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Letter to the Editor
Concepts and methods when considering negative symptom course: a reply

We would like to thank Carpenter & Kirkpatrick (2015) for highlighting the importance of distinguishing between primary and secondary negative symptoms in relation to our study (Savill *et al.* 2014). Their conclusion that 'the studies available for meta-analysis do not provide a basis for determining the stability of primary (core) negative symptoms' is one that we agree with. We acknowledge that identifying primary negative symptoms is a complex undertaking, which in all likelihood cannot be conducted unless secondary sources are controlled for in the design of the reviewed studies. Our aim was to try and evaluate the course of negative symptoms in what would be a relatively stable out-patient sample (which we acknowledge in itself is somewhat contentious), including both primary and secondary symptoms, rather than attempting to evaluate any change in primary negative symptoms alone. We did consider some established causes of secondary negative symptoms in the meta-regression; however, this was conducted principally as a method to assess whether the changes in symptoms detected in the meta-analysis were influenced by studies which implemented a much broader inclusion criterion.

In the multivariate meta-regression we found that negative symptom improvement was not greater in studies adopting a less restrictive inclusion criterion relating to positive or depressive symptoms, or a more stringent criterion relating to negative symptoms. This has since been supported by a recent *post-hoc* analysis of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial data (Lieberman *et al.* 2005), which found that the association between positive and negative symptom change in stable out-patients was relatively modest, and that implementing more stringent inclusion criteria as a way to address the pseudospecificity problem did not reduce the amount of adjusted negative symptom variance associated with positive symptom change (Dunayevich *et al.* 2014). We also found the change over time between different types of negative symptoms to be equal, rather than smaller in symptoms that are thought to be less influenced by secondary factors (i.e. restricted affect and avolition, as highlighted in the commentary). Such findings lead us to be highly cautious in attributing the detected changes predominantly to secondary negative symptoms as suggested by Carpenter & Kirkpatrick (2015), but equally we acknowledge that there is insufficient evidence to determine that this change is principally occurring in primary negative symptoms either. Therefore, we believe that it would be somewhat speculative to assume that the changes in negative symptoms we detected are either mainly primary or secondary in origin. In addition, whilst there does appear to be a degree of regression to the mean, as identified in the meta-regression, this effect appears fairly small and so this is unlikely to be the principal cause of this change.

Overall, we believe the findings presented in our review (Savill *et al.* 2014) may contribute to a better understanding of how the negative symptoms which patients experience develop over time (irrespective of their aetiology), and may help inform the design of future trials which attempt to treat negative symptoms. To determine the degree of change in primary negative symptoms, however, an alternative study methodology would be required.

Regarding the issue of negative symptoms being an unmet therapeutic need, the definition used was adopted from the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) statement which states that 'persistent and clinically significant negative symptoms are an unmet therapeutic need in a large proportion of cases' (Kirkpatrick *et al.* 2006, p. 215), as opposed to a more narrow definition which would only include primary negative symptoms. Last, the Cognitive and Negative Symptoms in Schizophrenia Trial (CONSIST) study (Buchanan *et al.* 2007) was identified in the electronic search, but did not meet the inclusion criteria given that the study sample included both in-patients (which eliminated the data from three of the five research sites) and patients diagnosed with schizo-affective disorder (which appeared to eliminate all of them).

Declaration of Interest

None.

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