

Correspondence

EDITED BY KHALIDA ISMAIL

Contents ■ Analysing the efficacy of clozapine ■ Parental age difference and schizophrenia ■ Physical illness and schizophrenia ■ Antidepressant effects of repetitive transcranial magnetic stimulation ■ Evidence in cannabis research ■ MRCPsych exams

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.

S. Karunakaran Kirwan Rehabilitation & Extended Care Unit, 138 Thuringowa Drive, Kirwan, Townsville, Queensland 4817, Australia

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.