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Review

The relative effectiveness of five antiepileptic drugs in treatment of benzodiazepine-resistant convulsive status epilepticus: A meta-analysis of published studies

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ABSTRACT

Purpose: Systematic evaluation of published evidence-base of the efficacy of five antiepileptic drugs – lacosamide, levetiracetam, valproate, phenytoin and phenobarbital – in convulsive benzodiazepine-resistant status epilepticus.
Methods: Data sources included electronic databases, personal communication, and back tracing of references in pertinent studies. These were prospective and retrospective human studies presenting original data for participants with convulsive benzodiazepine-resistant status epilepticus. Interventions were intravenous lacosamide, levetiracetam, phenobarbital, phenytoin and valproate. Outcome measured is clinically detectable cessation of seizure activity. Level-of-evidence was assessed according to Oxford Centre of Evidence-Based Medicine and The Cochrane Collaboration's Tool for Assessment of Risk. Twenty seven studies (798 cases of convulsive status epilepticus) were identified and 22 included in a meta-analysis. Random-effects analysis of dichotomous outcome of a single group estimate (proportion), with inverse variance weighting, was implemented. Several sources of clinical and methodological heterogeneity were identified.
Results: Efficacy of levetiracetam was 68.5% (95% CI: 56.2–78.7%), phenobarbital 73.6% (95% CI: 58.3–84.8%), phenytoin 50.2% (95% CI: 34.2–66.1%) and valproate 75.7% (95% CI: 63.7–84.8%). Lacosamide studies were excluded from the meta-analysis due to insufficient data.
Conclusion: Valproate, levetiracetam and phenobarbital can all be used as first line therapy in benzodiazepine-resistant status epilepticus. The evidence does not support the first-line use of phenytoin. There is not enough evidence to support the routine use of lacosamide. Randomized controlled trials are urgently needed.

1. Introduction

Status epilepticus (SE) is a neurological emergency with significant morbidity and mortality[1,2] and has to be treated in a timely manner before irreversible neuronal damage ensues.[3,4] Having a protocol for therapy is universally recommended, and standard protocols are widely accepted.[5,6] All of these recommend benzodiazepines as first line therapy[7–17] and there is now global consensus on this. In contrast, what action to take if benzodiazepines are ineffective is much less clear and there is perceived to be a lack of evidence to support the use of any particular agent currently employed in the protocols. Because of this paucity of evidence, this review was conducted with the aim of examining, critically, the evidence relating to the efficacy of five anti-epileptic drugs in the treatment of benzodiazepine-resistant status epilepticus. These medications are lacosamide, levetiracetam, valproate, phenytoin and phenobarbital. The last two drugs have been extensively used for this indication for many years, based largely on the evidence derived from the Veterans Affair Trial[8]; although it is worth noting that these medications were sometimes given as a first-line treatment in that study. The other three antiepileptic drugs have been more recently introduced, and although widely prescribed in this situation, are not licensed specifically for use in status epilepticus.

2. Methods

2.1. Aims

To identify, via reproducible methodology, all the available literature related to the use of the five anti-epileptic drugs in

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benzodiazepine-resistant status epilepticus, to assess the heterogeneity and reliability of the data, to analyze the extracted data to quantify the relative efficacy of these drugs, and to provide recommendations for the use of the latter in patients with benzodiazepine-resistant status epilepticus.

2.2. Patients, methods and analysis

A pre-specified protocol was followed for the search, extraction, and analysis of data following the methodology of the "*Systematic Reviews: Centre of Review and Dissemination's guidance for undertaking reviews in health care*" published by the Centre of Review and Dissemination, University of York[18] and "*Cochrane Handbook of Systematic Reviews of Intervention*".[19] Patients reported in the published papers were included in the analysis if they fulfilled the eligibility criteria set out in Table 1. All patients with convulsive status epilepticus, of any type, and who had failed to respond to benzodiazepine therapy and were thus given one of the five study drugs as second-line therapy were included, regardless of age or other clinical variable.

Internet-based searches were implemented through the online databases MEDLINE and EMBASE, both accessed via Ovid (see supplementary material 1 for search protocol). The search results from the two databases were combined with the duplicates excluded. In addition, the references in the bibliographies of the relevant papers were individually searched and back-traced. In several instances, the authors of the identified studies were contacted via email or telephone, to answer specific queries relating to data analysis in their papers (notably to ascertain details of such aspects as the numbers of patients treated who were benzodiazepine-resistant and their outcome).

The papers were selected for the review by screening the search results by title and abstract for eligibility. The filtered studies would, then, be read as a whole, subjected to the inclusion criteria, stratified according to the intervention of interest, and scrutinized for their level of evidence and risk of bias. Then, they would go through data extraction, tabulation, pooling then meta-analysis, if eligible for the latter.

Table 1
Eligibility criteria.

Participants	Patients with status epilepticus who have been resistant to initial therapy with benzodiazepines were included. Only human studies and studies of convulsive (motor) status epilepticus were included. In some studies, simple and complex partial seizures were not subdivided, and it is thus possible that some non-convulsive cases were included; however where a study exclusively included non-convulsive status epilepticus, it was not considered. There was no restriction by age groups, co-morbidities or epilepsy background.
Interventions	Intravenous lacosamide, levetiracetam, valproate, phenytoin, and phenobarbital as second line therapy after failure of benzodiazepines. No dose or rate restrictions were specified.
Comparators	None
Outcomes	The variable extracted was cessation of seizure activity (other outcomes were also sought but are not reported here including, mortality, new neurological deficit, and tolerability). Cessation of seizure activity, or the drug's efficacy, was defined differently by different authors in the selected papers, and definition was, therefore, reported as a variable and acknowledged as one of the several sources of heterogeneity.
Study design	Original papers with any study design were included. There was no restriction on the number of patients in case series. All studies which provided data on outcome following treatment with one (or more) of the five drugs were included, whether these were controlled or uncontrolled and whether or not a comparator was included.

Papers were excluded where original data was not presented (for example reviews and expert opinions), which were published in non-English languages without abstract/accredited translation for the required data, where the drugs were used in more advanced stages of status epilepticus (where benzodiazepines, then anaesthetics and other antiepileptic drugs had been used before the medications of interest), and where data extraction/interpretation was not possible.

The papers were classified into levels according to the Oxford Centre of Evidence Based Medicine (CEBM).[20] In case of randomized trials and non-randomized prospective studies, assessment of the risk of bias was performed using *the Cochrane Collaboration's Tool for Assessment of Risk*.[21]

Data was extracted by filling out a proforma by one reviewer; the process was supervised by the other reviewer. Data were then analyzed using both STATA® 11 (by StataCorp LP, Texas, USA) and Comprehensive MetaAnalysis version 2 (CMA2®-by Biostat®, New Jersey, USA). The protocol is based on dichotomous outcome analysis of a single group estimate: inverse variance weighting is performed for each estimate, followed by random-effects analysis of the pooled estimates of all the studies describing an intervention, taking in consideration both the within-study and between-studies variances. The protocol and formulae for the random effect meta-analysis are given in the supplementary material 2. Single-patient case reports were not included in the meta-analysis due to lack of statistical dispersion. There was one case of epilepsia partialis continua found in the review, but as it was a single-patient report, it was not included in the meta-analysis.

The reasons for choosing random-effects model are varying sample sources, demographics, aetiology, and types of seizures, treatment with different doses, timing of administration, and definitions of outcome. All the aforementioned differences are substantial sources of heterogeneity that make fixed-effect meta-analysis unsuitable. The random-effects model was not chosen based on a statistical heterogeneity test.[22] However, heterogeneity was quantified via I^2, a statistic used to quantify how much of the variability in the results is due to real heterogeneity rather than a random sampling error.[23]

3. Results

3.1. Characteristics of publications analyzed

A total of 2754 papers were identified on MEDLINE/EMBASE (see supplementary material 1) from which 2652 papers were excluded due to non-relevance. From the remaining 102 (with an added 6 papers from reference tracing), only 27 papers were retrieved for data extraction. Some studies covered two or three drugs; therefore, the number of papers from summation of studies per drug was 32. The papers included consist of 1 randomized double-blinded trial, 5 open-label trials, 18 case series and 3 case reports. They described 798 episodes of convulsive status epilepticus.

The levels of evidence of the studies are as follows: level 4 (18 studies, 66%), level 4- (3 studies, 11%), level 2b (5 studies, 19%), and, level 1b (1 study, 4%) (see supplementary material 3). For prospective studies, assessment of the risk of bias was also performed, the results of which are illustrated in Table 2. It is worth noting that neither the prospective studies nor the single randomized controlled trial are registered at the NIH Clinical Trial Centre (http://clinicaltrials.gov/ct2/home).

Sources of heterogeneity were multiple; these include study design (retrospective, prospective, randomized and non-randomized, blinded and non-blinded), demographics (age, gender,

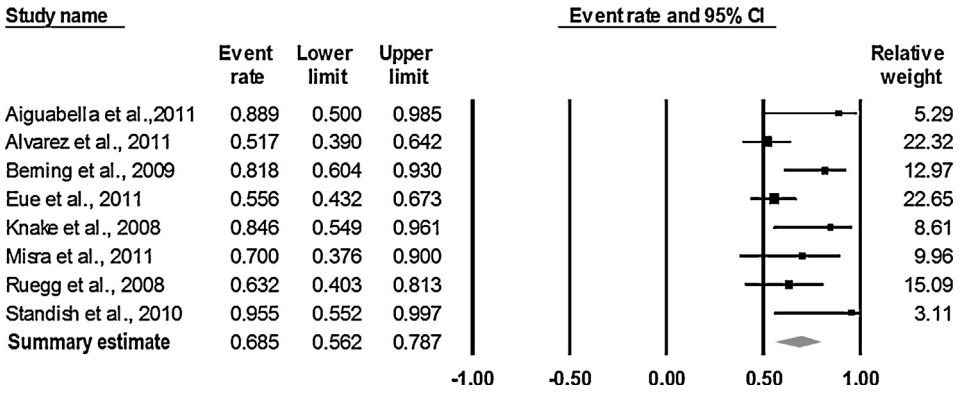

Fig. 1. Forest plot for efficacy of levetiracetam; CI: confidence interval.

comorbidities, and previous medications), intervention characteristics (dosage, rate of infusion, manufacture, drug levels), and condition characteristics (aetiology, semiology of seizures, duration of seizures to be considered status epilepticus, duration of status before intervention), response characteristics (time to seizure termination, presence of follow up period for re-emerging seizures).

The definition of status epilepticus varied between studies: 10 papers (37%) used 5-min duration, while 5 other studies (18.51%) specified the classical 30-min definition. Ten- and 20-min durations of status were the criteria for 2 papers (3.7%, each); while 15-min minimum was the criterion for 2 other studies (7.4%). In 8 studies (29.6%), a definition for status epilepticus was not specified. The definition of response to the intervention varied as well. 14 papers (51.9%) specified a time-window in which seizure termination was considered favourable. The most common specification was termination of seizures within 30 min of infusion (6 papers, 22.2%); other definitions include 3 min, 15 min, 20 min, 1 h, 12 h (1 paper for each, 3.7%), 24 h (2 papers, 7.4%) and 48 h (1 paper, 3.7%). A variable period of seizure freedom was a secondary endpoint in 9 studies. The most common time-window was 24 h (5 papers, 18.5%); other specified windows include 6 h, 12 h, 48 h and 7 days (1 paper for each, 3.7%). No temporal definition of response was given in 12 papers (44.4%). One study (3.7%) linked the time condition for seizure freedom to the end of infusion.

Considering the above mentioned sources of heterogeneity, I^2 was relatively low and within acceptable limits. The raw data from the publications included in the analysis are available in the supplementary material 4. Because of the heterogeneity or absence of data on variables such as age, time of administration, prior epilepsy, concurrent AEDs and AED levels, data was not stratified according to these variables, although in any future study (particularly in a randomized controlled trial) these would be important variables to consider.

3.2. Findings

3.2.1. Lacosamide

After applying the search methods, 109 papers were identified, from which only 13 were retrieved, due to non-relevance of the rest. From these 13, only 2 papers met the inclusion criteria. The papers described treatment of a total of 70 patients with status epilepticus of varying aetiologies, semiologies and stages.[24,25] The authors provided further data indicating which patients met our inclusion criteria (i.e. second-line treatment after benzodiazepine failure). Only 4 patients met these criteria, a number too small to permit meta-analysis (see supplementary material 4 for details).

3.2.2. Levetiracetam

From original 345 papers identified from the search, 318 were excluded by title/abstract screening. While 4 studies were added via bibliography tracing, 21 studies were excluded after reviewing the whole article. Thus, only 10 papers contributed to this review, addressing the use of levetiracetam in 206 SE episodes.[26–36] Two reports were excluded from meta-analysis because each reported only a single patient.[28,31] The mean efficacy from the remaining 8 studies was 68.5% (95% CI: 56.2–78.7%; Fig. 1). Heterogeneity assessed by I^2 was 12%. Averaged weighting of each contributing study is available on the forest plot as percentage. Two papers, those of Eue et al. (2011)[26] and Alvarez et al. (2011)[36], contribute the most to these statistical results.

3.2.3. Phenobarbital

From 537 search results, 520 studies were excluded via the title/abstract screening due to non-relevance. Seventeen papers were retrieved of which 3 papers, reporting treatment of 43 episodes of benzodiazepine-resistant status epilepticus, were considered eligible for inclusion.[37–39] One case report was excluded from the meta-analysis.[39] The Meta-analysis revealed a mean efficacy of 73.6% (95% CI: 58.3–84.8%; Fig. 2). I^2 was 0% due

Table 2
Assessment of the risk of bias in prospective studies.

Study name	Selection bias: random sequence generation	Selection bias: allocation concealment	Performance bias: blinding (masking)	Detection bias: blinding of outcome assessment	Attrition bias: incomplete outcome data	Reporting bias: selective outcome reporting
Agarwal et al. (2007)	Unclear	Unclear	Unclear	Low	Unclear	High
Chen et al. (2011)	Low	High	High	Low	Low	Low
Kokwaro et al. (2003)	High	High	High	High	Low	Low
Misra et al. (2011)	Low	Unclear	Unclear	Low	Unclear	Unclear
Ogutu et al. (2003)	Unclear	Unclear	Unclear	Low	Low	Low
Malamiri et al. (2012)	Low	Low	Low	Low	Low	Low

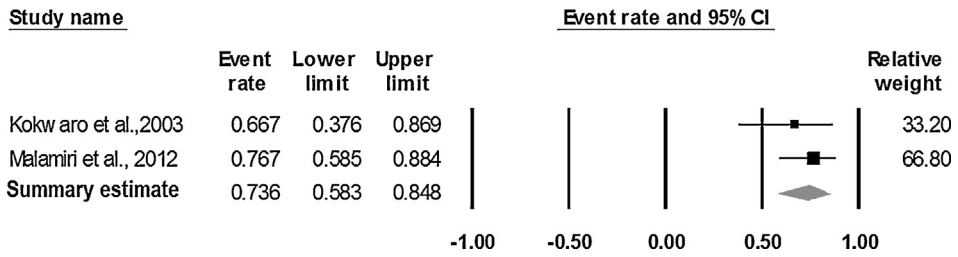

Fig. 2. Forest plot for efficacy of phenobarbital; CI: confidence interval.

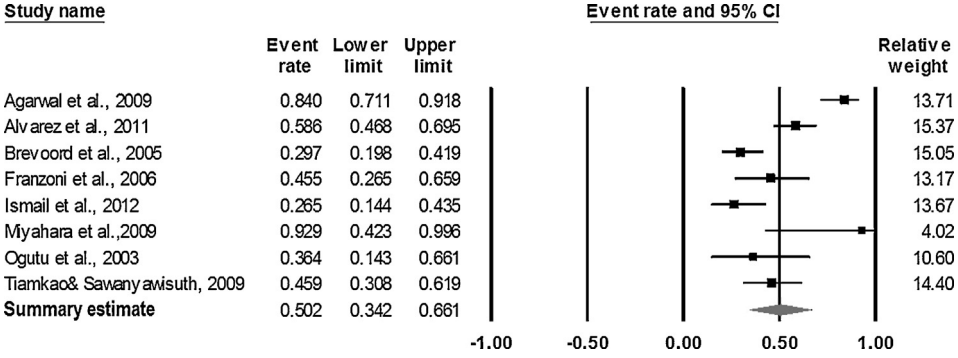

Fig. 3. Forest plot for efficacy of phenytoin; CI: confidence interval.

to the number of studies taken, rendering Q statistic = 1 (see supplementary material 2 for complete reference of the random-effects model). Averaged weighting of each contributing study is available on the forest plot as percentage, with Malamiri et al. (2012)[38] contributing to more than two thirds of the statistical weight.

3.2.4. Phenytoin

There were 996 papers as the result of the protocol used for databases search. 968 papers were excluded via title/abstract screening. The remaining 28 papers were retrieved for further inspection. Only 8 studies, reporting 294 episodes of status epilepticus, meet the inclusion criteria.[36,40–46] Meta-analysis of the pooled effect sizes showed a mean efficacy of 50.2% (95% CI: 43.2–66.1%; Fig. 3). Heterogeneity via I^2 was calculated to be 16.45%. Averaged weighting of each contributing study is available on the forest plot. Alvarez et al. (2011)[36] and Brevoord et al. (2005)[43] seem to contribute the most to the statistical results.

3.2.5. Valproate

After applying the search protocol, 767 results were identified. Seven hundred forty two papers were excluded due to non-relevance by title/abstract screening; 2 were added via reference tracing to give a net total of 27 papers. These were assessed, and finally 9 papers, describing treatment in 251 benzodiazepine-resistant episodes, were included.[36,38,45–51] One case report was excluded from the meta-analysis[51] while the remaining 8 studies yielded a mean effect size for the efficacy of valproate of 75.7% (95% CI: 63.7–84.8%; Fig. 4). Heterogeneity calculated via I^2 was 12.73%. Averaged weighting of each contributing study is available on the forest plot as percentage. Alvarez et al. (2011)[36] and Chen et al. (2011)[50] seem to contribute the most to the statistical results.

4. Discussion

4.1. Limitations

To the best of our knowledge, this is the first attempt, to review the five antiepileptic drugs for use in patients with status epilepticus who have failed to respond to initial benzodiazepine treatment (as recommended by most of the current protocols), and to implement a meta-analysis of the findings.

The strength of the study is its strictly applied inclusion criteria, and the systematic search, method and analysis. However, the investigation revealed a number of important limitations:

a. The number of studies that have addressed the effectiveness of second-line therapy is small (27 papers).

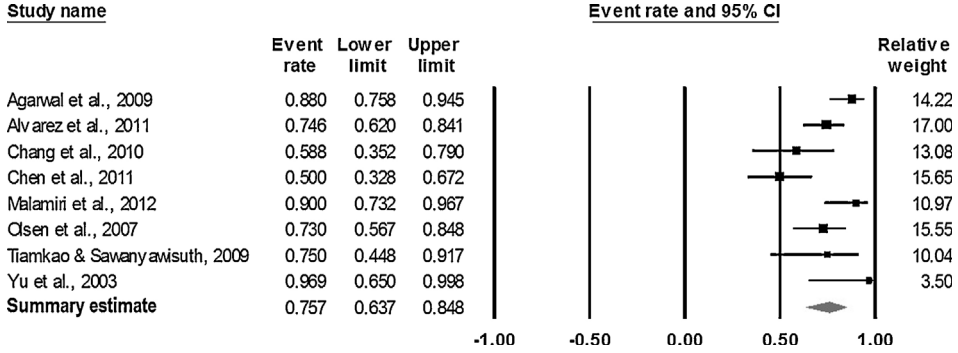

Fig. 4. Forest plot for efficacy of valproate; CI: confidence interval.

b. The studies are mostly observational and retrospective (21; 77.7%).
c. There is near-total absence of randomized double-blinded trials (Class I evidence) to compare the interventions (1; 3.7%).
d. For the few prospective studies, most are open-label (5; 18.5%), with high risk of bias in multiple domains.
e. There is also a lack of homogeneity in the findings – few studies sharing comparable questions, outlines of methodology, aims, or even definitions of variables (such as status epilepticus) and main endpoints (such as the response or its duration). This has caused significant clinical and statistical heterogeneity, and limited an original intention to study the influence of variables in correlation analysis. In addition, this heterogeneity compromises the strength of evidence derived from this review, as the confounders cannot be taken, statistically, into account.
f. The random-effects model adopted for the meta-analysis has resulted in estimates with wide confidence intervals (i.e. larger uncertainty) and, therefore, less powerful impact.
g. In some settings, current practice is to use second-line treatment immediately or very soon after a full dose of benzodiazepine, especially diazepam, to avoid the potential of recurrence of seizures. Neither this practice nor the adequacy of first line treatment was appropriately assessed in the participating studies.

These limitations are important. Any decisions about drug therapy need to be made in the knowledge that the published literature is not wholly adequate and that the evidence base on which to make comparisons of studies of different designs, with different definitions and which do not consider other variables is poor. Such a situation though is not uncommon in other clinical settings, particularly in relation to emergency therapy. Certainly, better quality studies are needed before gold-standard recommendations can be made. One main outcome of our analysis is to highlight these weaknesses. Nevertheless, advice regarding therapy is needed, even in the absence of optimal data.

4.2. Choice of drugs

Here we present our findings from the meta-analysis and narrative findings regarding side-effects from the published literature for each drug. In making comparisons, in the absence of any randomized controlled trial (RCT) in which direct comparisons are reported, our conclusions must be inevitably to an extent subjective. Furthermore, as emphasized in the sections on limitations, there are other important clinical factors which influence outcome in status epilepticus. Our recommendations are therefore provisional and indirectly based, but made on what we consider the best available evidence. We have focused on adult SE and there are suggestions for some drugs that efficacy in paediatric populations may differ. Cost-benefit assessments would also be useful, but cannot be made as controlled data related to comparison of side-effects and complication rates, and other economic variables are not systematically reported. One particular issue of interest would be whether treatment, especially in refractory cases, may sometimes worsen outcome. This requires separate and specific study.

4.2.1. Lacosamide

There is not enough evidence to recommend using lacosamide routinely in the treatment of benzodiazepine-resistant status epilepticus at present, despite the accumulating studies commending on its efficacy in individual cases. Nevertheless, the drug has favourable properties including a possible novel mode of action and an absence of significant side-effects and interactions, which might favour its use in the future especially for patients with co-morbidities and those on polytherapy.[52] From these studies, it is clear that Lacosamide can be effective and safe, in a 200–400 mg bolus dose range in adult patients; however, the magnitude of this efficacy cannot, yet, be compared to the other medications. Data on its usage and dosing in paediatric SE is lacking.

4.2.2. Levetiracetam

The estimated mean efficacy of levetiracetam is 68.5%, when infused in doses between 1000 and 3000 mg in young adults, or 20 mg/kg. Experience is relatively limited, but suggests to date that the drug is free of significant adverse-effect and well tolerated in paediatric, adult and elderly populations and in those with comorbidities. It has neither common cardio-respiratory side-effects nor drug–drug interactions.[53]

4.2.3. Phenobarbital

Phenobarbital has an estimated efficacy, in the meta-analysis, of 73.6%; however, the confidence interval was very wide (95% CI: 58.3–84.8%), making the clinical relevance of this result unclear. This efficacy, when supported by a potential neuroprotective effect, is a significant advantage. Disadvantages include adverse effects that limit its use, such as respiratory depression, hypotension, severe sedation, tolerance and the potential for drug interactions.[6,54]

4.2.4. Phenytoin

Phenytoin had a mean efficacy estimate of 50.2%. In the reported studies, phenytoin was administered in doses classically recommended to produce a therapeutic blood level, but it is well-established that drug level monitoring is needed in view of the non-linear kinetics of phenytoin.[55–57] This was, often, not reported (87.5% of studies did not report the levels), and one possible reason for relatively low efficacy reported in some patients may have been inadequate levels. Another possible explanation is the fact that lower cerebral concentrations of phenytoin in animal models are found in lesional brain foci of seizure activity.[58–61] Other disadvantages are the absence of data substantiating its use for older population (due to expected high rate of cardiovascular adverse-events) and for neuroprotection, where it may also be detrimental in certain types of brain injury.[62] Advantages, though, are its long duration of action, fast CNS entry,[63–65] availability and large experience accrued over decades of use. The side-effects of IV phenytoin include significant cardio-respiratory risks (cardiac arrhythmia, hypotension, reduced cardiac output)[66,67] and also risks of thrombosis and inflammation at the injection site sometimes resulting in distal ischaemia (the 'purple-glove' syndrome).[68–71] In view of the above points, although phenytoin is often considered the drug of first choice in benzodiazepine-resistant status, the published evidence does not appear to support this practice.

4.2.5. Valproate

The meta-analysis found the mean efficacy of valproate to be 75.7%. The fact all the comparative, prospective and randomized studies include valproate as one of their two or three arms gives more power to the statistical analysis. In addition to its high efficacy in acute situation, follow-up seizure freedom rates were also higher, and the drug was well-tolerated, even with large doses (−up to 100 mg/kg) and rates of infusion (up to −6 mg/kg/min). It is free of cardio-respiratory side effects which is an important advantage. However, high doses of IV valproate are likely to cause hyperammonaemia and in susceptible patients, it is likely that ammonia concentrations could rise to very high and potentially dangerous levels although data on this is lacking.[72,73] There is a risk of hepatic and pancreatic toxicity, and valproate encephalopathy.[73] There is also a theoretical risk that the use of high dose

valproate will exacerbate a bleeding tendency due to its effects on platelets and platelet function[74], which might carry risks in some situations in status epilepticus (for instance in acute stroke), but to the best of our knowledge no such side-effects have been reported in practice in status epilepticus.

4.3. Other factors influencing outcome

Several significant factors may influence the chance of seizure cessation and final outcome(s) of status epilepticus. These have been outlined as sources of heterogeneity above, and include variables such as the adequacy of first line therapy, the duration of status epilepticus before treatment was initiated, the aetiology of seizures, the age of the patients, and dosage and rate of infusion of the drug. This meta-analysis could not analyze these variables or use them to interpret the outcome differences because of missing data.

Several other observations were made about outcome from this analysis of the literature. First, there seems wide agreement that the duration of seizures before treatment was inversely related to the probability of clinical seizure cessation, whatever treatment is chosen, i.e. the longer the seizures prior to treatment, the less likely they are controlled by medications.[40,42,43,46,48,50] Second, aetiology is a most important variable to account for both treatment failure and adverse long-term outcome, with symptomatic seizures carrying the poorest response to second-line treatment.[30,36,43,50] Finally, there are a variety of findings about whether seizure type influences outcome in the various studies of drug effect, and no agreement on this point.[26,33,36,48] These data require further research via prospective designs of future studies in which multiple variables are controlled to explore the effects of individual factors on primary and secondary treatment outcomes.

4.4. Recommendations for treatment

Although there are few controlled studies and a general poverty of data, we consider that the data reviewed above provide sufficient evidence for limited recommendations to be made. The highest efficacy was attributed to valproate, levetiracetam and phenobarbital. Each of these drugs has differing advantages and drawbacks. Taken altogether, it is our view that any of these three could have claim to be first line therapy in benzodiazepine-resistant status epilepticus in most patients. There are differing clinical situations where one might be preferred over the others – for instance the avoidance of phenobarbital where the risk of hypotension or respiratory depression are significant or the avoidance of valproate where there is a particular susceptibility to hyperammonaemia or hepatic failure (possibly in children with mental handicap). We consider that the many disadvantages of IV phenytoin, linked to its lower efficacy, make this an unattractive choice for first-line therapy in benzodiazepine-resistant cases despite its wide usage in this situation globally. Lacosamide is a much newer compound with theoretical advantages, but the published experience is so slight that more studies are required, in our view, before it can be recommended as either a first or second-line antiepileptic drug in benzodiazepine-resistant status epilepticus.

From this literature review, the following dosages in adults seem most commonly or effectively employed: valproate – 20–30 mg/kg as a bolus dose with a maximal infusion rate of 6 mg/kg/min; levetiracetam – bolus dose of 20 mg/kg or 1000–2000 mg in a rate of 1–1.5 mg/kg/min or 100 mg/min; phenobarbital 20 mg/kg at a rate of 50–75 mg/min; phenytoin 15–20 mg/kg in a rate of 50 mg/min; lacosamide 400 mg with an infusion rate of 40–80 mg/min. These doses apply to adults without systemic complications such as hepatic, renal or mitochondrial disease (the latter being a particular contra-indication to the use of valproate) or those with other conditions or comorbidities which might interfere with their prescription.

These recommendations are made, we fully recognize, on an evidence base which is small and inadequate. Comparison with existing guidelines and reviews could be made, but these too are based generally on an inadequate controlled data base. More definitive recommendations can only be made on the basis of well-conducted randomized trial data, preferably with each medication compared to another. From the participating studies, only the paper of Malamiri et al.[38] fulfilled all the criteria of a successful randomized double-blinded trial in status epilepticus therapeutics. There is a proposed study – the Established Status Epilepticus Treatment Trial (ESETT)[75] – currently in the planning stage, and it is hoped that this study will greatly improve the evidence on which to base recommendations.

Conflict of interest

This paper is based on the MSc thesis by ZY, which was supervised by SDS. ZY was funded by a scholarship from the Higher Committee of Education Development in Iraq (HCED), and has not conflicts of interest to declare. SDS has received travel grants and speakers honoraria from UCB, the manufacturers of levetiracetam and lacosamide; his potential conflicts of interest in past 3 years or the foreseeable future are: Speakers honoraria and/or advisory board membership of UCB, Eisai, GSK, Johnson and Johnson, Ranbaxy and Bial.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.seizure.2013.12.007.

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