3   World Health Organization. *Suicide rates. Data by country*. WHO, 2016. Available at http://apps.who.int/gho/data/node.main.MHSUICIDE?lang=en (accessed 8 Dec 2016).

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Clozapine in treatment-resistant schizophrenia

In an era when 11 meta-analyses are published every day, there are sometimes 2 on the same topic which do not agree. As such a situation can be very confusing, systematic reviewers should discuss their findings in the light of existing reviews to make the differences understandable to readers.[1] In a pairwise meta-analysis by Siskind *et al*,[2] clozapine was shown to be superior to other first- and second-generation antipsychotics in treatment-resistant schizophrenia, which is in sharp contrast to our recently published network meta-analysis on the same topic.[3] As the publication of the two studies overlapped, the authors could not discuss the results of the other. Thus, readers might find themselves confused and unable to understand where the discrepancies lie.

First of all, there are differences in included trials. Siskind *et al* included studies in children and adolescents (Kumra 1996, 2008), whereas we did not because we considered that this population requires different pharmacological treatment from adult patients. They included Chinese studies (Cao 2003, Shaw 2006, Wang 2002), whereas we did not because it has been reported that studies from mainland China are often not reliable.[4] Moreover, Siskind *et al* included the study by McEvoy *et al* (from CATIE phase II) assuming that it was a blind trial, but this did not hold true for the crucial clozapine arm, which was open label. Last but not least, five studies (Breier 1999, Conley 2003, Daniel 1996, Honigfeld 1984 and McGurk 2005) were missed by our colleagues. There are also differences in the use of end-point or change data and the handling of short-term and long-term studies.

Finally, a major difference lies in the statistics applied in the two meta-analyses. Siskind *et al* conducted a pairwise meta-analysis, whereas we conducted both a network and a pairwise meta-analysis. But even in the pairwise meta-analysis alone, results differed. Siskind *et al* combined all comparator drugs versus clozapine, ignoring possible efficacy differences between the various comparators, which may explain the significant heterogeneity in many outcomes, limiting the robustness of the results. In our pairwise meta-analysis of all clozapine trials, even lumping the other antipsychotics and comparing them with clozapine revealed no significant difference in overall symptoms. We found clozapine to be better than the first-generation antipsychotics chlorpromazine and haloperidol, but not better than the second-generation antipsychotics olanzapine, risperidone and ziprasidone.

Whether the superiority of clozapine has been sufficiently proven by blinded trials is essential for clinical practice. Therefore, we and our Australian colleagues plan a joint re-analysis of these meta-analytic data.

Declaration of interest

In the past 3 years, S.L. has received honoraria for lectures from Eli Lilly, Lundbeck (Institute), Pfizer, Janssen, BMS, Johnson and Johnson, Otsuka, Roche, Sanofi, ICON, AbbVie, AOP Orphan, and Servier; for consulting/advisory boards from Roche, Janssen, Lundbeck, Eli Lilly, Otsuka, and TEVA; and for the preparation of educational material and publications from Lundbeck Institute

and Roche. Eli Lilly has provided medication for a clinical trial led by S.L. as the principal investigator.

1   Helfer B, Prosser A, Samara MT, Geddes JR, Cipriani A, Davis JM, et al. Recent meta-analyses neglect previous systematic reviews and meta-analyses about the same topic: a systematic examination. *BMC Med* 2015; **13**: 82.

2   Siskind D, McCartney L, Goldschlager R, Kisely S. Clozapine *v.* first- and second-generation antipsychotics in treatment-refractory schizophrenia: systematic review and meta-analysis. *Br J Psychiatry* 2016; **209**: 385–92.

3   Samara MT, Dold M, Gianatsi M, Nikolakopoulou A, Helfer B, Salanti G, et al. Efficacy, acceptability, and tolerability of antipsychotics in treatment-resistant schizophrenia: a network meta-analysis. *JAMA Psychiatry* 2016; **73**: 199–210.

4   Woodhead M. 80% of China's clinical trial data are fraudulent, investigation finds. *BMJ* 2016; **355**: i5396.

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Authors' reply: We agree with Samara and Leucht that clinicians can feel overwhelmed by the vast quantity of published meta-analyses and variety of methodologies. It is therefore important that protocols for potential meta-analyses are published on open access repositories such as PROSPERO to reduce the risk of duplication. Unfortunately, we were unaware of the 2016 Samara *et al*[1] meta-analysis at the time of conducting ours, as they did not register their protocol on PROSPERO, only including a protocol as a supplementary document at the time of publication.

The results of the two meta-analyses were broadly similar.[1,2] Our primary outcome, difference in total psychotic symptoms over the short and long term, showed that clozapine was not superior to other antipsychotics in long-term studies, which corresponds to the results of Samara *et al*. We did find that clozapine was superior to other antipsychotics for positive symptoms in the short and long term, an important finding for clinicians, patients and their carers.

There are key differences between the meta-analyses. First, Samara *et al* did not divide by study duration. We separated studies that reported data before 3 months from those that reported data after 3 months. We feel that it is inappropriate to include results from a 6-week study with those from a 78-week study. Second, unlike Samara *et al*, we conducted sensitivity analyses on the effects of pharmaceutical funding and found that studies without such funding favoured clozapine more strongly.

There remains debate as to the validity of network meta-analyses. They are at higher risk of bias, and require an underlying assumption that all included interventions should be jointly randomisable.[3] This is clearly not the case for people with treatment-refractory schizophrenia, as some will have previously been on the same antipsychotics that are the intervention arm of other trials.

We identified and excluded four of the five papers listed as 'missed' by Samara and Leucht as they did not have usable data. The other, Honigfeld (1984), provided 4-week data for total psychotic symptoms, which, when included, did not alter the short-term results. We note that Samara *et al* did not include Honigfeld (1984) in their analysis. Similarly, excluding McEvoy's partially blinded study made little difference.

Samara and Leucht were inaccurate regarding what was included in our meta-analysis. Although we included studies from different age groups, children were excluded on sensitivity analyses, making no difference to the results. We also reported sensitivity analyses of comparisons with first- and second-generation antipsychotics, as well as specific antipsychotics, in our original article.