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Psychosocial intervention for negative symptoms: a note on meta-analyses

Lutgens *et al*'s interesting paper[1] describes the results of their meta-analytic study on the effect of psychosocial interventions on negative symptoms for people with psychosis. Despite commending the aims of the study we have some methodological reservations on the results presented.

We believe that the studies included are only a partial representation of the research conducted on the therapeutic modalities considered. For example, we have recently completed a meta-analysis on the effect of cognitive remediation on negative symptoms.[2] Our study had a similar time frame to Lutgens *et al*'s, and the same participant inclusion criteria. Our search retrieved 45 eligible studies, compared with only 16 retrieved by Lutgens *et al*, in their neurocognitive therapies category. We believe that this is due to their search strategy, which included the term 'negative symptom' and therefore retrieved only studies with this term in the abstracts. This had two effects: it was more likely to retrieve studies reporting positive findings; and when investigating interventions not specifically designed to target negative symptoms it missed a large body of studies across all the therapeutic modalities considered.

The nature of the control condition is also important when considering effect sizes. Lutgens *et al* conflated passive with active control conditions. Active control conditions for one study (e.g. cognitive remediation) were then considered active treatment conditions in subsequent analyses. We also noted some overlap in the therapy groups considered. Both art and music and exercise therapy included dance-based interventions. The miscellaneous category adds to the limited clarity of the category definitions by considering comprehensive 'care packages', such as in Garety *et al*,[3] which include medication management and allocation to a psychosocial intervention among a number recommended by clinical guidelines (i.e. family therapy or cognitive–behavioural therapy (CBT)). These limitations, in our view, make it difficult to reliably compare effect sizes from the intervention groups considered.

We also wish to point out some methodological considerations that may limit the accuracy of the results reported. First, it appears that the authors considered only end-of-therapy data in estimating effect sizes. This does not account for relative change. In other words, this method considers symptom reduction of a hypothetical 3 points on a negative symptoms scale to be equivalent in individuals entering the study with an initial score of 5 or of 23. The importance of taking into account baseline levels in meta-analysis is clear and it is considered best practice.[4] There is also evidence that the DerSimonian–Laird method has limitations compared with methods using restricted maximum likelihood estimators.[5]

Last, it is unclear how the authors considered the treatment that participants received as part of treatment as usual (TAU). They state: 'Compared with TAU, 59% (10/17) of studies reported CBT to be more effective at the end of treatment'. From this statement one might assume that participants received either TAU (e.g. medication) or CBT. In all likelihood, studies compared CBT + TAU with TAU only.

1 Lutgens D, Gariepy G, Malla A. Psychological and psychosocial interventions for negative symptoms in psychosis: systematic review and meta-analysis. *Br J Psychiatry* 2017; **210**: 324–32.

2 Cella M, Preti A, Edwards C, Dow T, Wykes T. Cognitive remediation for negative symptoms of schizophrenia: a network meta-analysis. *Clin Psychol Rev* 2017; **52**: 43–51.

3 Garety PA, Craig TKJ, Dunn G, Fornells-Ambrojo M, Colbert S, Rahaman N, et al. Specialised care for early psychosis: symptoms, social functioning and patient satisfaction. Randomised controlled trial. *Br J Psychiatry* 2006; **188**: 37–45.

4 Achana FA, Cooper NJ, Dias S, Lu G, Rice SJ, Kendrick D, et al. Extending methods for investigating the relationship between treatment effect and baseline risk from pairwise meta-analysis to network meta-analysis. *Stat Med* 2013; **32**: 752–71.

5 Veroniki AA, Jackson D, Viechtbauer W, Bender R, Bowden J, Knapp G, et al. Methods to estimate the between-study variance and its uncertainty in meta-analysis. *Res Synth Methods* 2016; **7**: 55–79.

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Authors' reply: In their thoughtful comments about our study, Cella & Preti raised several important points about some of the current challenges and limitations of research synthesis methods.[1]

In systematic reviews, search strategies need to strike a balance between specificity with regard to the research question at hand and sensitivity to capture the broadest number of relevant studies. Given that our only outcome of interest was negative symptoms in psychotic disorders, we included the term 'negative symptom' in our search strategy, as well as 26 synonyms of negative symptoms and associated terms, and broad keywords for psychosocial interventions. Our search retrieved a comprehensive 4136 non-duplicate studies from five major databases. Although some studies might have been missed, their omission from our review is unlikely to have been systematic, and our findings are overall consistent with those from a previous review.[2] We do agree with Cella & Preti that publication bias could be a problem – it is a common threat to almost all reviews – and we found some evidence of it, which we reported in the paper. We also acknowledge that the general intervention categories in our review might not perfectly match the various psychosocial interventions that have been tested in the literature. Our goal was to provide readers with a broad sense of the benefits of different intervention approaches for negative symptoms. Care was given to fully present the characteristics and quality of each study in the paper and online supplement.

Cella & Preti pointed out that our meta-analysis could have focused on change scores rather than endpoint scores of negative symptoms to account for baseline differences in groups. This

approach may be more efficient under certain circumstances. In randomised trials, however, both approaches can be assumed to provide the same underlying intervention effects if the trials are adequately randomised: the difference in mean endpoint scores will be the same on average as the difference in mean change scores. To our knowledge, the decision for using one measure over another is currently not resolved, with evidence suggesting that endpoint scores tend to produce more conservative estimates.[3] Cella & Preti further suggested applying a restricted maximum likelihood estimation method to the meta-analysis. Research synthesis methodology is a developing field and there is no consensus at present on the best approach for random-effects meta-analysis. Although valuable alternatives to random-effects estimation methods have been developed,[4] DerSimonian–Laird remains the most widely used approach and an adequate method in most scenarios.[5]

Finally, Cella & Preti raised two points about the way control conditions were handled in the review. We would like to reassure readers that we did not double-count studies by considering active control conditions for one analysis as active treatment conditions in another analysis. We further wish to clarify that treatment participants in all trials received the psychosocial intervention as an adjunct to treatment as usual (TAU), as doing otherwise would be considered unethical.

1 Higgins JP, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. John Wiley & Sons, 2011.

2 Elis O, Caponigro JM, Kring AM. Psychosocial treatments for negative symptoms in schizophrenia: current practices and future directions. *Clin Psychol Rev* 2013; **33**: 914–28.

3 Fu R, Holmer HK. Change score or follow-up score? Choice of mean difference estimates could impact meta-analysis conclusions. *J Clin Epidemiol* 2016; **76**: 108–17.

4 Cornell JE, Mulrow CD, Localio R, Stack CB, Meibohm AR, Guallar E, et al. Random-effects meta-analysis of inconsistent effects: a time for change. *Ann Intern Med* 2014; **160**: 267–70.

5 DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. *Contemp Clin Trials* 2015; **45**(Pt A): 139–45.

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The clinical utility of the ADI-R and ADOS in diagnosing autism

Larson *et al*[1] report on a major study on psychosis in autism, which is an important topic.[2] They point out that their sample is non-representative, but then use the Autism Diagnostic Interview-Revised (ADI-R) and Autism Diagnostic Observation Schedule (ADOS) for clinical diagnosis. This vastly increases the non-representativeness of the sample unnecessarily and takes it a very long way away from autism in the general population. The criteria they used to define autism are very narrow concepts of the disorder. Clinical diagnoses based on this narrow view tell us very little about autism as seen in routine clinical practice, where professionals throughout the world now accept that the broader autism phenotype. I see many parents who come to me in great distress knowing that their child has autism and that the school also observed this, but having been told that their child did not have autism according to the ADI-R. This instrument is not appropriate to making a sole diagnosis of autism in clinical practice. It not uncommonly misses high-functioning autism. In addition, Ventola *et al*[3] have shown that the ADI-R was significantly 'under-diagnosing toddlers'. How biased and unrepresentative the patients in this survey can be seen by Professor Gillian Baird's work on autism in the general population.[4] Indeed, using these narrow criteria gives a prevalence of autism of 25 per 10 000. When you use the broader autism spectrum, you get a truer rate of 116 per 10 000. One of the problems also is that the National Institute for Health and Care Excellence (NICE) guidelines on the diagnosis of autism,[5] which are accepted throughout the world, are not followed. These state that there is no specific instrument recommended for diagnosis of autism and that identification depends on a clinical diagnosis by an experienced clinician. Dorothy Bishop, Professor of Developmental Neuropsychology at the University of Cambridge, told Adam Feinstein that, 'If it could be shown that there were real benefits in accuracy of diagnosis from adopting this lengthy procedure, then I'd be happy to say: "Okay". But the originators of the instrument have never demonstrated [this] – it is really more an article of faith with them'.[6] Feinstein also reports that, at the prestigious International Meeting for Autism in London in 2009, senior autism researchers 'lambasted' these narrow instruments 'for missing many cases of autism'.

1 Larson FV, Wagner AP, Jones PB, Tantam D, Meng-Chuan L, Baron-Cohen S, et al. Psychosis in autism: comparison of the features of both conditions in a dually affected cohort. *Br J Psychiatry* 2017; **210**: 269–75.

2 Fitzgerald M. Schizophrenia and autism/Aspergers syndrome: overlap and difference. *Clin Neuropsychiatry* 2012; **9**: 171–6.

3 Ventola PE, Kleinman J, Pandey P, Barton M, Allen S, Greene J, et al. Agreement among four diagnostic instruments for autism spectrum disorders in toddlers. *J Autism Dev Disord* 2006; **36**: 839–47.

4 Baird G, Simonoff E, Pickles A, Chandler S, Loucast Meldrum D, Charman T. Prevalence of disorders of the autism spectrum disorder in a population cohort of children in South Thames: the Special Needs and Autism Project. *Lancet* 2006; **368**: 210–5.

5 National Institute for Health and Care Excellence. *Autism: Recognition, Referral, Diagnosis and Management of Adults on the Autism Spectrum*. British Psychological Society & Royal College of Psychiatrists, 2012.

6 Feinstein A. *A History of Autism*. Wiley–Blackwell, 2010.

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Author's reply: Professor Fitzgerald comments on the 'real-life' utility of the ADI-R and ADOS. It is his view that this may have limited the representativeness of our sample with respect to the autistic presentation. However, the ADI-R or ADOS were used only for inclusion/exclusion when we were referred participants who did not have an existing clinical diagnosis of autism spectrum disorder (ASD). This was a small number of participants ($n = 19$), and the number who were excluded because they did not meet cut-offs was even smaller ($n = 8$). It is interesting to note that our experience actually supports Fitzgerald's observations, in that participants in the research did differ significantly from a comparison sample of people with ASD in terms of their ADI-R scores, as discussed in our article.[1]

The wider question alluded to in Fitzgerald's letter is one of categorical diagnoses and the utility of boundaries. Obviously,