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Routine enquiry about violence and abuse is needed for all mental health patients

I am pleased that Brooker and colleagues have highlighted their finding of poor recording of sexual violence and abuse in care programme approach (CPA) documentation in England.[1] It seems timely to highlight the international developments in this area, which are of relevance for staff seeing patients with mental disorders in general, not only patients receiving CPA support.

It is now well established that people with mental disorders are more likely to have been victims of violence and abuse (and/or to have witnessed it as children) than the general population, and that they continue to be at increased risk of being a victim of violence.[2,3,4] The World Health Organization (WHO) has a violence prevention strategy (http://www.who.int/violence_injury_prevention/violence/en/), and both the WHO and the World Psychiatric Association[5] have highlighted domestic and sexual violence as major determinants of mental ill health; a competency-based curriculum has recently been published for medical students and psychiatrists.[6] In the UK, the National Institute for Health and Care Excellence (NICE) public health guideline PH50 has recommended routine enquiry about experiences of domestic violence in mental health settings, and NICE clinical guideline CG89 recommends that childhood maltreatment is considered when assessing a range of physical, sexual and emotional problems. Violence and abuse, including physical, sexual and emotional abuse, are sadly still highly prevalent and, as England's Chief Medical Officer has argued, general practitioners and mental health professionals need to routinely ask people with mental health problems about current and historical violence and abuse.[3] However, routine enquiry alone is not enough; services need to train professionals so they know how to ask and respond sensitively and have protocols in place for appropriate care when violence or abuse is identified. In addition, there is a small but growing evidence base on the association between mental disorders and perpetration of domestic violence and abuse; therefore, domestic violence and abuse perpetration also need to be identified by mental health professionals for comprehensive risk assessment.[7]

Declaration of interest

L.M.H. was a member of the steering group at the World Psychiatric Association which wrote the competency-based curriculum,[6] and was a member of the NICE PH50 guideline development group.

1 Brooker CGD, Tocque K, Brown M, Kennedy A. Sexual violence and abuse and the care programme approach. *Br J Psychiatry* 2016; **209**: 359–60.

2 Khalifeh H, Johnson S, Howard LM, Borschmann R, Osborn D, Dean K, et al. Violent and non-violent crime against adults with severe mental illness. *Br J Psychiatry* 2015; **206**: 275–82.

3 Davies SC. *Annual Report of the Chief Medical Officer 2013, Public Mental Health Priorities: Investing in the Evidence.* Department of Health, 2014.

4 Anderson F, Howard L, Dean K, Moran P, Khalifeh H. Childhood maltreatment and adulthood domestic and sexual violence victimisation among people with severe mental illness. *Soc Psychiatry Psychiatr Epidemiol* 2016; **51**: 961–70.

5 World Psychiatric Association. *WPA Position Paper on Intimate Partner Violence and Sexual Violence Against Women.* WPA, 2016.

6 World Psychiatric Association. *The World Psychiatric Association (WPA) International Competency-Based Curriculum for Mental Health Care Providers on Intimate Partner Violence and Sexual Violence against Women.* WPA, 2016.

7 Oram S, Khalifeh H, Howard LM. Violence against women and mental health. *Lancet Psychiatry* 2017; **4**: 159–70.

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International suicide rates versus adequate treatments

Thornicroft and colleagues recently reported on the undertreatment of people with major depressive disorder (MDD) in 21 countries.[1] Their conclusions suggest that better diagnosis and treatment of major depression worldwide, particularly in low-income countries, should improve health outcomes. Such improvements should contribute, in particular, to reducing rates of suicide, which are closely associated with MDD.[2]

Accordingly, we considered relationships between the reported national rates of treatment for MDD overall or for identified cases who wanted treatment,[1] versus annual suicide rates as reported by the World Health Organization.[3] In data available from 12 countries of greater versus 8 of lesser wealth listed by Thornicroft *et al*,[1] annual suicide rates averaged 9.48 (95% CI 6.80–12.2) *v.* 5.31 (2.23–8.40) respectively per 100 000 ($t = 2.27$, $P = 0.04$). Rates of minimally adequate treatment of identified MDD cases differed correspondingly: 48.2% (40.9–55.5) *v.* 28.7% (14.0–43.4) among those who wanted treatment ($t = 3.01$, $P = 0.008$), and 23.4% (19.6–27.3) *v.* 7.36% (3.35–11.4) for MDD cases overall ($t = 6.28$, $P < 0.0001$). Moreover, there was a strong, direct, linear correlation between greater rates of treatment (by either measure) and higher suicide rates ($r_s = 0.644$, $P = 0.005$; slope for rates of treatment of those wanting it: 0.154 (0.049–0.260), $t = 3.09$, $P = 0.006$).

These observations are sobering in indicating: (a) surprisingly low observed rates of minimally adequate treatment for MDD, especially in less affluent countries, and (b) absence of lower suicide rates with greater rates of treatment. However, we propose that the various numerical estimates involved are susceptible to errors of ascertainment. Notably, the relatively low reported suicide rates in less affluent regions may, at least partly, reflect incomplete reporting. Low observed rates of treatment, instead, probably reflect complex differences that may include ascertainment errors, less access to care (lower clinician density and economic factors) and cultural factors, between relatively wealthy and poor countries. Efforts to reduce morbidity and mortality, including reduction of suicide risks, by improving recognition and treatment of MDD are highly laudable. However, their demonstration may require relatively challenging, within-region outcome measures, such as valid comparisons of suicide rates before versus after interventions aimed at improving clinical care.

1 Thornicroft G, Chatterji S, Evans-Lacko S, Gruber M, Sampson N, Aguilar-Gaxiola S, et al. Undertreatment of people with major depressive disorder in 21 countries. *Br J Psychiatry* 2017; **210**: 119–24.

2 Tondo L, Baldessarini RJ. Suicidal behavior in mood disorders: response to pharmacological treatment. *Curr Psychiatry Rep* 2016; **18**: 88–99.

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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.