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Concepts and methods when considering negative symptom course

Savill *et al.* (2014) assess stability in negative symptoms that they regard as core aspects of schizophrenia. Using data from a broad range of studies, they conclude that negative symptoms improve consistently with all treatments, including placebo and treatment as usual. Their meta-analysis confirms what has long been observed, that negative symptom ratings tend to improve when other symptoms are reduced. However, negative symptom ratings with the Positive and Negative Syndrome Scale (PANSS), Brief Psychiatric Rating Scale (BPRS) and Scale for the Assessment of Negative Symptoms (SANS) are broad and do not correspond closely with Kraepelin's (1971) 'weakening of the well-springs of volition' or Bleuler's (1950) restricted affect. Ratings of asociality, for example, will include active social withdrawal based on paranoia, reduced interest based on depressed affect, inadequate energy based on sedative drug effects, and preoccupation with voices that interfere with social intercourse. These are secondary sources of negative symptoms. Primary negative symptoms are considered a direct manifestation of schizophrenia pathophysiology (Carpenter *et al.* 1988; Carpenter, 1996) and are more likely to be trait pathology than transitory secondary negative symptoms. An example is asociality involving low drive for social interaction based on indifference and a lack of reinforcement by social interaction.

The authors state that 'primary negative symptoms refer to negative symptoms which are present both within and during periods of positive symptom exacerbation'. This is a definition of enduring or persistent negative symptoms, but determining that persistent negative symptoms are the core pathology described by Kraepelin and Bleuler requires a differential diagnosis since secondary sources may also be persistent. Savill *et al.* (2014) provide an informative discussion of the primary *versus* secondary distinction in negative symptoms and cite the consensus workshop report on the clinical trial design required to assess efficacy of a treatment for negative symptoms. They correctly point out that persistent negative symptoms are an appropriate clinical target in clinical trials

as advocated by Buchanan (2007). However, such clinical trials do not address the primary *versus* secondary issue regarding negative symptoms. The Schedule for the Deficit Syndrome (Kirkpatrick *et al.* 1989) is the established method for separating primary from secondary negative symptoms. With this methodology typically 20–25% of schizophrenia cohorts have primary negative symptoms, even less in first-episode cases. Hence most of the subjects in their meta-analysis probably do not have primary negative symptoms even if persistent, and most of the studies cited do not require persistent negative symptoms as an inclusion criterion. The reported findings appear principally based on changes in secondary negative symptoms. Statistical adjustments have not been validated for eliminating confounding by secondary sources, and the studies reviewed do not use the methodology that addresses pseudospecificity in negative symptom change (Kirkpatrick *et al.* 2006) where secondary sources are controlled by design.

Our group reported the Cognitive and Negative Symptoms in Schizophrenia Trial (CONSIST) study that implemented the clinical trial design for testing efficacy for persistent negative symptoms with D-cycloserine, glycine and placebo (Buchanan *et al.* 2007). There was no evidence for negative symptom change in this context. Although not included in the meta-analysis, this study appears to meet inclusion criteria, but may serve as an exception that clarifies the rule.

Negative symptoms are often transitory, need not be stable, tend to be an aspect of general improvement, and treatment algorithms have been proposed for secondary negative symptoms (Carpenter *et al.* 1985). Primary negative symptoms of avolition and restricted affect historically apply to some, not all, persons with schizophrenia. This aspect tends to be trait pathology and no treatment to date has established efficacy. This is the negative symptom pathology that is considered an unmet therapeutic need and relates to the concepts of Kraepelin and Bleuler.

The authors address an important question, but the studies available for meta-analysis do not provide a basis for determining the stability of primary (core) negative symptoms. It is generally observed that patients entering clinical trials improve regardless of treatment assignment. Entering at a stage of increased symptoms and the advantages of time, often enhanced clinical care, and the effect of expectation may account for improvement. The symptom reductions common in

schizophrenia trials include secondary sources of negative symptoms. This, in addition to regression to the mean, may contribute substantially to the findings reported.

Declaration of Interest

None.

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