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Letter to the Editor

Response to Zhang et al.: Levetiracetam vs. brivaracetam for adults with refractory focal seizures: A meta-analysis and indirect comparison

To the Editor,

We read with interest the meta-analysis and indirect comparison of levetiracetam and brivaracetam recently presented by Zhang et al. (*Seizure* 2016;39:28–33) [1]. We would like to raise two points in response. Firstly, some methodological elements common to indirect comparisons have not been addressed in the published work. Secondly, the use of network meta-analyses of clinical trials to produce valid evidence of the comparative efficacy and safety of antiepileptic drugs (AEDs) has previously been called into question, which was not discussed by the authors. Both of these points lead us to believe that, given the presented evidence, this publication overstates its comparative conclusions and treatment recommendations.

We have a number of methodological concerns:

1. While the search strategy is presented in full in the Appendix, the rationale for excluding a number of randomised controlled trials from the evidence base is not described [2–4]. Each of these excluded trials has the potential to alter the results of the analysis.
2. A formal assessment of how known trial design differences (e.g. duration of titration and formulation) affect the validity of the comparison is not presented.
3. The heterogeneity between trial populations for a small selection of patient baseline characteristics is acknowledged through the assessment of I^2 values but not controlled for in the comparison, in contrast to the basic principles of indirect comparisons [5]. In addition, the selected baseline characteristics may not be the only potential confounders.
4. The trials used in the analysis were published between 2000 and 2015; recruitment spanned a substantially longer period of time. It is well known that AED trial populations have changed over this period of time [6], for instance with regards to region, prior treatment attempts, and comorbidity profile. This is exemplified by large differences in placebo response (between 7.4% and 39.3%). No heterogeneity assessment is presented for these potentially confounding characteristics, which is needed to determine the validity of the comparison.
5. Furthermore, it has been shown that placebo-response differences cannot be fully accounted for by measured patient baseline characteristics only. Even using advanced matching techniques on patient-level data to control for confounding, unmeasured confounding between the brivaracetam and levetiracetam populations remained [7]. The presence of unmeasured confounding further undermines the validity of comparison between these trials.
6. Some of the studies in the meta-analysis included doses that were found to be non-therapeutic in the pivotal studies and have not been approved for clinical use (brivaracetam 5, 20 and 25 mg/day; levetiracetam 500 mg/day). As such, a brivaracetam dose of 5 mg/day should not be compared to a levetiracetam dose of 1000 mg/day.
7. Considering the presented confidence intervals, only one of the 36 comparisons reaches significance. Broad conclusions on potential differences in efficacy and safety for levetiracetam and brivaracetam are therefore not supported by the totality of evidence presented.

The concerns highlighted above are not unique to the current work. The conduct of indirect comparisons between AEDs is complicated greatly by the design and population differences between the trials, which can lead to confounding and bias [8].

We would like to note that whereas most indirect comparisons conducted to date have found minor or no significant differences between AEDs (as in Zhang et al.), clinicians make individualised and informed treatment choices daily, and real-world experience often highlights the differences between AEDs and the value of choice (as will also be the case for levetiracetam and brivaracetam). Indeed, for this reason the utility of indirect comparisons for clinical decision-making has been questioned in the literature [8–10] and concerns have been raised that, in the era of personalised medicine, undue reliance on statistical approaches "*may inappropriately limit patients' choices*" [11].

Conflict of interest statement

SB and MC are employees of UCB Pharma; CB has received personal fees for scientific advisory boards, speaking activities, and congress travel from Desitin,Eisai, Otsuka, Pfizer, and UCB Pharma. He has received research support from Otsuka and UCB Pharma; PK has received personal fees for advisory boards from Lundbeck and UCB Pharma and for speaker activities from Eisai, Sunovion, and UCB Pharma. He has received research support from Eisai and Lundbeck.

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