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Treatment of Schizophrenia Negative Symptoms: Future Prospects

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New findings from neuroscience, genetics, and experimental psychology have emerged that provide alternative explanations of many negative symptoms. We review the continuing limitations in treatment and discuss possible sources of heterogeneity among negative symptoms. We also anticipate conceptual uncertainties that may arise with forthcoming treatment developments.

Key words: negative symptoms/schizophrenia/treatment/construct validity

Available Treatments

While the introduction of second-generation antipsychotics (SGAs) during the 1990s was accompanied by reports suggesting that these agents comprised a breakthrough in the treatment of negative symptoms,[1] in current practice, recovery for the patient with negative symptoms has remained elusive. Currently available treatments for negative symptoms appear to have modest benefits, with the result that negative symptoms continue to disproportionately limit patient recovery. Treatment guidelines recommend that to optimize functional outcomes for patients with schizophrenia, psychosocial programs or psychiatric rehabilitation should be combined with pharmacological management.[2] Yet for patients with negative symptoms, participation in these programs may not only be more difficult to facilitate, but also less efficacious. According to one study, patients with the more severe "deficit" form of schizophrenia who were enrolled in social skills training experienced less benefit than non-deficit patients.[3]

That available pharmacological treatments to reduce the burden of negative symptoms have limited benefits is evident from accumulated recent intervention studies consistently showing either small effect sizes or inconsistent results. In particular, the expectation that negative symptoms would show differentially improved responsiveness to SGAs compared with first-generation neuroleptics has not been realized to a degree that is clinically significant. Almost all the large clinical trials of SGAs include analyses of efficacy for negative symptoms, many using statistical procedures to reduce the influence of secondary sources such as extrapyramidal symptoms, demoralization, and sedation. However, the accumulated results from these studies suggest that the effect size of SGAs for negative symptoms is modest.[4] Although this is not uniformly true in all studies,[5,6] it appears consistent with the experience of many clinicians.

Use of adjunctive agents has likewise yet to emerge as a consistently beneficial strategy for negative symptoms. Although case reports of the efficacy of co-medication strategies with selective serotonin reuptake inhibitors (SSRIs), glutamatergic compounds, and estrogen are available,[7] none has convincingly established efficacy, and their use does not appear to have become widespread in clinical practice, with the possible exception of antidepressants. Even within research on the benefits of antidepressants, however, studies have yielded inconclusive results. Almost all have been characterized by small sample size and failure to control for change in secondary negative symptoms.[8]

Probably the best-studied experimental adjuncts are glutamate modulators, including the NMDA agonists glycine and D-serine, which produced significant reductions in persistent negative and cognitive symptoms when added to antipsychotics in preliminary studies,[9,10] but which have not been have not been consistently efficacious in larger subsequent studies.[11] Of additional concern, D-Cycloserine, a partial agonist at the glycine recognition site of the NMDA receptor, improved negative symptoms when added to conventional antipsychotics but actually worsened them when added to clozapine.[12] Case reports relating to the use of acetylcholinesterase inhibitors galantamine,[13] rivastigmine,[14] and Donepezil[15] have recently been published, but as yet there are no reports from larger prospective studies.

The disappointments in the effectiveness of SGAs and available co-medications do not appear to have been accompanied by a vigorous search by the pharmaceutical

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industry for new pharmacological approaches for treating negative symptoms. The industry may be reacting to these disappointments by directing their efforts to therapeutic targets that may have a higher likelihood of success.

Uncertainties in the Construct

In addition to modest treatment efficacy, a decade of accumulated data from intervention studies reveals inconsistencies in the *pattern* of responsiveness among negative symptoms. A review of Clozapine's impact on negative symptoms among refractory patients, for example, demonstrated benefits for negative symptoms restricted to anhedonia.[16] By contrast, in a study of Olanzapine among non-refractory patients, benefits for negative symptoms were observed in all factors except anhedonia and asociality.[17] Although methodological factors may explain some of the discrepancies, factor analyses of two of the most widely used instruments measuring negative symptoms, the SANS[18] and the SDS,[19] imply that they may measure more than one domain. If true, the variability in the pattern of treatment responsiveness may reflect differences in etiopathophysiologies among these domains. A number of sources have critically reviewed SANS[20–23] and SDS.[24]

That there are potential sources of heterogeneity among negative symptoms, as suggested by the modest effect size and inconsistent pattern of symptom responsiveness in clinical trials, is consistent with the clinical observation that a variety of patients appear to have ratable negative symptoms. It has long been known, for example, that individual negative symptoms can exist in a variety of neurological disorders. Apathy, for example, is observed in neurodegenerative disorders, including fronto-temporal and Lewy-body dementias, in supranuclear palsy, in Huntington's disease, and is frequently observed in frontal as well as basal ganglia and thalamic disorders. More recently, studies by schizophrenia researchers have established relationships between individual negative symptoms and abnormal frontal lobe circuitry. Among these relationships, abnormalities in neural circuits governing both eye tracking[25] and olfaction[26] appear impaired in patients with deficit negative symptoms, and olfactory deficits appeared associated with avolitional symptoms.

Apart from specific associations between individual negative symptoms and structural abnormalities, emerging evidence from experimental psychology suggests that inherited temperament phenotypes govern patterns of affiliation, motivation, and perseverance. Probably the best-known and most applicable model to the negative symptom construct is Robert Cloninger's, which used psychometric rating scales, animal research, and genetic studies to construct a model of heritable temperament dimensions including novelty seeking, harm avoidance, reward dependence, and persistence.[27] Cloninger's Temperament and Character Inventory,[28] a self-report questionnaire that includes questions related on personality traits, also shows areas of important overlap with both the SANS and the SDS, including questions related to an individual's tendency to seek out new things, to feel challenged in unfamiliar social situations, and to perceive an absence of purpose. In work by Akiskal, temperament factors have been shown to influence clinical outcome,[29] raising the question of whether temperament variants in patients with schizophrenia—a tendency against novelty seeking, for example—could be a source of variance in treatment for negative symptoms.

Future Challenges

Because of the current limitations in treatment responsiveness, it can be expected that the pharmaceutical industry will in the future develop innovative adjunctive treatments targeting negative symptoms to be used in conjunction with antipsychotics. There are indications that new approaches to understanding and treating negative symptoms are emerging. Already, research is underway identifying linkages between temperament traits and gene polymorphisms. The D4 dopamine receptor[30] and the 5 HTTLPR transporter gene[31] have been linked with abnormalities in novelty seeking and harm avoidance, respectively, although more recent research has not replicated these findings.[32] Simultaneously, autism researchers have begun investigating the roles of the pituitary hormones Oxytocin and Vasopressin on affiliative behaviors, based on their apparent role in pair-bonding behaviors among prairie voles.[33]

For clinicians, meaningful interpretation of any forthcoming data on new adjunctive treatment will depend on a clarification of the nosology of negative symptoms. The current understanding, that negative symptoms are restricted to schizophrenia and form a single domain, appears less certain than previously.

A definitive conceptualization would need to address whether negative symptoms should be considered homogeneous or heterogeneous, categorical or dimensional, and whether and how they are distributed beyond patients with schizophrenia, as suggested by some studies.[34,35]

Simultaneously, to evaluate patient responsiveness to proposed co-medications, consideration should be given to refining the existing rating instruments. Although the instruments used to measure negative symptoms were designed for research application, they are already used by clinicians, and their use in this context is likely to become more common. Common difficulties experienced in the use of SANS and the SDS relate to the inherent difficulty of rating patients' subjective experience, the vagueness of the anchor points, and the possible influence of secondary causes, including psychosocial and

cultural factors. Possible options include refining the anchor points to incorporate more concrete data and the possible inclusion of performance measures.

In its MATRICS initiative supporting the development of pharmacological agents to improve cognition in schizophrenia, NIMH attempted to foster greater collaboration between industry, academia, and regulators. The recent NIMH initiative to address barriers to improved treatment for schizophrenia negative symptoms is encouraging. If progress is to be made in the treatment of negative symptoms, increased collaboration between the basic sciences and clinical research over potential sources of heterogeneity should also be encouraged.

References

1. Fleischhacker WW. New drugs for the treatment of schizophrenic patients. *Acta Psychiatr Scand Suppl.* 1995;388:24–30.
2. Lauriello J, Lenroot R, Bustillo J. Maximizing the synergy between pharmacotherapy and psychosocial therapies for schizophrenia. *Psychiatr Clin North Am.* 2003 Mar;26(1): 191–211.
3. Kopelowicz A, Liberman R, Mintz J, Zarate R. Comparison of efficacy of social skills training for deficit and nondeficit negative symptoms in schizophrenia. *Am J Psychiatry.* 1997; 154(3):424–425.
4. Leucht S, Pitschel-Walz G, Abraham D, Kissling W. Efficacy and extrapyramidal side effects of the new antipsychotics olanzapine, quetiapine, risperidone and sertindole compared to conventional antipsychotics and placebo. A meta-analysis of randomized controlled trials. *Schizophr Res.* 1999;35:51–68.
5. Tollefson G, Bealey C, Tran P, Street J, et al. Olanzapine versus Haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. *Am J Psychiatry.* 1997;154: 457–474.
6. Davis J, Chen N. Clinical profile of an atypical antipsychotic: Risperidone. *Schizophr Bull.* 2002;28:43–61.
7. Möller HJ. Management of the negative symptoms of schizophrenia: new treatment options. *CNS Drugs.* 2003;17(11): 793–823.
8. Buchanan RW, Brandes M, Breier A. Treating negative symptoms: pharmacological strategies. In: Breier A, ed. *The New Pharmacotherapy of Schizophrenia.* Washington, D.C.: American Psychiatric Press; 1996:179–204.
9. Heresco-Levy U. Double-blind, placebo-controlled, crossover trial of glycine adjuvant therapy for treatment-resistant schizophrenia. *Br J Psychiatry.* 1996;169(5):610–617.
10. Heresco-Levy U. Comparative effects of glycine and D-cycloserine on persistent negative symptoms in schizophrenia: a retrospective analysis. *Schizophr Res.* 2004;66(2–3):89–96.
11. Carpenter WT Jr, Buchanan RW, Javitt DC, Marder SR, Schooler NR, Hereco-Levy U, Gold JM. Is glutamatergic therapy efficacious in schizophrenia? Annual Meeting, American College of Neuropsychopharmacology, San Juan, Puerto Rico, Dec 2004.
12. Goff DC, Henderson DC, Evins AE, Amico E. A placebo-controlled crossover trial of D-cycloserine added to clozapine in patients with schizophrenia. *Biol Psychiatry.* 1999;45(4): 512–514.
13. Rosse RB. Adjuvant galantamine administration improves negative symptoms in a patient with treatment-refractory schizophrenia. *Clin Neuropharmacol.* 2002;Sep25(5):272–275.
14. Lenzi A, Maltinti E, Poggi E, Fabrizio L, Coli E. Effects of rivastigmine on cognitive function and quality of life in patients with schizophrenia. *Clin Neuropharmacol.* 2003; 26(6):317–321.
15. MacEwan GW, Ehmann TS, Khanbhai I, Wrixon C. Donepezil in schizophrenia—is it helpful? An experimental design case study. *Acta Psychiatr Scand.* 2001;104(6):469–471.
16. Buchanan R, Breier A, Kirkpatrick B, Ball P, et al. Positive and negative symptom response to clozapine in schizophrenic patients with and without the deficit syndrome. *Am J Psychiatry.* 1998;155(6):751–760.
17. Tollefson GD, Beasley CM Jr, Tran PV, Street JS, Krueger JA, et al. Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. *Am J Psychiatry.* 1997;154(4):457–465.
18. Andreasen NC. Negative symptoms in schizophrenia: definition and reliability. *Arch Gen Psychiatry.* 1982;39:784–788.
19. Kirkpatrick B, Buchanan R, McKenney P, Alphs L, et al. The schedule for the Deficit Syndrome: an instrument for research in schizophrenia. *Psychiatry Res.* 1989;30:119–123.
20. Schuldberg D, Quinlan DM, Glazer W. Positive and negative symptoms and adjustment in severely mentally ill outpatients. *Psychiatry Res.* 1999;85(2):177–188.
21. Axelrod BN, Goldman RS, Woodard JL, Alphs LD. Factor structure of the negative symptom assessment. *Psychiatry Res.* 1994;52(2):173–179.
22. Keefe RS, Harvey PD, Lenzenweger MF, Davidson M, et al. Empirical assessment of the factorial structure of clinical symptoms in schizophrenia: negative symptoms. *Psychiatry Res.* 1992;44(2):153–165.
23. Peralta V, Cuesta M. Negative symptoms in schizophrenia: a confirmatory factor analysis of competing models. *Am J Psychiatry.* 1995;152(10):1450–1457.
24. Yale S, Goetz R, Marcinko L, Amador X, et al. A latent factor analysis of the Deficit Syndrome criteria. Presented at the American College of Neuropsychopharmacology Conference, 2003.
25. Hong LE, Avila MT, Adami H, Elliot A, Thaker GK. Components of the smooth pursuit function in deficit and nondeficit schizophrenia. *Schizophr Res.* 2003;63(1–2):39–48.
26. Malaspina D, Coleman E, Goetz RR, Harkavy-Friedman J, et al. Odor identification, eye tracking and deficit syndrome schizophrenia. *Biol Psychiatry.* 2002;51(10):809–815.
27. Cloninger CR. *Feeling Good: The Science of Well Being.* Oxford: Oxford University Press; 2004.
28. Cloninger CR. A systematic method for clinical description and classification of personality variants. A proposal. *Arch Gen Psychiatry.* 1987;44:573–588.
29. Akiskal HS, Hantouche EG, Allilaire JF. Bipolar II with and without cyclothymic temperament: "dark" and "sunny" expressions of soft bipolarity. *J Affect Disord.* 2003;73(1–2): 49–57.
30. Benjamin J, Li L, Patterson C, Greenberg BD, Murphy DL, Hamer DH. Population and familial association between the D4 dopamine receptor gene and measures of Novelty Seeking. *Nat Genet.* 1996;12(1):81–84.
31. Katsuragi S, Kunugi H, Sano A, Tsutsumi T, et al. Association between serotonin transporter gene polymorphism and anxiety-related traits. *Biol Psychiatry.* 1999;45(3):368–370.

32. Malhotra AK, Virkkunen M, Rooney W, Eggert M, et al. The association between the dopamine D4 receptor (D4DR) 16 amino acid repeat polymorphism and novelty seeking. *Mol Psychiatry.* 1996;1(5):388–391.
33. Young LJ. Oxytocin and vasopressin as candidate genes for psychiatric disorders: lessons from animal models. *Am J Med Genet.* 2001;105(1):53–54.
34. Ratakonda S, Gorman J, Yale S, Amador X. Characterization of psychotic conditions. *Arch Gen Psychiatry.* 1998; 55:75–81.
35. Toomey R, Kremen W, Simson J, Samson J, et al. Revisiting the factor structure for positive and negative symptoms: evidence from a large heterogeneous group of psychiatric patients. *Am J Psychiatry.* 1997;154:371–377.