Original article

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A common reference-based indirect comparison meta-analysis of intravenous valproate *versus* intravenous phenobarbitone for convulsive status epilepticus

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ABSTRACT – *Objective*. To compare intravenous valproate (IV-VPA) with intravenous phenobarbitone (IV-PB) in the treatment of established generalised convulsive status epilepticus (GCSE). Efficacy and safety were estimated using a common-reference based indirect comparison meta-analysis (CRBMA) methodology. *Methods*. Randomised controlled trials (RCTs) investigating the use of IV-VPA or IV-PB *versus* intravenous phenytoin (IV-PHT) for GCSE were identified by a systematic search of the literature. A random effects model was used to estimate Mantel-Haenszel odds ratios (ORs) for efficacy and safety of IV-VPA or IV-PB *versus* IV-PHT in a standard meta-analysis. Adjusted indirect comparisons were then made between VPA and PB using the obtained results. *Results*. CRBMA showed that VPA does not lead to significantly higher seizure cessation (OR 1.00; 95% CI: 0.36-2.76) compared to PB, although it exhibits fewer adverse effects (OR 0.17; 95% CI: 0.04-0.71). Results of this CRBMA are consistent with results of a recently published head-to-head comparison of IV-VPA and IV-PB. *Conclusion*. There is insufficient evidence to demonstrate superiority of IV-VPA over IV-PB for the treatment of GCSE in terms of efficacy. Some direct and indirect comparisons suggest that VPA has a better safety profile than PB. However, the limited numbers of underpowered RCTs included in this meta-analysis are not sufficient to justify a change in clinical practice. More rigorous and appropriately powered RCTs are therefore required to definitively determine the efficacy and tolerability of VPA for the treatment of GCSE.

Key words: clinical trial, randomized controlled, systematic review, meta-analysis, phenobarbitone, status epilepticus, valproic acid

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Generalised convulsive (tonic-clonic) status epilepticus (GCSE) is the most common and life-threatening form of status epilepticus (SE) (DeLorenzo *et al*., 1995) with attributable mortality ranging from 3 to 35% (Cascino, 1996). Therefore, it represents a medical and neurological emergency both in adults (DeLorenzo *et al*., 1995; Cascino, 1996) and children (Berg *et al*., 1999; Berg *et al*., 2004), requiring rapid intervention with antiepileptic treatment.

Several antiepileptic drugs (AEDs) are available as alternative and competing interventions for the treatment of GCSE. However, most information in the literature regarding treatment of GCSE derives from clinical trials comparing one AED with intravenous phenytoin (IV-PHT) (Prasad *et al*., 2005). These studies therefore provide only a partial fragment of the whole picture. Knowing the efficacy and safety of an AED relative to IV-PHT is useful, however, it would be ideal to know how all the different options rank against each other and how vital these differences are in effect size between all the available drugs (Brigo, 2011).

Only one randomised controlled trial (RCT), conducted in a paediatric population, directly compared intravenous valproate (IV-VPA) with intravenous phenobarbitone (IV-PB) (Malamiri *et al*., 2012). Until further data from direct head-to-head clinical trials comparing IV-VPA with IV-PB are available, other methods may be used to make comparisons between these AEDs in the treatment of GCSE.

Systematic reviews and meta-analyses of RCTs with similar design are useful, although limited. Classical meta-analyses of RCTs focus on direct, pairwise comparisons between two treatments (*e.g*. treatment A *versus* treatment B). However, direct head-to-head comparisons are not available for all treatments, such that definite data on treatment effect cannot be estimated. However, it is possible to estimate the indirect effect of treatment A *versus* treatment B using evidence from trials comparing treatment A with treatment C, and trials comparing treatment B with treatment C (Tudur Smith *et al*., 2007). The key assumption for this indirect comparison is that of exchangeability of the treatment effect across all included trials (ICWG, 2009). The validity of indirect comparisons based on a common comparator (also known as "*adjusted indirect comparison*" [Song *et al*., 2003] or "*common reference-based indirect comparison*" [ICWG, 2009]) depends upon the internal validity and similarity of the included trials (Song *et al*., 2003). Therefore, meta-analyses based on common reference-based indirect comparisons represent a useful tool where direct comparisons do not exist or are scarce.

We therefore decided to undertake a systematic review with meta-analysis of IV-VPA compared with IV-PB for the treatment of established GCSE in patients across all age groups, indirectly estimating their efficacy and safety through a common reference-based indirect comparison meta-analysis. Hence, the aim of this study was to provide further information on the antiepileptic role of IV-VPA in the treatment of GCSE and to ascertain whether an indirect comparison meta-analysis is reliable and consistent with results of direct head-to-head RCTs.

Methods

This review was guided by a written pre-specified protocol describing research questions, review methods, and plan for data extraction and synthesis. The protocol is available online at: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42012003104.

Criteria for considering studies for this review

Results of RCTs comparing IV-VPA or IV-PB against IV-PHT for the treatment of GCSE were included in the meta-analysis using the inclusion criteria outlined by Prasad *et al*. (2005) and Brigo *et al*. (2012).

Briefly, we included RCTs, blinded or unblinded, and excluded uncontrolled and non-randomised trials. Patients from any age group who presented to a hospital or emergency medical department, and diagnosed with GCSE at any stage, including refractory GCSE, were included. SE was defined as "*more than five minutes of: (i) continuous seizures; or (ii) two or more discrete seizures between which there is incomplete recovery of consciousness*" (Lowenstein *et al*., 1999). The same definition was adopted for studies on GCSE in children (Shinnar *et al*., 2001).

We planned to separately consider SE continuing after the first-line treatment (benzodiazepine) from "refractory SE", defined as a SE not responding both to first-line and second-line (another AED, usually PHT) treatment.

We considered all trials in which IV-VPA or IV-PB were compared with IV-PHT and which were included in previously published systematic reviews (Prasad *et al*., 2005; Brigo *et al*., 2012). Trials were not excluded on the basis of dose, duration of treatment, or length of follow-up.

We updated the search results using the same strategies outlined in previously published systematic reviews (Prasad *et al*., 2005; Brigo *et al*., 2012), assessing the methodological quality of RCTs, not previously included with the methods adopted by Brigo *et al*. (2012).

Search methods

A comprehensive review of the literature of computerised databases, as well as searches to find unpublished trials, was performed to minimise publication bias.
The following electronic databases and data sources were searched:
– MEDLINE (January 1966–October 2012), accessed by PubMed;
– EMBASE;
– Cochrane Central Register of Controlled Trials (CENTRAL) (accessed April–October 2012); MeSH terms "valproic acid" and "status epilepticus" were used as well as the following free terms in multiple search strategies with Boolean operators (see Appendix 1 in Brigo *et al*., 2012) to find relevant articles: "valproate", "valproic acid", "status epilepticus", "clinical trials", and "randomized controlled trials". We also conducted a search using a high-sensitivity strategy for the search of RCTs (Robinson and Dickersin, 2002);
– Hand-searching of the references quoted in the identified trials;
– Contact with the pharmaceutical company Sanofi Aventis (Depakin) to identify unpublished trials or data missing from articles;
– Contact with authors and known experts to identify any additional or unpublished data.
All resulting titles and abstracts were evaluated and any relevant article was considered. There were no language restrictions.

Methodological quality assessment

Trials were scrutinised and the methodological quality of all included studies was evaluated. Quality assessment included the following aspects of methodology: study design, definition and clinical relevance of outcomes, type of control, method of allocation concealment, total study duration, completeness of follow-up, intention to-treat analysis, data concerning adverse effects, risk of bias, and conflict of interests. The randomised trials were judged on the reported method of allocation concealment and the risk of bias as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011) (Higgins and Green, 2011).

Types of outcome measures

We chose dichotomous primary outcomes in order to obtain "hard" outcome measures of both treatment efficacy and safety. Odds ratios (ORs) for binary outcomes were chosen because they are associated with less heterogeneity in meta-analysis than risk differences or relative risks (Deeks, 2002).
The following outcomes (reported in studies meeting the inclusion criteria) relevant to the efficacy and safety of the intervention drug (IV-VPA or IV-PB *versus* IV-PHT) were collected:
– *efficacy*: the number of patients with clinical seizure cessation within 30 minutes after the start of drug administration;
– *tolerability and safety*: the number of patients experiencing adverse effects of any type.
We also planned to consider mortality among outcomes, provided that a stratified randomisation for SE aetiology was made (hence ensuring that this extremely relevant clinical aspect was equally distributed in the control and experimental groups), or that enough information on aetiology was reported in the studies, thus permitting a subgroup analysis in order to relate mortality to SE aetiology.

Statistical analysis

We used statistical methods in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011) (Higgins and Green, 2011) to measure treatment effect.
For each outcome, an intention-to-treat primary analysis was made in order to include all patients in the treatment group to which they were allocated, irrespective of the treatment they actually received.
Analyses were conducted using Revman 5 (conventional meta-analysis for each AED), Excel and R 2.15.1 (common reference-based indirect comparison meta-analysis).

Conventional meta-analysis per AED

A conventional meta-analysis of comparisons between each AED (VPA or PB) and IV-PHT was undertaken. Results from individual trials for each AED (IV-VPA and IV-PB, each compared against IV-PHT) were pooled by using random effects, inverse variance, and weighted meta-analysis (DerSimonian and Laird, 1986).
Each outcome was analysed by calculating ORs for each trial with uncertainty expressed as 95% CIs. For each outcome, a weighted treatment effect across trials was calculated. The Mantel-Haenszel method was used to estimate the OR statistic and to combine ORs (Emerson, 1994).

Random effects model

Pairwise meta-analyses were performed by synthesizing studies that compare the same interventions using a random effects model (DerSimonian and Laird,

1986) to incorporate the assumption that the different studies are estimating different, yet related, treatment effects (Higgins and Green, 2011). Adjusted indirect comparison using the fixed effect model tend to underestimate standard errors of pooled estimates (Glenny *et al*., 2005; ICWG, 2009). Thus, we used the random effects model for the quantitative pooling in both direct and adjusted indirect comparisons (DerSimonian and Laird, 1986).

Assessment of heterogeneity

Visual inspection of the forest plots was used to investigate the possibility of statistical heterogeneity. Homogeneity among trial results was evaluated using a standard χ^2 test and the hypothesis of homogeneity was rejected if the *p* value was less than 0.10.

Assessment of statistical heterogeneity was supplemented using the I-squared (I^2) statistic which provides an estimate of the percentage of variability due to heterogeneity rather than a sampling error (Higgins *et al*., 2003).

The interpretation of I^2 with regards to heterogeneity was performed according to Higgins and Green (2011). The possible sources of heterogeneity were assessed and discussed.

Suitability of indirect comparisons

The suitability of indirect comparisons was investigated by considering whether studies were suitably similar and by adopting the framework for assessing exchangeability assumption proposed by ICWG (ICWG, 2009).

Common reference-based indirect comparisons by combining meta-analyses of AEDs

Comparison method

We conducted a common reference-based indirect comparison meta-analysis, which is a method of synthesizing information from trials addressing the same question but involving different interventions. For a given comparison, for example A *versus* B, direct evidence is provided by studies that compare these two treatments directly. In other terms, for the direct comparisons, comparison of the result of group A with the result of group B within a RCT give an estimate of the efficacy of intervention A *versus* B. However, indirect evidence is provided when studies that compare A *versus* C and B *versus* C are analysed jointly.

Because none of the included trials directly compared IV-VPA with IV-PB, an adjusted method of indirect comparison between IV-VPA and IV-PB was performed using the results of two meta-analyses (*e.g.* IV-VPA *versus* IV-PHT and IV-PB *versus* IV-PHT).

Statistical analysis

To perform common reference-based indirect comparisons, we used the method suggested by Bucher *et al*. (1997) which was adopted in previous reviews (Otoul *et al*., 2005): the indirect comparison of IV-VPA and IV-PB was adjusted by the results of their direct comparisons with IV-PHT (common intervention).

This adjusted method aims to overcome the potential problem of different prognostic characteristics between study participants among trials, and it is valid if the relative efficacy of interventions is consistent across different trials. In order for this indirect comparison to be valid, the overall characteristics of the trials included in the meta-analyses should not differ systematically.

The comparison between each AED and other AEDs was performed using the ORs derived from the conventional meta-analyses.

Comparison of each binary outcome measure was performed using the log of OR and its variance derived from the meta-analyses (Bucher *et al*., 1997). The logs of the OR of each meta-analysis are asymptotically normally distributed and statistically independent. The estimate of the treatment effect (*i.e.* IV-VPA *versus* IV-PB) was therefore calculated by the difference (diff) between the logs of the 2 ORs:

$$\text{Diff} = \ln \text{OR}_{\text{VPA}} - \ln \text{OR}_{\text{PB}} :$$

The 95% confidence interval of this estimated effect was derived from the standard error of the difference:

$$\left(\left(\ln \text{OR}_{\text{VPA}} - \ln \text{OR}_{\text{PB}}\right) \pm \left(1.96 \times \text{SE}\left(\text{diff}\right)\right)\right)$$

where SE (diff) = (variance (ln OR $_{\text{VPA}}$) + variance (ln OR $_{\text{PB}}$))$^{1/2}$. Back transformation was then performed to give the OR and its 95% CIs for the indirect comparisons.

By convention, ORs >1 indicate that the outcome is more likely in the group receiving IV-VPA than in the group receiving IV-PHT. The same was applied for IV-PB. For the indirect comparisons, an OR >1 indicates that the outcome is more likely associated with IV-VPA than with IV-PB. A *p* value of 0.05 was considered to be statistically significant.

Data obtained from indirect comparison meta-analysis were compared with the results of the RCT conducted by Malamiri *et al*. (2012) in order to evaluate the consistency of the results between the direct and indirect comparisons.

Results

An updated search conducted using the same strategies outlined in Prasad *et al*. (2005) and Brigo *et al*. (2012) yielded no new trials other than those already included in previously published systematic reviews.

Table 1. Characteristics of included studies.

	Misra *et al.*, 2006 (published data only)	**Gilad *et al.*, 2008 (published and unpublished* data)**	**Treiman *et al.*, 1998 (published data only)**
Methods			
Comparison	IV VPA *versus* IV PHT	IV VPA *versus* IV PHT	IV PB *versus* IV PB
Study design	RCT	RCT	RCT
Follow-up	Duration not reported	24 hours	12 hours
Participants			
Number of pts	68 pts: 35 in IV VPA and 33 in PHT.	27 pts: 18 in VPA and 9 in PHT	186 pts: 91 in PB and 95 in PHT
Location of trial	India; 1 centre	Israel 1 centre.	Multicentre
Inclusion criteria	Convulsive SE	Age >18 yrs. SE (all subtypes)	Age >18 yrs. GCSE
Definition of SE followed	See *Table 2*	See *Table 2*	See *Table 2*
Exclusion criteria	Non-convulsive and subtle SE, hypotension, cardiac arrhythmia, congestive heart failure, pregnancy, pancreatitis, drug allergy, need of immediate neurosurgery.	Age <18 yrs, abnormal liver function tests or toxic serum levels of VPA known from history or caregiver information.	Age <18 yrs, pregnancy, neurological emergency requiring immediate surgical intervention, specific contraindication to therapy with hydantoin, benzodiazepine, or barbiturate drugs.
Age (years)	Children (≤15 years): VPA=8, PHT=4 Adults (>15 years): VAP=27, PHT=29	VPA=50±8, PHT=53±9	Individual information on patients allocated to PB or PHT arm not explicitly reported.
Sex	Males: VPA=24, PHT=17 Females: VPA=11, PHT=16	Males: VPA=12, PHT=7 Females: VPA=6, PHT=2	Information on patients allocated to PB or PHT arm not explicitly reported
Interventions			
Group VPA	VPA 30 mg/kg in 100 mL saline infused over 15 min.	VPA: 30 mg/kg given over 20 min. diluted in 50 mL of saline.	PB: 15 mg/kg given with maximal 100 mg/min rate of administration.
Group control	PHT 18 mg/kg in 100 mL saline infused immediately at a rate of 50 mg/min.	PHT 18 mg/kg in 100 mL of saline infused over 20 min; no maintenance dose.	PHT 18 mg/kg with maximal 50 mg/min rate of administration.

Hs: hours; min: minutes; Pts: patients; SE: status epilepticus; VPA: valproate acid; PHT: phenytoin.
*provided by Dr Gilad regarding patients with SE.

Hence, three studies (two comparing IV-VPA with IV-PHT, and one reporting data on IV-PB compared against IV-PHT), with a total of 287 patients were included (*table 1*) (Treiman *et al*., 1998; Misra *et al*., 2006; Gilad *et al*., 2008).

Despite our intention, it was impossible to carry out separate analyses for different stages of SE, given the variable definitions used in different studies (*table 2*) and the lack of data. A further analysis of other relevant aspects of clinical and methodological variation among studies (age of participants, use of VPA as first or second-line AED, time to treatment, time of administration in terms of length of IV infusion, and dosage and maintenance of AED) was also not feasible given the lack of sufficient data. Moreover, none of the included studies performed a stratified randomisation for SE aetiology (ensuring an adequate and equal distribution of this feature among control and experimental groups) in order to perform a subgroup analysis to relate mortality to SE aetiology.

In the study of Misra *et al*. (2006), some patients received both drugs (VPA and PHT) for control of SE. However, individual data for patients receiving only one drug (10 patients seizure-free/23 on VPA monotherapy; 8/14 on PHT monotherapy) were reported, thus data from this trial is included in the meta-analysis. This is the reason why the number of patients included in the different outcomes analysed in the meta-analysis is different.

Risk of bias in included studies

All studies were described as RCTs. Given the inadequate random sequence generation and/or inadequate allocation concealment methods, all studies had a high or unclear risk of selection bias. In the study of Misra *et al*. (2006), randomisation was performed by one and evaluation was performed by another investigator, both of whom were unaware of the treatment protocol. One study (Treiman *et al*., 1998) was described as blinded double-blinded, whereas in the other study (Gilad *et al*., 2008), blinding was not explicitly reported and it was not specified whether similar comparison drugs were used. However, the "hard" outcomes chosen in all studies are probably not influenced by lack of blinding. As a consequence, all studies have a low risk of performance and detection bias.

Furthermore, only one study (Treiman *et al*., 1998) specified that efficacy outcome was defined as seizure cessation occurring at a specified time *after the start* of drug administration, whereas the other two studies (Misra *et al*., 2006; Gilad *et al*., 2008) did not specify whether efficacy was evaluated at a specified time *after the start* or at *the end* of treatment administration.

Conventional meta-analysis per AED

IV-VPA versus *IV-PHT: clinical seizure cessation after drug administration*

There were two studies with 95 participants. No significant statistical heterogeneity among trials was detected. There was no statistically significant difference in clinical seizure cessation after drug administration between the VPA and the PHT group (36/53 *versus* 21/42 participants; OR: 1.81; 95% CI: 0.60-5.52) (*figure 1*).

IV-VPA versus *IV-PHT: adverse effects*

There were two studies with 64 participants. No significant statistical heterogeneity among trials was detected. Compared with PHT, VPA was associated with a statistically lower risk of adverse effects (4/41 *versus* 8/23 participants; OR: 0.22; 95% CI: 0.06-0.87) (*figure 2*).

In the study of Misra *et al*. (2006), hypotension occurred in 2/33 patients treated with IV-PHT, respiratory depression in 2/33 patients treated with IV-PHT, and 1/35 patients under IV-VPA treatment. Liver dysfunction occurred in 2/33 patients in the PHT group, compared

Table 2. Definitions of status epilepticus used in included studies.

Study	Definition
Misra *et al*., 2006 *Convulsive SE*	2 or more convulsive seizures without full recovery of consciousness between the seizures or continuous convulsive seizures lasting >10 min
Gilad *et al*., 2008	Continued seizure activity >30 min or 2 or more sequential seizures without full recovery between seizures
Treiman *et al*., 1998	Overt generalised convulsive status epilepticus: ≥2generalised convulsions, without full recovery of consciousness between seizures, or continuous convulsive activity for >10 min

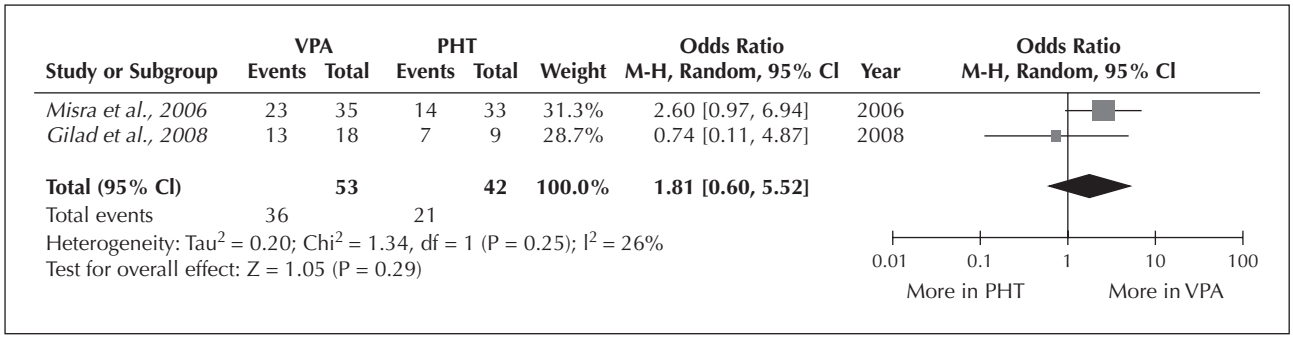

Figure 1. Intravenous valproic acid (VPA) *versus* intravenous phenytoin (PHT). Clinical seizure cessation after drug administration. Data from the study of Gilad *et al*. (2008) were kindly provided by the principal investigator of the study.

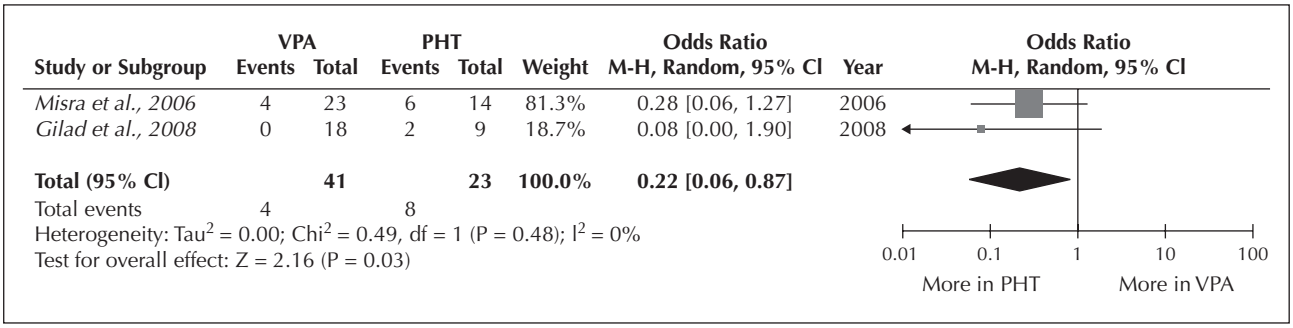

Figure 2. Intravenous valproic acid (VPA) *versus* intravenous phenytoin (PHT). Adverse effects.
Data from the study of Gilad *et al*. (2008) were kindly provided by the principal investigator of the study.

with 3/35 in the VPA. In the study of Gilad *et al*. (2008), no adverse effects occurred in the VPA group, whereas in the PHT group, 1/9 patients had cardiac arrhythmia and 1/9 hyponatraemia.

IV-PB versus *IV-PHT: clinical seizure cessation after drug administration*
One study (Treiman *et al*., 1998) with 192 participants was included. Statistical heterogeneity could not be evaluated. Compared to PHT, PB was not associated with a statistically significant difference in seizure cessation after drug administration (53/91 *versus* 44/101 participants; OR: 1.81; 95% CI: 1.02-3.20).

IV-PB versus *IV-PHT: adverse effects*
One study (Treiman *et al*., 1998) with 192 participants was included. Statistical heterogeneity could not be evaluated. Compared to PHT, PB was not associated with a statistically significant difference in occurrence of adverse effects (46/91 *versus* 44/101 participants; OR: 1.32; 95% CI: 0.75-2.34). Among 91 patients treated with IV-PB, 12 experienced hypoventilation, 31 hypotension, and three cardiac arrhythmia; among 101 patients receiving IV-PHT, 10 experienced hypoventilation, 27 hypotension, and 7 cardiac arrhythmia.

Common reference-based indirect comparisons by combining meta-analyses of AEDs

IV-VPA versus *IV-PB: clinical seizure cessation after drug administration*
Compared to PB, VPA was not associated with a statistically significant difference in seizure cessation after drug administration (OR: 1.00; 95% CI: 0.36-2.76).

IV-VPA versus *IV-PB: adverse effects*
Compared to PB, VPA was not associated with a statistically lower occurrence of adverse effects (OR: 0.17; 95% CI: 0.04-0.71).

Discussion

The results of the present meta-analysis suggest that IV-VPA is better tolerated and is as efficacious as IV-PB for the treatment of established GCSE.
The present meta-analysis was performed to estimate the efficacy and safety of IV-VPA relative to IV-PB using data from previously published systematic reviews. No new trials other than those already included in previously published systematic reviews were added in this meta-analysis.

Limitations of the review

The results of this meta-analysis should be read with caution and the following critical aspects should be considered regarding the overall pooled data.

The main limitation of this review is the small population of patients included in both comparisons. This aspect should be particularly taken into account, as small sample size may lead to a false negative error (statistical type II error, *i.e.* accepting a null hypothesis that is actually false) (Guyatt *et al*., 1995). Consequently, failure to prove that there is a difference in terms of efficacy between IV-VPA and IV-PB does not necessarily prove that there is no difference, as the included studies may have been underpowered to detect such a difference.

Whether the comparability of the included studies is enough to inform clinical practice remains a matter of debate. A recent study showed that even small differences in the timing of treatment can significantly change outcomes (Silbergleit *et al*., 2012), as shown previously (Alldredge *et al*., 2001). In all studies included in the present review, it was not reported how much time it took to deliver the drugs; a major determinant of the outcome is therefore unknown and could have represented a relevant source of clinical heterogeneity among trials, reducing the appropriateness of performing indirect-comparison meta-analysis.

Compared to studies comparing VPA with PHT, the rate of adverse events with PHT was higher in the study of Treiman *et al*. (1998), where hypotension and hypoventilation were observed in both PB and PHT groups in about 30% and 10% patients, respectively. Considering that the PHT doses were the same, the difference in PHT tolerability is probably due to clinical heterogeneity among patients included in the different studies. No detailed clinical information on age, gender or aetiology of epilepsy of patients experiencing adverse events was explicitly reported in the studies. However, it is possible that such a discrepancy in occurrence of adverse effects under PHT is due to differences in sample size and aetiology of epilepsy across different studies. Furthermore, unlike the study of Treiman (which was conducted in an adult population), 10% patients treated with PHT in studies comparing VPA with PHT were aged less than 15 years (4/42 patients), hence probably less prone to develop adverse effects.

In this review, the comparisons between IV-VPA and IV-PB were made indirectly using data generated from individual comparisons *versus* IV-PHT. A more appropriate approach would have been to conduct clinical trials involving the two AEDs, thus, allowing a direct comparison between them.

In both comparisons (VPA *versus* PHT and PB *versus* PHT), all included studies used VPA or PB as the first agent given. However, the choice of PHT as comparator was probably inadequate as it has been demonstrated to be inferior to lorazepam (Treiman *et al*., 1998; Prasad *et al*., 2005). Moreover, all included studies compared IV-VPA or IV-PB with IV-PHT used at approximately the same dosage, hence, using the same comparator (both in terms of drug and of dosage). The similarity of the common comparator is a prerequisite for performing adequate indirect comparisons as it allows for exchangeability of the treatment effect across all included trials. In fact, the validity of the adjusted indirect comparison depends on the assumption that the two sets of controlled trials are sufficiently similar for moderators of relative treatment effect (Song *et al*., 2009).

Conversely, all included studies did not provide enough details regarding the stages of GCSE which were considered, thus this relevant source of clinical heterogeneity could not be assessed in detail.

However, we adopted a pragmatic approach, since meta-analyses by their nature address broader questions than individual studies, without necessarily producing debatable results as a consequence of too much heterogeneity. RCTs included in this meta-analysis inevitably differ in their characteristics, but the choice of a rather broad definition of SE (Lowenstein *et al*., 1999) represents a sort of "least common denominator", and thus does not undermine the appropriateness of pooling the data. The validity of the results derived from a meta-analysis which supports the efficacy and tolerability of AEDs may depend on the definition of SE. Meta-analyses that cover both initial and refractory SE may be more informative than those that exclude refractory SE. However, the transferability of research results into a homogeneous clinical set is another topic that should be addressed (Brigo *et al*., 2012)

Despite the possible sources of clinical and methodological heterogeneity among included studies, we considered it appropriate to summarise data in a meta-analysis, and also on the basis of what was previously documented by other authors in a Cochrane systematic review on SE (Prasad *et al*., 2005). The review analysed studies which demonstrated heterogeneity with regards to SE definition, type (convulsive and non-convulsive) and aetiology, AED dosage, demographic characteristics of participants, and time of AED administration and their dosage. Despite this primary intention, a further analysis of most relevant aspects of clinical and methodological variation among studies (SE definitions, age of participants, use of VPA or PB as first or second-line AED, time to treatment, time of administration in terms of length of IV infusion, and dosage and maintenance of AED) was not feasible due to a lack of information.

The above limitations indicate that an indirect comparison based on meta-analysis may not be a reliable substitute for comparative clinical trials, in which two or more AEDs are compared head-to-head, or for long-term clinical experience. Nevertheless, in the absence of such studies, the adjusted indirect method may provide some evidence of the relative efficacy and safety of competing AEDs.

In terms of efficacy and tolerability, the results of this indirect comparison meta-analysis are consistent with those of a recently published RCT directly comparing IV-VPA with IV-PB in children (Malamiri *et al*., 2012). In this RCT, no statistically significant differences were found with regards to efficacy between the two drugs (OR: 2.74; 95% CI: 0.63-11.82), whereas a statistically significant greater occurrence of adverse effects was found in patients allocated to IV-PB (OR: 0.11; 95% CI: 0.03-0.36).

Conclusions

Currently, there is no evidence (from either direct or indirect comparisons) supporting superiority of IV-VPA over IV-PB for the treatment of GCSE in terms of efficacy. Some data derived from both direct and indirect comparisons suggest that IV-VPA has a better safety profile than IV-PB. However, the limited numbers and the poor quality of RCTs (with small numbers of patients) included in this systematic review are not sufficient to justify a change in clinical practice.

Further comparative clinical trials are therefore required to verify the results obtained by meta-analyses and adjusted indirect comparisons, and provide physicians with pertinent information serving as the rationale for clinical decisions regarding treatment of GCSE.

More rigorous RCTs of VPA *versus* an appropriate comparator, conducted in a well-defined population with a sufficient sample size to detect a difference between the comparator, are required in order to provide reliable data regarding the efficacy and tolerability of VPA in the treatment of GCSE. □

Disclosures.
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