Did you add the same study twice in the meta-analysis?

I read with interest the systematic review of pharmacotherapy for schizophrenia and mixed-handyness. I would be grateful if the authors could clarify the same as 'Friedman 2007' (same drugs, same comparisons, same colleagues. Looking at Fig. 2 of the paper and at the online-only meta-analysis, the studies 'Eli Lilly' is the same as 'Martenyi 2007' and 'Pfizer 589' is the same as 'Friedman 2007' (same drugs, same comparisons, same sample size). I would be grateful if the authors could clarify the matter.

1 Hoskins M, Pearce J, Bethell A, Dankova L, Barbui C, Tol QA, et al. Pharmacotherapy for post-traumatic stress disorder (PTSD) by Mathew Hoskins and colleagues. Looking at Fig. 2 of the paper and at the online-only supplemental file, however, it seems to me that two unpublished studies have been counted twice in the meta-analysis. As far as I can see from the information reported in the review, the study 'Eli Lilly' is the same as 'Martenyi 2007' and 'Pfizer 589' is the same as 'Friedman 2007' (same drugs, same comparisons, same sample size). I would be grateful if the authors could clarify the matter.

Authors’ reply: Professor Cipriani helpfully questions duplication of data from two unpublished studies in our review. We could not get access to the unpublished material for ‘Eli Lilly’ and ’Pfizer 589’, even after contacting the pharmaceutical companies, and instead relied on the raw data sets obtained from previous reviews.

We have contacted Dr Friedman, who has confirmed that Pfizer 589 was subsequently published as ‘Friedman 2007’. We have also contacted the authors of ‘Martenyi 2007’, but are, as yet, unable to confirm if this is the published ‘Eli Lilly’ paper. This seems distinctly possible, as the sample sizes are the same but it is important to note that Eli Lilly only released Treatment Outcome PTSD Scale data and not Clinician Administered PTSD Scale data to the National Institute of Health and Care Excellence reviewers.

When the ‘Pfizer 589’ data are removed, it changes the outcome for sertraline, which now demonstrates a small but statistically significant advantage over placebo in reducing the severity of clinician-rated PTSD symptoms (8 studies, n = 1271, SMD –0.16 (95%CI –0.31 to –0.02), χ² = 33%). This means that paroxetine, fluoxetine, venlafaxine and sertraline can be considered as potential treatments for PTSD.

The outcome for the trauma-type sub-analysis for sertraline is still statistically insignificant (3 studies, n = 278, SMD –0.42 (95%CI –1.03 to 0.19), χ² = 81%). ‘Eli Lilly’ was not included in the meta-analysis of individual agents v. placebo. The overall meta-analysis of selective serotonin-reuptake inhibitors (SSRIs) v. placebo, when ‘Eli Lilly’ and ‘Pfizer 589’ are removed, is now slightly more in favour of SSRIs (19 studies, n = 3350, SMD –0.27 (95%CI –0.37 to –0.16), χ² = 45%); see revised forest plot (here Fig. 1).

Fig. 1 Revised meta-analysis of selective serotonin reuptake inhibitors v. placebo (SMD, standardised mean difference).
Schizophrenia and mixed-handedness

The new meta-analysis by Hirnstein & Hugdahl\(^1\) shows that schizophrenia is robustly associated with non-right-handedness and thus makes a strong case for genetic links between schizophrenia, brain lateralisation and handedness. The association was obtained meta-analytically for psychometrically assessed handedness, and it was even stronger when handedness was assessed behaviourally. Of interest, the available evidence also allowed the tentative conclusion that this association might foremost be driven by mixed-handedness, rather than left-handedness, thus suggesting that the strength of handedness, rather than its direction, might actually be linked to schizophrenia.

With regard to this possibility, we emphasise that assessment and classification reliability is a pervasive problem in handedness research. Studies in this field often treat handedness as a binary variable, comprising only right \(v\). left preferences, and frequently merely use single-item measures, or arbitrary criteria for handedness classification, when multi-item inventories are used.

However, recent evidence\(^2\) shows that psychometrically assessed handedness is in fact taxonic and discrete – that is, a matter of qualitative, rather than quantitative, differences consisting of the taxa of right-, left- and mixed-handedness. Similarly, psychometrically assessed footedness, earedness, and eyedness all consist of these three taxa, which, together with handedness, might be explained by underlying sidedness, which also consists of the above three taxa. Further, handedness has been found to be a biased indicator of mixed-sidedness, which might be explained by ubiquitous external and societal pressures promoting right-hand preference among actual non-right-handers.\(^3\) It therefore appears that footedness, obviously being less influenced by such external pressures, is the most important predictor of sidedness.\(^4\)

Given these facts, it is interesting to note that the Hirnstein & Hugdahl meta-analysis was still able to hint at mixed-handedness as the probable factor driving the association between schizophrenia and non-right-handedness, thereby making a convincing case for the power of the meta-analytical approach, which, through data aggregation, might overcome methodological problems of individual studies. In addition, increasing the classification reliability of handedness has recently aided in clarifying the hypothesised seasonal pattern of birth months among left-handed men,\(^4\) a hypothesis for which the available previous evidence had been highly inconsistent.

We thus recommend utilising psychometrically validated scales, along with a trichotomous classification, in investigations on schizophrenia and handedness, expecting that mixed-handedness might turn out to be more relevant than left-handedness for explaining this link. Further, we recommend intensifying research specifically with regard to footedness, which might be more important with regard to brain lateralisation than handedness,\(^5\) and might provide more direct, and thus more robust, behavioural evidence for the links between schizophrenia and brain lateralisation.

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References
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