

## Correspondence

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### 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.<sup>1</sup> 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.<sup>2</sup> 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.<sup>3</sup> Failure to reject the null at this effect size means that the null would not be surprising at this particular value.<sup>4</sup> 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.

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**Authors’ reply:** We thank Dr Temmingh for his interest in our paper.<sup>1</sup> The use of sulpiride in CUTLASS-1 was discussed in the original report<sup>2</sup> and subsequent correspondence.<sup>3</sup> The Cochrane review of sulpiride in schizophrenia<sup>4</sup> 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.<sup>5</sup> 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 D<sub>2</sub> and D<sub>3</sub> receptors,<sup>6</sup> characteristics of both drugs that question the validity of the typical *v.* atypical classification.

We acknowledge in the paper<sup>1</sup> 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.<sup>7</sup> 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