Correspondence

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Analysing the efficacy of clozapine

Dr Moncrieff (2003) has suggested that the advantage of clozapine in treatment-resistant schizophrenia, when compared with conventional antipsychotics, may not be substantial. This appears to be discordant with an earlier meta-analysis (Wahlbeck *et al*, 2000). As clozapine's advantage in treatment-resistant schizophrenia is well accepted in psychiatry and is reflected in most practice guidelines, any questions about its validity need careful scrutiny. Clues to the disagreement between meta-analyses on the same topic can often be found in the studies that are included or excluded, the ways in which the data are abstracted and in the interpretation of the results (Jadad *et al*, 1997).

Dr Moncrieff included two studies in her analysis that were not in the earlier meta-analysis: Essock *et al* (1996) and Kane *et al* (2001).

The Essock *et al* (1996) study was a naturalistic study with serious methodological deficiencies from the perspective of determining efficacy of clozapine treatment. The randomisation was imperfect. The study was not blinded. The study population was poorly defined in terms of diagnosis. Later application of the Structured Clinical Interview for DSM–III–R Personality Disorders to a subgroup of the study population picked up diagnoses including bipolar disorder, organic mood disorder and one case of 'no disorder'. 'Crossovers' were allowed, with nearly 66% of the control group receiving clozapine at some time. There was no restriction on the prescription of other medications, with patients in both groups receiving other psychotropic medications, including other antipsychotics. An intention-to-treat analysis would be meaningless given the number of crossovers. Also, analysis of data with crossovers excluded is unlikely to be informative as it would end up comparing a small subgroup of responders in either arm of the study. The validity of including this study in the meta-analysis is questionable. This is particularly relevant as the 'forest plot' in Moncrieff's analysis reveals that this is the only study where the effect size is in the opposite direction (i.e. unfavourable to clozapine). Thus, inclusion of this study would dilute the effect size of clozapine and vice versa.

Moncrieff's handling of the data from the Kane *et al* (2001) study also raises questions. In this longer-duration study, patients in both the control and experimental groups were allowed to drop out if they were not responding to the given treatment. A non-intention-to-treat analysis, as Dr Moncrieff has done, would end up comparing a small subgroup of responders in either group. An intention-to-treat analysis would have captured clozapine's strength; that is, showing that more patients on clozapine responded in comparison with the control group.

Despite these observations, Moncrieff's analysis produced an effect size of 0.38 (0.44 using a random effects model). In my opinion, this is not unimpressive given that clozapine is being compared with other medications with proven efficacy and not placebo.

Declaration of interest

I have attended local educational meetings sponsored by Novartis.

Essock, S. M., Hargreaves, W. A., Covell, N. H., *et al* (1996) Clozapine's effectiveness for patients in state hospitals: results from a randomized trial. *Psychopharmacology Bulletin*, **32**, 683–697.

Jadad, A. R., Cook, D. J. & Browman, G. P. (1997) A guide to interpreting discordant systematic reviews. *Canadian Medical Association Journal*, **156**, 1411–1416.

Kane, J., Marder, S. R., Schooler, N. R., *et al* (2001) Clozapine and haloperidol in moderately refractory schizophrenia: a 6-month randomized and double-blind comparison. *Archives of General Psychiatry*, **58**, 965–972.

Moncrieff, J. (2003) Clozapine *v.* conventional antipsychotic drugs for treatment-resistant schizophrenia: a re-examination. *British Journal of Psychiatry*, **183**, 161–166.

Wahlbeck, K., Cheine, M., Essali, A., *et al* (2000) Clozapine versus typical neuroleptic medication for schizophrenia. *Cochrane Library*, issue 3. Oxford: Update Software.

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Dr Moncrieff (2003) re-analysed the data of a Cochrane meta-analysis by Wahlbeck *et al* (2000) on the comparison between clozapine and conventional antipsychotic drugs for treatment-resistant schizophrenia. After selecting nine randomised controlled trials and analysis she concluded that the Cochrane review might have overestimated the effects of clozapine as she found a lower overall effect. This was explained by the use of data from intention-to-treat analysis in the largest included study by Rosenheck *et al* (1997) and inclusion of the large study by Essock *et al* (1996), which was excluded in the Cochrane review.

There are good reasons for reporting the results from the studies by Rosenheck *et al* (1997) and Essock *et al* (1996) separately from the other seven studies rather than giving the overall results. These two studies are long-term studies with durations of 1 and 2 years, respectively. The study populations were much larger than most of the other studies, which were short-term studies lasting 6–29 weeks. The two long-term studies found a small to no difference in treatment effect between clozapine and the conventional antipsychotic. These results have a large negative impact on the overall effect because of the large study populations. However, the use of intention-to-treat analysis will result in smaller differences between the clozapine and control group the longer the study lasts, because drop-outs are classified as relapses irrespective of the reason for discontinuation. Longer studies tend to have larger drop-out rates, as is also apparent in this meta-analysis, resulting in smaller differences between study groups.

Reporting the results from the short-term and long-term studies separately will probably show that clozapine has a higher treatment effect than that reported by Moncrieff. Short-term studies explore the pharmacological efficacy of a medicine whereas long-term studies explore the treatment effect in daily practice and can be influenced by the patient's willingness to continue treatment. These results should be reported separately.

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Rosenheck, R., Cramer, J., Xu, W., *et al* (1997) A comparison of clozapine and haloperidol in hospitalized patients with refractory schizophrenia. Department of Veterans Affairs Cooperative Study Group on Clozapine in Refractory Schizophrenia. *New England Journal of Medicine*, **337**, 809–815.

Wahlbeck, K., Cheine, M., Essali, M. A., *et al* (2000) Clozapine versus typical neuroleptic medication for schizophrenia. *Cochrane Library*, issue 3. Oxford: Update Software.

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Author's reply: Dr Karunakaran rightly points out some problems with the interpretation of the Essock *et al* (1996) naturalistic study of clozapine. However, despite its imperfections, that study deserves some attention, both because it was a large study and because its naturalistic design attempted to replicate the conditions in which clozapine would be given in real clinical practice. The randomisation was not imperfect but unbalanced. The study was indeed not blinded, but this usually favours the experimental treatment, in this case clozapine. Application of the Structured Clinical Interview for DSM–IV confirmed that 95% of cases had a diagnosis of schizophrenia or schizoaffective disorder. It is indeed difficult to decide what outcome data to use, as I mention in my paper. However, despite the number of crossovers, an intention-to-treat analysis in such a large sample would be expected to show some difference if the effect of clozapine is substantial. In the Kane *et al* (2001) study I did use intention-to-treat data, but also repeated the analysis with non-intention-to-treat data, because of the curiously high drop-out rate in the comparison group.

My analysis was meant to draw attention to the fact that results of different studies are quite discrepant. The largest study to date, and one that appears to be methodologically robust, found only slight differences between clozapine and haloperidol, which are of doubtful clinical relevance (Rosenheck *et al*, 1997). In this situation simply quoting the results of a meta-analysis may be misleading.

Dr Kho is right to point out that long-term studies find smaller effects. This cannot be attributed to drop-out rates in the Rosenheck *et al* (1997) study, at least, where the higher drop-out rate in the haloperidol group would tend to produce an inflated difference between clozapine and the comparator drug. We also cannot assume that short-term studies simply measure pharmacological effects and long-term studies are confounded by non-compliance. Drugs may have different short- and long-term pharmacological effects. Short-term studies might be more likely to be confounded by non-specific factors such as differential expectations of treatments.

Essock, S. M., Hargreaves, W. A., Covell, N. H., *et al* (1996) Clozapine's effectiveness for patients in state hospitals: results from a randomized trial. *Psychopharmacology Bulletin*, **32**, 683–697.

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Parental age difference and schizophrenia

To offer hypotheses based simply on clinical experience is pathetically out of date. Perhaps it may be allowed, for a moment, in deference to my advancing years.

Fifty years ago, with some other purpose in mind, I surveyed some 370 cases of schizophrenia in young men. It struck me that, with mild but undue frequency, there was a tendency for their parents' ages to be unusual in one of two ways – either by there being a >10-year age difference in the couple, or by the mother being older than the father. In decades of practice since, my impression has remained that this association with schizophrenia occurs a little too often to be accidental. Of course, to prove that would have required time, money, thousands of cases, and the inclination to undertake a major statistical enterprise, and none of those was in my reach.

It is therefore gratifying now to find that, at long last, my hypothesis has been solidly supported, albeit inadvertently, by Zammit *et al* (2003). They demonstrate, in a 26-year follow-up of some 50 000 teenagers, that advancing paternal age is a risk factor for schizophrenia, while maternal age is not – the latter being a significant negative finding to which, however, they pay no further attention. Since this means that, compared with the normal population, people with schizophrenia tend to have fathers who are older but mothers who are not, it follows necessarily that the age difference between the parents also tends to be greater than in the general population.

This does away with Zammit *et al*'s hypothesis that advancing paternal age is pathogenic for schizophrenia by virtue of increasing germ cell mutations. There is no need to invoke genetic mutation with age, given the linkage they have uncovered, in passing, between parental age difference and schizophrenia. A more economical hypothesis is that to be born to a statistically off-centre parental couple is a risk factor for schizophrenia – or, in more ordinary language, there is some psychological risk in being the child of an odd couple.

Are there other social oddities waiting to be identified statistically in schizophrenogenic couples?

Zammit, S., Allebeck, P., Dalman, C., *et al* (2003) Paternal age and risk for schizophrenia. *British Journal of Psychiatry*, **183**, 405–408.

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Authors' reply: Dr Bourne suggests that as advancing paternal, but not maternal age is associated with schizophrenia, then people with schizophrenia tend to have fathers who are older than the normal population, but mothers who are not. This is incorrect. In our study, as others have previously shown, advancing maternal age *is* associated with schizophrenia, but this association can be explained by paternal age, a consequence of the fact that there is strong correlation between parental ages.

Dr Bourne makes an interesting point, however, based on his observations in clinical practice that large differences in parental ages may result in some sort of psychological risk factor for schizophrenia in the offspring. In fact, the absolute difference between parental ages in our study is associated with schizophrenia in the crude analysis, but this association is eliminated after adjusting for the effects of paternal age (Table 1). As paternal age increases,

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