Assessing the Robustness of Direct Meta-Analysis in the Presence of Heterogeneity

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BACKGROUND

Statistical Background

- Systematic reviews and meta-analyses have become an indispensable tool for practitioners, researchers, and decision makers to remain up to date with an ever-expanding volume of health evidence. However, between-study heterogeneity (e.g., differences in population, methodology, or results) can limit the reliability of results from meta-analyses.

- Recently, Dechartres and colleagues highlighted an ongoing dilemma when performing meta-analysis: deciding which trials to combine. In the presence of heterogeneity, a meta-analysis of all trials may produce a precise but biased estimate.

- The authors used a four-pronged assessment of the robustness of findings in a large body of meta-analyses, comparing the results of a meta-analysis of all trials to those in: 1) the single most precise trial, 2) a meta-analysis restricted to the 25% largest trials, 3) a limit meta-analysis that adjusted for small-study effects, and 4) a meta-analysis restricted to trials with low overall risk of bias.

- The study identified notable differences in the estimation of treatment outcomes in meta-analyses depending on the strategy used. The authors concluded that the instability in findings and the consequent shift in conclusions stress the need for systematic sensitivity analyses.

Schizophrenia

- Schizophrenia is a chronic and disabling severe mental disorder affecting more than 21 million people worldwide.

- Second-generation ("atypical") antipsychotics (SGAs) have become increasingly popular as the first-line drug treatment for people with schizophrenia. However, there is continuing debate as to how much SGAs improve outcomes compared with conventional antipsychotics.

- Previous reviews have noted considerable heterogeneity in analyses of SGAs, including those investigating the results of trials evaluating the same antipsychotic and comparator drugs. Although some reviewers attempt to understand the origins of this heterogeneity by performing subset analyses or meta-regression, sensitivity analyses are not routinely performed.

OBJECTIVE

- This study applied current methods that have been proposed to address the difficulties presented by heterogeneity to recent systematic reviews, in order to assess robustness of the reviews' findings.

METHODS

Data

- Recently published Cochrane systematic reviews that contained five or more trials investigating the effects of atypical antipsychotics in patients with schizophrenia were identified.

- Seven unique direct comparisons from three Cochrane reviews qualified for analysis.

- These include aripiprazole versus clozapine, quetiapine, risperidone, ziprasidone, and olanzapine; quetiapine versus risperidone; and risperidone versus olanzapine.

Outcome Definition

- The Positive and Negative Syndrome Scale (PANSS) was chosen as the endpoint of interest given its clinical importance in the area of schizophrenia, its use of a standardized scoring system, and its popularity in the field.

- This schizophrenia scale has 30 items, each defined on a 7-point scoring system (1 = absent, 7 = extreme). It constitutes four scales measuring positive and negative symptoms, their differential, and general severity of illness. A low score indicates lesser severity.

Statistical Analysis

- As well as a conventional random-effects meta-analysis of all trials, the following approaches were applied to each direct comparison:

  - Analysis of the single most-precise trial, that is, the trial with the narrowest confidence interval
  - A conventional meta-analysis restricted to only the largest trials, defined as those having the largest 25% of sample size within a meta-analysis
  - A limit meta-analysis that includes all trials and adjusts for small study effects, as described by Rucker et al. and implemented in R by Schwarzer et al.
  - A conventional meta-analysis restricted to trials with a low risk of attrition bias (incomplete outcome data) according to the Cochrane risk of bias tool.

CONCLUSIONS

- The results of this study show that estimates of the mean difference in PANSS total score in meta-analyses of atypical antipsychotics in schizophrenia patients are generally robust under alternative analysis strategies.

- Further, the results demonstrate the value of confirmatory sensitivity analysis.

- Routine sensitivity analyses are recommended to assess the robustness of findings and validate conclusions in the presence of heterogeneity.

- However, such strategies may not be as informative in reviews of drug trials with similar sample sizes as they would in more heterogeneous settings.

REFERENCES

See handout for references.

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