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. Nevertheless, 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 at well-motivated, pre-agreed effect sizes?

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.

Declaration of interest


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 vs. DSM-IV. Often studies include outcomes such as psychotic, depressive or other symptoms instead of a diagnostic category, 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.

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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.


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