Correspondence

EDITED BY KHALIDA ISMAIL

Contents

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.


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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term studies find smaller effects. This meta-analysis may be misleading.

relevance (Rosenheck)
light differences between clozapine and schizophrenia: a re-examination.

however, despite its imperfections, that study does not rely on the comparator drug. We also cannot be attributed to drop-out rates in the Kane et al. 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.

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Dr Bourne suggests that as advancing paternal 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 paternal 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,
The difference between maternal and paternal ages must also increase given the biological age threshold for motherhood. However, in younger fathers with older mothers, even large differences in paternal ages is not associated with increasing risk of schizophrenia. In contrast, the association between advancing paternal age and risk of developing schizophrenia is not altered by adjusting for parental differences. The hypothesis of increasing germ cell mutations remains the most likely explanation for this association between advancing paternal age and risk of schizophrenia.

Antidepressant effects of repetitive transcranial magnetic stimulation

The report by Martin et al. (2003) seems in conflict with previous meta-analyses of repetitive transcranial magnetic stimulation (rTMS) (Holtzheir et al., 2001; McNamara et al., 2001; Burt et al., 2002). We wish to provide a broader context for interpreting these results.

The analysis by Martin et al. was designed to minimise type 1 error – to identify the level of confidence that can be placed in purported antidepressant effects of rTMS. It combined only studies with similar methodologies, included only studies that met high standards of randomisation and blinding, and analysed only end-point depression ratings (rather than analysing change scores or controlling for baseline depression severity). With this approach, the review found a statistically significant effect size for high-frequency (>1 Hz) rTMS applied to the left prefrontal cortex (-0.35, 95% CI -0.66 to -0.04, P<0.03), but did not find evidence that antidepressant effects were clinically significant or that they persisted over time.

The other meta-analyses attempted to minimise type 2 error – to identify whether there is reason to believe that rTMS might have significant antidepressant properties warranting further investigation. They combined studies with different methodologies and calculated effect sizes based on changes in depression severity over time. Such a technique can be important when analysing studies where different treatment arms may start at different baselines. Using these analytic techniques, prior meta-analyses found effect sizes for high-frequency, left prefrontal rTMS ranging from 0.5 to 0.8, suggesting that rTMS does
indeed have statistically significant antidepressant effects. However, these analyses all agree that the clinical significance of these effects is not yet established.

The results of the Martin et al review do not suggest at all that rTMS has no antidepressant effects. On the contrary, this methodologically rigorous review identifies statistically (but not clinically) significant, short-term antidepressant effects for 2 weeks of high-frequency, left prefrontal rTMS and recommends further studies to establish efficacy and identify optimal parameters. Even more importantly, numerous studies have shown that rTMS alters brain functioning, with effects ranging from altered gene expression in animals to modified cerebral perfusion in humans; in many cases, these effects are very similar to those seen with established antidepressant treatments.

With these points in mind, we offer the following recommendations to help guide use of rTMS in clinical and research settings.

(a) Given the small clinical effects seen with rTMS in studies to date, it does not seem that rTMS is appropriate for widespread clinical use at this time.

(b) Large, multi-site trials are warranted to clarify the antidepressant effects of rTMS.

(c) Future studies of rTMS should incorporate several improvements in study design, including appropriate (and well-documented) randomisation, adequate blinding of subjects and therapists (probably requiring an improved sham condition), and better assessment of the duration of any antidepressant effects.

(d) More research should be directed at clarifying which patient and treatment characteristics might lead to greater antidepressant effects with rTMS.

(e) More research should be directed at identifying and testing potential mechanisms by which rTMS produces antidepressant effects.

Evidence in cannabis research

The article by Coffey et al (2003) regarding adolescent precursors of cannabis dependence has a number of substantial problems in the measures used, the analysis of data and the reporting and discussion of their findings. One of the study’s major findings is that the 'relationship between cannabis dependence and persistent frequent drinking in adolescence changed direction, from a risk association in the univariate model to a protective association in the adjusted model' (Coffey et al, 2003: p. 333, emphasis added). The use of the term protective implies causality, rather than the negative correlation which more accurately portrays the statistical relationship. It also tacitly implies a value judgement that heavy drinking is preferable to cannabis dependence.

This study utilises logistic regression for the majority of its statistical analysis without adequately considering some important caveats. First and foremost, as already mentioned, correlation does not equal causality. This is particularly the case when there are a substantial number of independent variables associated with the dependent variable. In the case of cannabis use, as the authors point out, there are many independent variables related to cannabis use, such as socio-economic status (not discussed), parental drug use patterns (not discussed), antisocial behaviour, cigarette smoking and level of education, to name a few that are known. Statistical texts (e.g. Gravetter & Wallnau, 1996) point out that to gain the best measure from the use of logistic regression, there should be few independent variables that are unrelated to each other and that a regression solution is extremely sensitive to the combination of variables that is included in it” (Tabachnick & Fidell, 1996: p. 126).

These issues are particularly concerning when such papers can be reported in the mass media (as this study was) on a topic such as cannabis use, which generates strong public responses and is the forum for a great deal of misinformation and manipulation of research results to suit political and ideological agendas. The simple acknowledgement of study limitations would substantially improve the quality of the debate surrounding such a complex social, psychological and medical problem.


The media response to Coffey et al (2003) was predictable. ‘Anti-drug campaigners say new research, showing one in three teenagers who smokes cannabis weekly becomes hooked by their early 20s, proves that it should not be treated as a “soft” drug. The shocking study found teens who used cannabis every week were at high risk of addiction’ (Lawrence, 2003). Coffey is quoted as saying, ‘The message here is that
cannabis is not as harmless as we had thought earlier’ – an amazing conclusion from a study where only 1% of the respondents identified as dependent reported social consequences of their use, while the most prevalent symptom (10%) was persistent desire. In everyday parlance, they smoked because they liked it.

Use of the very broad categorisations of the DSM is especially worrisome. Clinicians using these guidelines apply them to people presenting with problems. The use of such categorisations in research, however, constitutes imprecise criteria to determine a person’s dependence, resulting in the phenomenon being grossly overreported.

Researchers have been able to generate dependency by applying these same criteria to behaviours as diverse as jogging, shopping, sex, prayer and mountain climbing. In fact, these activities were found to be as addictive as cannabis (Franklin, 1990).

Problems include the disjunctive nature of the criteria (dependency can be ascribed to two people with absolutely no symptoms in common), and the essentially subjective way in which the characteristics are defined. The lack of specificity in the measurement of cannabis dependence results in subjective measures being presented as objective and an over-reliance on the interpretive framework brought to bear. How did the authors differentiate between ‘wants’ and what DSM characterises as ‘needs’? Was this differentiation communicated to respondents? The study fails to differentiate respondents with no dysfunction associated with their dependence from those with significant cannabis-related problems.

Finally, the only index of consumption employed is frequency of use. This is most unsatisfactory; a ‘smoke’ is not a standardised measure and the consequent lack of any demonstrable association between tetrahydrocannabinol consumption and the dependence syndrome begs the question, dependent on what? Preparing a joint? Inhaling deeply?

**Authors’ reply:** In response to Dr Miller we would like to state some general principles, to clarify our methodology and provide some additional results. First, we have no argument with the truism that causality cannot be inferred from correlation. Dr Miller seems to overlook the fact that, despite widespread awareness of the dangers of determining causality, the terms ‘risk’ and ‘protective’ are commonly used to describe associations identified in longitudinal studies. Indeed, identifying and interpreting such associations is the primary reason for conducting cohort studies. The reiteration of standard caveats should not be necessary in every article arising from these studies and would make for very tedious reading indeed.

The potential for inadequate control of confounding by unmeasured or omitted confounding factors is always a possibility in any multivariate analysis. Researchers are inevitably constrained by the measures they have at their disposal which, in turn, result from the constraints of research directions, design, responder burden and so on. Dr Miller criticises us for omitting standard measures while including correlated measures. In terms of the former, we assessed the influence of both parental education and metropolitan residence on cannabis dependence but as there was no evidence of univariate associations for either measure they were unlikely to be confounders (parental education, reference group ‘some secondary school’: OR 0.8 (95% CI 0.5–1.3); incomplete secondary OR 1.0 (95% CI 0.6–1.6); school in metropolitan Melbourne: OR 1.0 (95% CI 0.6–1.5)). As they were uninformative, these findings were omitted from the article in the interests of parsimony and conserving space. As the report focused on adolescent behavioural and mental health predictors of cannabis dependence, both parental substance use and peer substance use, although likely to be predictors, were not considered relevant to the question. Indeed, they were omitted from the analysis as their inclusion could have masked the associations of interest, exactly as Dr Miller describes.

We acknowledge that confounding occurred between some of the explanatory measures included in the multivariate analysis. We illustrated and discussed in some detail the confounding that occurred between early-onset cannabis use, cigarette smoking and antisocial behaviour. Furthermore, the interaction between problematic alcohol use and weekly cannabis use to which Dr Miller objects arose as post hoc examination of confounding.

Mr Palmer misunderstands the denominator of the reported symptom prevalences: we described overall symptom prevalence in the 1601 participants. Symptom prevalences in participants classified as being cannabis dependent were reported in an earlier publication and were: tolerance 17%, withdrawal 74%, unintentioned use 84%, persistent desire 91%, excessive time spent obtaining, using or recovering from use 74%, social consequences of use 18% and continued use despite acknowledged health problems 63% (Coffey et al, 2002). Furthermore, participants classified as dependent cannabis users reported compulsive and out-of-control use more frequently than those classified with dependent alcohol use. That there is gathering evidence of social, physical and mental health harm, including dependence, arising from long-term cannabis use is now beyond debate. For a brief and informative review of the current literature on this topic see Ashton (2002).

Mr Palmer debates what really constitutes cannabis dependence. That young people ‘are smoking because they like it’ does not preclude the possibility that they may be dependent. Alternatively, they may be using it to stop feeling awful, in the self-medication paradigm. He quotes an assertion that other non-challenging behaviours performed persistently may also fit dependence criteria. This may be so, but the harm that arises from these activities is a moot point. The issue that concerns us, and that we used the current gold standard instrument in population research to identify, is that cannabis dependence inevitably prolongs heavy use. No measure applied at interview can be considered to be completely sensitive and specific for all the reasons that Mr Palmer states but the unreported assertion that the ‘phenomena [are] grossly overreported’ is unsupportable in the light of extensive developmental and confirmatory work performed in treatment and non-treatment settings (e.g. Nelson et al, 1999). We do not consider it a problem that individuals can be classified as dependent with different combinations of symptoms – conversely, we need to increase our understanding of symptom combinations and their significance (Nelson et al, 1999).

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**Lawrence, J. (2003)** Teenagers addicted to pot. Sunday Mail (Queensland), 6 April.

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The final point that Mr Palmer makes is to query the validity of our measure of cannabis use. He appears to have misread the definition – we did not ask about ‘smokes’ at all. We asked participants how often they ‘used cannabis’ without specifying the method of delivery. We assume the word ‘used’ is unambiguous and involves ingestion in some manner.

Finally, we follow no political agenda but seek only to inform the general public and policy makers using sound epidemiological evidence resulting from good study design, careful analysis and cautious interpretation. Our article represents a step towards filling the evidence void in the current polarised debate about important public health and policy issues surrounding cannabis use (Strang et al, 2000).


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MRCPSych exams
I read with interest the informative editorial on the MRCPSych examination by Dr Tyrer and Professor Oyebode (2004). I agree with the authors’ view that examinations require continuous assessment and refinement and also note their admission that political and external factors are likely to drive further changes.

However, I am still puzzled to note their ambiguity over defining the direction of change in the future. They give three examples of potential future directions: modularisation of courses with assessment at the conclusion of modules; continuation of high-stakes tests; and regrading of the record of in-service training (RITA) as an exit examination at the completion of higher specialist training. However, their description of these examples is vague.

This is an era of heightened societal expectations, increased regulatory control and external scrutiny of professionals. There remains at least a theoretical possibility of external quality assurance standards and mechanisms being imposed on the medical Royal Colleges, including the Royal College of Psychiatrists.

Eraut (1994) has argued that a professional’s competence has at least two dimensions, scope and quality. Scope concerns what a person is competent in – the range of roles, tasks and situations for which their competence is established or may be reliably inferred. Quality concerns judgements on the quality of that work along a continuum. Determining the acceptable and measurable cut-off points on the quality dimension for senior house officers, specialist registrars and consultants remains an important task for the profession.

Schon (1987) has argued that if professionals are blamed for ineffectiveness and impropriety, their schools are blamed for failing to teach the rudiments of effective and ethical practice. Greater emphasis on the processes of training, reflective practice, training the trainers, continuing professional development, relevant educational research and interprofessional learning would help to sustain and enhance the profile of psychiatry in the society. The profession requires a clear direction from its leaders.

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Authors’ reply: We have noted Dr Faruqui’s comments on our editorial. Dr Faruqui believes we should be more specific about recommendations for psychiatry examinations in the future, and argues that we have been ambiguous in not defining the format for future psychiatry examinations in more detail.

The Royal College of Psychiatrists is not able independently to direct the course of examinations in the future. The Postgraduate Medical Educational and Training Board has indicated what principles should hold in postgraduate examinations, and the Royal College of Psychiatrists follows these as well as observing the practices of the other medical Royal Colleges.

There is a move to include workplace assessments as part of the panoply of assessment of competence. The methods to achieve this have not yet been fully described or, indeed, evaluated. The degree to which this kind of assessment will form part of the assessment of a candidate in a future MRCPsych examination has not been made explicit.

This is the present state of affairs. We are not expressing our own opinions in this part of the editorial; we are indicating the present state of play. We believe that competence is judged by public examinations and that performance is measured by workplace assessments that approximate to what occurs in the real world. Quality of work is not assessed in examinations and we do not believe that this is part of the remit of examination boards.

Declaration of interest
S.T. is the immediate past Chief Examiner of the Royal College of Psychiatrists and F.O. is the present Chief Examiner and is a member and examiner of the Professional Licensing Assessment Board of the General Medical Council.

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