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

Peluso et al report on the differential effect of first-generation antipsychotics (FGAs) vs. second-generation antipsychotics (SGAs) in ameliorating or exacerbating extrapyramidal side-effects (EPS) in a secondary analysis of the CUtLASS-1 trial data. 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. 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. Failure to reject the null at this effect size means that the null would not be surprising at this particular value. 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 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 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.5

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 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.

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Epidemiological challenges in systematic reviews

We agree with Brugha and colleagues that the field of psychiatric epidemiology poses particular challenges to systematic reviewers. 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. 1,2,3 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 vs DSM-IV. Often studies include outcomes such as psychotic, depressive or other symptoms instead of a diagnostic category, vs second-generation antipsychotic drugs in schizophrenia – reply. Arch Gen Psychiatry 2007; 64: 979–80.


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