

Correspondence

Edited by Kiriakos Xenitidis and
Colin Campbell

Contents

- Extrapyramidal side-effects and antipsychotics: are second-generation agents still indicated?
- Epidemiological challenges in systematic reviews

Extrapyramidal side-effects and antipsychotics: are second-generation agents still indicated?

Peluso *et al* report on the differential effect of first-generation antipsychotics (FGAs) *v.* second-generation antipsychotics (SGAs) in ameliorating or exacerbating extrapyramidal side-effects (EPS) in a secondary analysis of the CUTLASS-1 trial data.¹ They report their findings as ‘essentially null’ and mention that there is weak evidence for clinically significant differences in emergent or relieved EPS between FGAs and SGAs. These findings, although based on a secondary analysis, pose interesting and important challenges for the focus of future research, but also raise some questions about the interpretation of negative study findings.

The majority of participants (49%) in the FGA group were prescribed sulpiride, a substituted benzamide that has been demonstrated in a meta-analysis to have a significantly lower propensity to cause EPS than other FGAs.² It could be argued that it would not be unusual to find little difference between the two groups, as the FGA group was biased towards sulpiride selection.

A priori odds ratios of 2 and 0.5 were selected as clinically relevant, but no reason is given for this choice. The choice of this cut-off seems arbitrary. The authors conclude that their results are ‘essentially null’ and that these two classes of drugs could be used with equivalence in EPS. Although equivalence is possible, failure to reject the null hypothesis does not imply that the null hypothesis is true or that treatments are equal.³ Failure to reject the null at this effect size means that the null would not be surprising at this particular value.⁴ However, given a power of 78%, this implies a relatively high chance (22%) of a type 2 error. In some cases, even a reduction of 20% in EPS occurrence can be clinically meaningful. The CUTLASS study would be underpowered even if a true effect existed at this effect size. Confidence limits around the EPS outcomes also appear to be wide at a number of time points. Although negative findings in superiority trials are important to report, it should be noted that some may argue that meaningful scientific evidence centres on replicated falsification.

In turn, the dichotomisation of EPS outcome measures, instead of using changes in continuous EPS scores over multiple time points in a longitudinal design and analysis strategy, could potentially underestimate any treatment effect.

Nevertheless, these findings raise important points for the design of superiority trials. Given the lack of superior efficacy in symptom relief of most SGAs, if the presence of EPS has become the *sine qua non* for treatment switches to SGAs, would this not highlight the importance of adequately powered trials where the primary outcome would be EPS? In addition, in trials where EPS is only a secondary outcome, as is commonplace, is it not necessary that this outcome be adequately powered at well-motivated, pre-agreed effect sizes? Although of global importance in the current economic climate, this would be particularly important for low- and middle-income countries where funding authorities meticulously scrutinise the benefits of more expensive treatments.

- 1 Peluso MJ, Lewis SW, Barnes TRE, Jones PB. Extrapyramidal motor side-effects of first- and second-generation antipsychotic drugs. *Br J Psychiatry* 2012; **200**: 387–92.
- 2 Soares BG, Fenton M, Chue P. Sulpiride for schizophrenia. *Cochrane Database Syst Rev* 2000; **2**: CD001162.
- 3 Nickerson RS. Null hypothesis significance testing: a review of an old and continuing controversy. *Psychol Methods* 2000; **5**: 241–301.
- 4 Aberson C. Interpreting null results: Improving presentation and conclusions with confidence intervals. *Journal of Articles in Support of the Null Hypothesis* 2002; **1**: 36.

Henk S. Temmingh, Consultant Psychiatrist and lecturer, Acute Adult Admissions Unit, Department of Psychiatry, University of Cape Town, Valkenberg Hospital, Private Bag X1, Observatory, South Africa. Email: henk.temmingh@uct.ac.za

doi: 10.1192/bjp.2013.247

Authors’ reply: We thank Dr Temmingh for his interest in our paper.¹ The use of sulpiride in CUTLASS-1 was discussed in the original report² and subsequent correspondence.³ The Cochrane review of sulpiride in schizophrenia⁴ concluded that extrapyramidal side-effects (EPS) may be less frequent for individuals taking sulpiride but that no result regarding either direct or proxy measures of EPS reached statistical significance. Moreover, the review includes a report that sulpiride seemed to cause problems with increased prolactin levels and galactorrhoea.⁵ Claims that the drug shows particular efficacy against negative symptoms were not supported by trial data. Thus, any evidence that sulpiride is a particularly atypical typical antipsychotic is, at best, not strong. It is similar to amisulpride in its chemical structure and receptor pharmacology, with highly selective affinity for pre- and post-synaptic D₂ and D₃ receptors,⁶ characteristics of both drugs that question the validity of the typical *v.* atypical classification.

We acknowledge in the paper¹ that a cautious approach is needed when undertaking a secondary analysis of any trial data because sample size will have been predicated on the primary, not secondary, hypothesis, and because many hypothesis tests may be undertaken; type 1 and 2 statistical errors lie in wait even for a Cochrane review. That is why we defined a doubling or halving of EPS as a clinically meaningful effect size to use in conjunction with significance testing. This was a matter of clinical judgement rather than being completely arbitrary. Like the conventional 5% cut-off used in significance testing, we hope it has some value while acknowledging that all these decisions are subject to controversy.⁷ In deciding to dichotomise EPS in this way, we were aiming to keep things simple and avoid erroneous conclusions from multiple secondary analyses.

We agree that the findings raise important points for the design of superiority (and non-inferiority) trials, and for crucial policy decisions based on health economic evidence. However, we hope that the findings may also remind clinicians that older antipsychotic drugs may be worth a thought when trying to find the right medicine for a particular patient.

Declaration of interest

In the past 3 years, S.W.L. has received advisory board fees from Janssen-Cilag and speaker fees from AstraZeneca; T.R.E.B. has spoken at an event sponsored by Lilly; P.B.J. is a member of a scientific advisory board for Roche, and has received research support from GlaxoSmithKline and a speaker fee from Lilly.

- 1 Peluso MJ, Lewis SW, Barnes TRE, Jones PB. Extrapyramidal motor side-effects of first- and second-generation antipsychotic drugs. *Br J Psychiatry* 2012; **200**: 387–92.
- 2 Jones PB, Barnes TR, Davies L, Dunn G, Lloyd H, Hayhurst KP, et al. Randomized controlled trial of the effect on Quality of Life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the

Latest Antipsychotic Drugs in Schizophrenia Study (CUTLASS 1). *Arch Gen Psychiatry* 2006; **63**: 1079–87.

- 3 Jones PB, Barnes TRE, Elton P, Davies L, Dunn G, Lloyd H, et al. First- vs second-generation antipsychotic drugs in schizophrenia – reply. *Arch Gen Psychiatry* 2007; **64**: 979–80.
- 4 Soares BG, Fenton M, Chue P. Sulpiride for schizophrenia. *Cochrane Database Syst Rev* 2000; **2**: CD001162.
- 5 Weizman A, Maoz B, Treves I, Asher I, Ben David M. Sulpiride-induced hyperprolactinemia and impotence in male psychiatric outpatients. *Prog Neuropsychopharmacology Biol Psychiatry* 1985; **9**: 193–8.
- 6 Schoemaker H, Claustre Y, Fage D, Rouquier L, Chergui K, Curet O, et al. Neurochemical characteristics of amisulpride, an atypical dopamine D2/D3 receptor antagonist with both presynaptic and limbic selectivity. *J Pharmacol Exp Ther* 1997; **280**: 183–97.
- 7 Glaser DN. The controversy of significance testing: misconceptions and alternatives. *Am J Crit Care* 1999; **8**: 291–6.

Michael J. Peluso, MPhil, Yale School of Medicine, Harkness Hill, ESH 219, 367 Cedar Street, New Haven, CT 06510, USA. Email: michael.peluso@yale.edu; **Shôn W. Lewis**, MD, University of Manchester; **Thomas R. E. Barnes**, DSc, Centre for Mental Health, Imperial College London; **Peter B. Jones**, MD, PhD, Department of Psychiatry, University of Cambridge, and Early Intervention Services for Cambridgeshire & Peterborough NHS Foundation Trust (CAMEO), UK

doi: 10.1192/bjp.2013.247a

Epidemiological challenges in systematic reviews

We agree with Brugha and colleagues that the field of psychiatric epidemiology poses particular challenges to systematic reviewers.¹ Heterogeneity between studies may arise from differences in outcomes and it is certainly true that psychiatry still lacks ‘biologically based gold standards’ regarding their definition. However, we disagree that these are necessarily linked. For the purpose of systematic reviews and meta-analyses, the issue is not to what extent an outcome is definable, with biological tests or otherwise; rather, how comparable individual studies are in their measurement of whatever outcome they use. For example, studies of schizophrenia defined by standard diagnostic tools such as the ICD-10, and applied using common operationalised criteria, should be looking at the same construct to a large extent. Definitions of physical health conditions also vary, even when specific tests are available for diagnosis. For example, definition of hypertension is not the same across national guidelines used in the USA and Europe.^{2,3} We acknowledge that differences exist in psychiatry between diagnostic tools which attempt to define the same or similar conditions, such as schizophrenia in ICD-10 v. DSM-IV. Often studies include outcomes such as psychotic, depressive or other symptoms instead of a diagnostic category, which can make comparison harder. Therefore, we recommend systematic reviews pay close attention to how outcome is defined in individual studies so that they are comparable. This should be considered as part of mandatory reporting of individual study quality in systematic reviews, as we have recently done,⁴ and as Brugha *et al* rightly encourage. Biologically based outcomes may help in due course but, currently, attention needs to be focused on the principle of comparability of outcomes we have now.

Another important contributor to heterogeneity is variation in exposure measurement which we think needs to be emphasised. In our systematic review and meta-analysis of premorbid IQ in schizophrenia, we found that the effect size varied as a result of differences in IQ testing methods and age at testing.⁵ Therefore,

as well as ensuring that measurement of exposure is similar across included studies, differences should be explored further by subgroup and sensitivity analysis.

With regard to meta-analysis, combining methodologically incomparable studies will have serious implications for the validity and generalisability of findings. For example, a pooled odds ratio of 1.34 was reported for schizophrenia for exposure to herpes simplex virus type 2 (HSV-2) in a recent meta-analysis.⁶ Unfortunately, this tells us very little because the reviewers conflated studies which considered HSV-2 infection in early life and subsequent schizophrenia (i.e. prospective designs) with those which considered the prevalence of infection in people with established schizophrenia (i.e. a cross-sectional design). Such differences may not be picked up by tests for heterogeneity. The responsibility for establishing that individual studies are sufficiently comparable in design and other aspects in order to justify combining their results in a meta-analysis lies with researchers conducting systematic reviews, as well as with the reader.

It was not clear from the meta-review how many original reviews followed some kind of guidelines. Guidelines for reporting of systematic reviews, including those of observational studies, already exist, such as Preferred reporting Items for Systematic reviews and Meta-Analyses (PRISMA) and Meta-analyses Of Observational Studies in Epidemiology (MOOSE). They include comprehensive checklists for the assessment, for example, of outcome, exposure, effects of bias and confounding in individual studies. We believe more widespread use of these guidelines, something that can be mandated by journal editors and peer reviewers, should greatly increase comparability of individual studies, and overall, lead to an improvement in the quality of systematic reviews and meta-analyses.

- 1 Brugha TS, Matthews R, Morgan Z, Hill T, Alonso J, Jones DR. Methodology and reporting of systematic reviews and meta-analyses of observational studies in psychiatric epidemiology: systematic review. *Br J Psychiatry* 2012; **200**: 446–53.
- 2 Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo Jr JL, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; **289**: 2560–72.
- 3 Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2007; **28**: 1462–536.
- 4 Kirkbride JB, Errazuriz A, Croudace TJ, Morgan C, Jackson D, Boydell J, et al. Incidence of schizophrenia and other psychoses in England, 1950–2009: a systematic review and meta-analyses. *PLoS One* 2012; **7**: e31660.
- 5 Khandaker GM, Barnett JH, White IR, Jones PB. A quantitative meta-analysis of population-based studies of premorbid intelligence and schizophrenia. *Schizophr Res* 2011; **132**: 220–7.
- 6 Arias I, Sorlozano A, Villegas E, de Dios Luna J, McKenney K, Cervilla J, et al. Infectious agents associated with schizophrenia: a meta-analysis. *Schizophr Res* 2012; **136**: 128–36.

Golam M. Khandaker, Wellcome Trust Clinical Research Fellow, EpiCentre Group, Department of Psychiatry, University of Cambridge, UK. Email: gm24@medschl.cam.ac.uk; **James B. Kirkbride**, **Peter B. Jones**, Department of Psychiatry, University of Cambridge, UK

doi: 10.1192/bjp.2013.248

Correction

Impact of ethnic density on adult mental disorders: narrative review. *BJP*, 2011, 11–19. Reference 48 should read: Schofield P,

Ashworth M, Jones R. Ethnic isolation and psychosis: re-examining the ethnic density effect. *Psychol Med* 2011; **41**: 1263–9.

doi: 10.1192/bjp.2013.248a