed positive psychopathology and the term negative symptoms was proposed to refer to the avolitional pathology and dulled inner emotional life described by Kraepelin.[6] However, it eventually became clear that extant negative symptom assessment methods included both primary negative symptoms, which were manifestations of schizophrenia pathophysiology, and secondary negative symptoms, which were caused by other factors. Examples of the latter are legion and include paranoid social withdrawal, antipsychotic medication induced restricted affect and apathy, depression induced anhedonia, and the consequences of impoverished social environments. The primary/secondary distinction has been addressed conceptually[7] with assessment instruments developed to specifically address this distinction[8,9] and an update is provided in this issue.[2]

The statement that an efficacious treatment for negative symptoms has not been developed is confusing and somewhat misleading. Clinical trials reporting a reduction in positive psychotic and other symptoms routinely document a concurrent reduction in negative symptoms. Negative symptoms may have a known secondary cause that provides a therapeutic target. If a patient has negative symptoms, the clinician is expected to do a differential diagnosis and, where a secondary cause is identified, to implement the appropriate therapeutic intervention. A logical decision tree, published in the *Schizophrenia Bulletin* in 1985,[10] suggested that if negative symptoms were secondary to psychosis then treat the psychosis, if secondary to a sedating drug then change the pharmacotherapy, if secondary to depression then treat depression, etc. In this context it is clear that we have treatments for negative symptoms. What is lacking is evidence for treatment efficacy of primary negative symptoms. Clinical trial design guidelines have been developed for efficacy testing of a treatment for primary negative symptoms.[11] The guidelines address directly the issue of pseudospecificity by minimizing and holding steady secondary sources of negative symptoms during the experimental period.

While primary negative symptoms are the target for investigating schizophrenia pathophysiology, they are inadequate as the sole target for clinical trials. Primary and secondary negative symptoms are easier to distinguish when secondary symptoms are transitory, state-like phenomena. But persistent negative symptoms are common in chronic forms of schizophrenia and differentiating primary from persistent secondary negative symptoms may be difficult. Persistent negative symptoms are proposed as the target for therapeutic discovery.[12] By definition they will have been resistant to current therapy regardless of whether primary or secondary. Moreover, estimates of the prevalence of persistent negative symptoms suggest that about two-thirds of people with chronic schizophrenia have persistent negative symptoms, whereas only about

one-third of the population will have primary negative symptoms. Similar to primary negative symptoms, the use of persistent negative symptoms also requires minimizing changes in known secondary causes of negative symptoms while testing an experimental treatment. The selection of study participants, who are clinically stable, with predefined levels of positive, depressive, and extrapyramidal symptoms and with significant persistent negative symptoms will result in a study sample enriched for persistent negative symptoms and support an efficacy claim for these symptoms if secondary sources remain stable. More challenging is efficacy evaluation in the context of an experimental treatment that is hypothesized to treat positive and negative symptom pathology simultaneously.[13]

Unfortunately, our field has, to a great extent, ignored these issues in the design of clinical studies; very few of the reported clinical trials on pharmacological, cognitive, or psychosocial therapies[14] have utilized clinical trials methods that address adequately pseudospecificity. It is disappointing for our field that most clinical trials are reported without even commenting that secondary negative symptoms confound interpretation of data.

The future may be brighter. Methods for gaining regulatory approval for efficacy are now clear. The persistent negative symptom construct provides a broader approach to the problem of appropriate clinical trial design, for which the primary negative symptom construct can be too restricting. New assessment tools for clinical trials, eg, Clinical Assessment Interview for Negative Symptoms (CAINS) and Brief Negative Symptom Scale (BNSS),[15] facilitate the assessment of the 2 negative symptom factors: expressive deficits and avolition.[1] The evaluation of the 2 separable components of the negative symptom construct allows for the potential to evaluate differential efficacy of new therapeutic approaches for these 2 components, ie, a drug may be effective for the avolition, but not the expressive component of negative symptoms. Furthermore, the evaluation of the 2 components may result in discovery of different pathophysiologies for these distinct components of the negative symptom construct. In this regard, new molecular targets may be identified for drug discovery. In addition, the delineation of unique neural circuits for these different negative symptom components may lead to the increased evaluation and use of neuromodulatory therapeutics. The negative symptom construct has been deconstructed with therapeutic implications for cognitive behavioral therapy.[16] And, in the near future may be tailored more specifically to one or the other negative symptom component and new hypotheses relating to emotional processing or to motivation may emerge in support of advances in cognitive and psychosocial therapeutics.

In the meantime, negative symptoms and associated dysfunction remain an unmet therapeutic challenge in the context of persistent and/or primary psychopathology.

Funding

Centers for Intervention Development and Applied Research (CIDAR; 5P50MH082999); 3/3-Social Processes Initiative in Neurobiology of the Schizophrenia(s) (1RO1MH102318).

Acknowledgments

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

References

1. Strauss G. A transdiagnostic review of negative symptom phenomenology and etiology. *Schizophr Bull*. 2017.
2. Kirkpatrick B. Primary, enduring negative symptoms: an update on research. *Schizophr Bull*. 2017.
3. Barch D. Paradigms for assessing hedonic processing and motivation in humans: relevance to understanding negative symptoms in psychopathology. *Schizophr Bull*. 2017.
4. Young J. Preclinical models to investigate mechanisms of negative symptoms in schizophrenia. *Schizophr Bull*. 2017.
5. Kraepelin E. *Dementia Praecox and Paraphrenia*. Melbourne, FL: Robert E Krieger Publishing Co Inc; 1971.
6. Strauss JS, Carpenter WT Jr, Bartko JJ. The diagnosis and understanding of schizophrenia. Part III. Speculations on the processes that underlie schizophrenic symptoms and signs. *Schizophr Bull*. 1974;11:61–69.
7. Carpenter WT Jr, Heinrichs DW, Wagman AM. Deficit and nondeficit forms of schizophrenia: the concept. *Am J Psychiatry*. 1988;145:578–583.
8. Heinrichs DW, Hanlon TE, Carpenter WT Jr. The Quality of Life Scale: an instrument for rating the schizophrenic deficit syndrome. *Schizophr Bull*. 1984;10:388–398.
9. Kirkpatrick B, Buchanan RW, McKenney PD, Alphs LD, Carpenter WT Jr. The Schedule for the Deficit syndrome: an instrument for research in schizophrenia. *Psychiatry Res*. 1989;30:119–123.
10. Carpenter WT Jr, Heinrichs DW, Alphs LD. Treatment of negative symptoms. *Schizophr Bull*. 1985;11:440–452.
11. Kirkpatrick B, Fenton WS, Carpenter WT Jr, Marder SR. The NIMH-MATRICS consensus statement on negative symptoms. *Schizophr Bull*. 2006;32:214–219.
12. Buchanan RW. Persistent negative symptoms in schizophrenia: an overview. *Schizophr Bull*. 2007;33:1013–1022.
13. Marder SR, Daniel DG, Alphs L, Awad AG, Keefe RS. Methodological issues in negative symptom trials. *Schizophr Bull*. 2011;37:250–254.
14. Fusar-Poli P, Papanastasiou E, Stahl D, et al. Treatments of Negative Symptoms in Schizophrenia: meta-analysis of 168 randomized placebo-controlled trials. *Schizophr Bull*. 2015;41:892–899.
15. Carpenter WT, Blanchard JJ, Kirkpatrick B. New standards for negative symptom assessment. *Schizophr Bull*. 2016;42:1–3.
16. Beck AT, Grant PM, Huh GA, Perivoliotis D, Chang NA. Dysfunctional attitudes and expectancies in deficit syndrome schizophrenia. *Schizophr Bull*. 2013;39:43–51.