To the Editor:

We read with great interest the meta-analysis by He et al on treatment of pulmonary arterial hypertension.\(^1\) The authors concluded that “in terms of clinical worsening and functional class amelioration, insignificant differences were found among iloprost, bosentan and sildenafil, but iloprost had the highest incidence of serious adverse events among the three drugs”.\(^1\) We have concerns about the method used in reaching these conclusions.

The authors used what Glenny et al\(^2\) describe as a “naïve comparison” in Tables 2, 3 and 4 of their paper to compare the relative efficacy of bosentan, sildenafil and iloprost. They pooled data from the treatment groups of separate randomised controlled trials (RCTs) and then compared these directly, using chi-square test, as though they had been randomised against each other. This approach is unreliable as it loses the benefits of randomisation within the individual trials\(^2,3\) and the result is subject to the biases associated with observational studies. Glenney et al reported that the naïve method showed a high rate of discrepancies in unpredictable directions in comparison to direct estimates.\(^2\) Gutlehrner and Moore state in discussion of this issue that unadjusted “naïve” comparisons should always be avoided.\(^4\)

Bucher et al have proposed an adjusted method for indirect comparisons that aims to overcome these potential problems.\(^5\) To illustrate this, in a situation where we have three treatments A, B and C, and A and C have been compared in RCTs and B and C have been compared in other RCTs. Using the Bucher’s adjusted indirect comparison method, the treatment effect for T\(_{AB}\) can be calculated by:

\[
T_{AB} = T_{AC} - T_{BC}
\]

where T represents the treatment effect (eg, log odds ratio) between the 2 interventions. The standard error is calculated as follows:

\[
SE(T_{AB}) = \sqrt{(SE(T_{AC})^2 + (SE(T_{BC})^2)}
\]

Because more than 2 drugs were involved, the authors could have adopted a Bayesian mixed treatment comparison approach,\(^6,7\) which is a logical extension of more standard meta-analytic methods. The relative effectiveness of several treatments can be estimated using this approach. The Bayesian approach has an additional advantage of being able to calculate direct probability statements for which treatment is the most effective, even when standard methods might determine no significant difference between treatments.\(^6,7\)

References


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