Schizophrenia Bulletin vol. 32 no. 2 pp. 223–224, 2006
doi:10.1093/schbul/sbj010
Advance Access publication on October 12, 2005

Commentary: Consensus Statement on Negative Symptoms

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The consensus statement provided by the workgroup is a valuable step toward stimulating new research in negative symptoms. It has been very clear for many years that ''negative symptoms'' play a critical role in producing the severe social and vocational disability experienced by many patients with schizophrenia. At the same time, advances in assessment, treatment, and the understanding of neurobiologic mechanisms have been slow at best. One example is the striking paucity of large-scale clinical trials that focus on patients selected on the basis of severe and persistent negative symptoms. Despite an enormous number of industry-sponsored trials involving second-generation antipsychotics, most of the data on response of ''negative symptoms'' comes from relatively short-term trials that focus on patients selected on the basis of positive symptoms (or, for longer-term trials, on the basis of clinical ''stability'').

Given the diverse domains included under the rubric of negative symptoms (ie, blunted affect, alogia, asociality, anhedonia, and avolition) and the potential for different neurobiologic substrates and different potential mechanisms of drug effect, more refinement and better validity and reliability in assessment (and assessment of change) strategies will be key.

In addition, it would be extremely valuable to have more objective (eg, speech analysis, motor activity, neurophysiologic, functional neuroimaging) measures of ''negative symptoms,'' which could be practically used as biomarkers to help in patient selection (and, possibly, in the assessment of drug effect).

The definition of clinically meaningful effect size calls to mind the same debate that has surrounded the development of medications for the enhancement of cognitive function. Unless clinical improvement can be linked to an impact on functional outcome, quality of life, caregiver burden, health care costs, or other meaningful outcome measures, we have to be very careful in not settling on measurable, but ultimately less than meaningful, changes.

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The problem of distinguishing primary and secondary negative symptoms in the context of co-administered dopamine antagonists remains a challenge. Although one could argue that if a clinically meaningful (ie, functional) drug effect is observed, the mechanism or distinction between primary and secondary becomes academic. This is perhaps as important a concern in failing to find a potential effect as well. The 1-year, placebo-controlled ziprasidone ''extended use'' trial in chronically hospitalized schizophrenia patients provides an important example of the challenge.[1] Comparable improvement in measures of negative symptoms occurred over the first 6 weeks in both placebo-treated and ziprasidone-treated patients, leading to the likely conclusion that withdrawal of previous medication and/or the effects of participating in the trial accounted for this improvement. Subsequently, ziprasidone-treated patients continued to improve, and placebo-treated patients did not. Without a long-term placebo control, it would have been difficult to appropriately interpret these results. Yet doing a long-term placebo-controlled trial in schizophrenia is highly problematic. Would it be sufficient to know that a putative treatment was superior to another drug, even if neither were superior to placebo, since all patients with schizophrenia should be treated with an active antipsychotic on an ongoing basis?

A number of studies have used statistical techniques to try to deal with potential confounds between, for example, subtle extrapyramidal symptoms (EPS) and negative symptoms. This is unrealistic in that subtle negative symptoms could be attributable to EPS that are not necessarily readily detectable on the existing measure of EPS as applied in most clinical trials. For example, in a large study of different fixed doses of conventional, long-acting antipsychotics, we saw significant differences in measures of blunted affect, emotional withdrawal, and psychomotor retardation between patients receiving standard dose and very low dose antipsychotic, but differences were not apparent on the rating scale used to measure EPS.[2] Even when such phenomena are measurable, if two phenomena are truly confounded, statistical strategies will not necessarily succeed in disentangling them.

The panel recommended a review of the prevalence of negative symptoms that are severe enough to merit therapeutic intervention and longitudinal studies that

reflect persistence of negative symptoms. It would also be important to have longitudinal studies that examine the evolution of negative symptoms in order to set the stage for "early intervention" trials that might facilitate the testing of compounds to mitigate, delay, or prevent the development of negative symptoms.

The recommendations of the panel are important and timely and will hopefully stimulate a new generation of efforts in this context.

References

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