Letter to the Editors

Network meta-analysis and the comparison of efficacy and tolerability of anti-epileptic drugs for treatment of refractory focal epilepsy

Gaetano Zaccara,¹ Sanjay M. Sisodiya,² Fabio Giovannelli,¹ Matthew C. Walker,² Dominic C. Heaney,² Heather Angus-Leppan,³ Tim Wehner,² Sofia H. Eriksson,² Rebecca Liu,³ Fergus Rugg-Gunn,² Simon D. Shorvon² & Josemir W. Sander²

¹Unit of Neurology, San Giovanni di Dio Hospital, Firenze, Italy, ²NIHR University College London Hospitals Biomedical Research Centre, UCL Institute of Neurology, London & Epilepsy Society, Chalfont Centre for Epilepsy, Chalfont St Peter and ³Royal Free Hospital, London, United Kingdom

We read with interest the recent paper on network meta-analysis [1] in which efficacy and tolerability of selected anti-epileptic drugs in people with refractory focal epilepsy were compared.

Whilst network meta-analysis may be a powerful tool, the validity of the results must depend on the selection of studies included. In this respect, we are curious about several methodological points. The authors include some studies but not others that are of the same nature. The authors deem as appropriate doses those that most experienced epilepsy clinicians would consider unusual and the results that emerge would be considered misleading by most experienced epilepsy clinicians.

Only one of the four drugs the authors suggest have efficacy and tolerability in focal epilepsies would be accepted as such by experienced epilepsy clinicians. Their recommendation of vigabatrin in this category is most surprising, given the significant adverse effects associated with its use. The paper illustrates the importance of ensuring that the results of any complex statistical process should always be checked against actual clinical experience. The authors selected for comparison only people receiving doses of the target drugs which they deemed appropriate. Despite the authors' claim that they chose the selected doses based on their clinical experience, the choice seems arbitrary, is out of keeping with clinical experience and is not based on any stated evidence. For instance, only someone with little clinical experience of oxcarbazepine would consider doses over 1800 mg day⁻¹ as appropriate. The dose of 2400 mg is poorly tolerated by most people. It is also unlikely that many people would tolerate doses of topiramate over 300 mg day⁻¹.

Several relevant studies were not included, without clear explanation. For instance, a key lacosamide study [2] was not included. The same apply for studies with topiramate [3] and levetiracetam [4]. Two relevant lamotrigine studies [5, 6] were also excluded. One could suggest that these were excluded as they were crossover studies, but then other crossover studies were included, such as a levetiracetam study [7]. It is imperative that consistent criteria are applied for study selection if this type of analysis is to be meaningful.

The authors conclude that in their mixed-treatment network meta-analysis, levetiracetam, vigabatrin, sodium valproate and gabapentin emerge as the anti-epileptic drugs with the best combination of short term efficacy and tolerability. As experienced epilepsy clinicians having seen many thousands of patients, we do not consider that valproate and gabapentin should be considered as first line anti-epileptic drugs for people with focal epilepsy, whilst any epilepsy clinician would know that the risk of visual field loss with vigabatrin is far too high to contemplate its regular use. The authors' recommendation on valproate appears to emanate from one old study comparing vigabatrin with valproate, in which a small number of people with epilepsy not controlled by carbamazepine were given either valproate or vigabatrin [8]. It is not clear why better quality data [9] were omitted from the analysis.

For these reasons, the conclusions cannot be considered particularly helpful. The need for answers to the questions the authors set out to address remains. One important thing to remember is that epilepsy, a symptom-complex, is not a single disease but a collection of many different conditions for which the current clinical trials paradigm is completely inappropriate [10, 11].

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author). All authors declare no support from any organization for the submitted work.

GZ has received speaker's or consultancy fees from Jansen-Cilag, UCB Pharma, GSK, Sanofi-Aventi and Eisai which are involved in the manufacture of antiepileptic drugs; SMS has received speaker's or consulting fees from UCB Pharma, Eisai and GSK; his institution has received research support from UCB Pharma, GSK and Eisai; MCW received speaker's fees from Eisai, UCB Pharma, Viropharma and GSK; DCH has received speaker's or consultancy fees from UCB Pharma and Eisai; SHE has received speaker's fee from UCB Pharma; TW has received travel support from UCB Pharma and GSK; FRG has received speaker's fee from Eisai, UCB Pharma and GSK; SDS has received speaker's or consultancy fees from UCB, Eisai, GSK, Bial, SAGE, Lundbeck; JWS has received speaker's or consulting fees from UCB Pharma and GSK; his institution has received research support from UCB Pharma, GSK and Eisai.

All authors declare no other relationships or activities that could appear to have influenced the submitted work.

REFERENCES

- 1 Bodalia PN, Grosso AM, Sofat R, Macallister RJ, Smeeth L, Dhillon S, Casas JP, Wonderling D, Hingorani AD. Comparative efficacy and tolerability of anti-epileptic drugs for refractory focal epilepsy systematic review and network meta-analysis reveals the need for long term comparator trials. *Br J Clin Pharmacol* 2013; 76: 649–67.
- 2 Chung S, Sperling MR, Biton V, Krauss G, Hebert D, Rudd GD, Doty P, SP754 Study Group. Lacosamide as adjunctive therapy for partial-onset seizures: a randomized controlled trial. *Epilepsia* 2010; 51: 958–67.
- 3 Topiramate in medically intractable partial epilepsies: double-blind placebo-controlled randomized parallel group trial. Korean Topiramate Study Group. *Epilepsia* 1999; 40: 1767–74.
- 4 Shorvon SD, Löwenthal A, Janz D, Bielen E, Loiseau P. Multicenter double-blind, randomized, placebo-controlled

trial of levetiracetam as add-on therapy in patients with refractory partial seizures. *European Levetiracetam Study Group. Epilepsia* 2000; 41: 1179–86.

- 5 Boas J, Dam M, Friis ML, Kristensen O, Pedersen B, Gallagher J. Controlled trial of lamotrigine (Lamictal) for treatment-resistant partial seizures. *Acta Neurol Scand* 1996; 94: 247–52.
- 6 Schapel GJ, Beran RG, Vajda FJ, Berkovic SF, Mashford ML, Dunagan FM, Yuen WC, Davies G. Double-blind, placebo controlled, crossover study of lamotrigine in treatment resistant partial seizures. *J Neurol Neurosurg Psychiatr* 1993; 56: 448–53.
- 7 Boon P, Chauvel P, Pohlmann-Eden B, Otoul C, Wroe S. Dose-response effect of levetiracetam 1000 and 2000 mg/day in partial epilepsy. *Epilepsy Res* 2002; 48: 77–89.
- 8 Brodie MJ, Mumford JP. Double-blind substitution of vigabatrin and valproate in carbamazepine-resistant partial epilepsy. *Epilepsy Res* 1999; 34: 199–205.
- 9 Willmore LJ, Shu V, Wallin B. Efficacy and safety of add-on divalproex sodium in the treatment of complex partial seizures. *Neurology* 1996; 46: 49–53.
- 10 Walker MC, Sander JW. Difficulties in extrapolating from clinical trial data to clinical practice: the case of antiepileptic drugs. *Neurology* 1997; 49: 333–7.
- 11 Friedman D, French J. Clinical trials for therapeutic assessment of antiepileptic drugs in the 21st century: obstacles and solutions. *Lancet Neurol* 2012; 11: 827–34.

RECEIVED

8 March 2013

ACCEPTED

15 March 2013

ACCEPTED ARTICLE PUBLISHED ONLINE

6 June 2013

CORRESPONDENCE

Dr Gaetano Zaccara MD, Unit of Neurology, San Giovanni di Dio Hospital, Via Di Torregalli 3, Azienda Sanitaria di Firenze, 50143 Firenze, Italy.
Tel.: +39 05 5719 2476
Fax: +39 05 5719 2280
E-mail: gaetano.zaccara@asf.toscana.it