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ARTICLE

Meta-analysis and cost-effectiveness of second-line antiepileptic drugs for status epilepticus

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Abstract

Objective

Compare the cost and effectiveness of nonbenzodiazepine antiepileptic drugs (non-BZD AEDs) for treatment of BZD-resistant convulsive status epilepticus (SE).

Methods

Decision analysis model populated with effectiveness data from a systematic review and meta-analysis of the literature, and cost data from publicly available prices. The primary outcome was cost per seizure stopped ($/SS). Sensitivity analyses evaluated the robustness of the results across a wide variation of the input parameters.

Results

We included 24 studies with 1,185 SE episodes. The most effective non-BZD AED was phenobarbital (PB) with a probability of SS of 0.8 (95% confidence interval [CI]: 0.69–0.88), followed by valproate (VPA) (0.71 [95% CI: 0.61–0.79]), lacosamide (0.66 [95% CI: 0.51–0.79]), levetiracetam (LEV) (0.62 [95% CI: 0.5–0.73]), and phenytoin/fosphenytoin (PHT) (0.53 [95% CI: 0.39–0.67]). In pairwise comparisons, PB was more effective than PHT ($p = 0.002$), VPA was more effective than PHT ($p = 0.043$), and PB was more effective than LEV ($p = 0.018$). The most cost-effective non-BZD AED was LEV (incremental cost-effectiveness ratio [ICER]: $18.55/SS), followed by VPA (ICER: $94.44/SS), and lastly PB (ICER: $847.22/SS). PHT and lacosamide were not cost-effective compared to the other options. Sensitivity analyses showed marked overlap in cost-effectiveness, but PHT was consistently less cost-effective than LEV, VPA, and PB.

Conclusion

VPA and PB were more effective than PHT for SE. There is substantial overlap in the cost-effectiveness of non-BZD AEDs for SE, but available evidence does not support the preeminence of PHT, neither in terms of effectiveness nor in terms of cost-effectiveness.

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Glossary

AED = antiepileptic drug; **BZD** = benzodiazepine; **CI** = confidence interval; **ICER** = incremental cost-effectiveness ratio; **LAC** = lacosamide; **LEV** = levetiracetam; **PB** = phenobarbital; **PHT** = phenytoin/fosphenytoin; **SE** = status epilepticus; **SS** = seizures stopped; **VPA** = valproate.

Status epilepticus (SE) is one of the most frequent neurologic emergencies, with an incidence of 17–23/100,000 in children and 4–15/100,000 in adults, affecting disproportionately young children and older adults.[1,2] Etiology, age, and duration of SE all affect outcome,[3,4] but duration is the factor most amenable to modification with a timely and effective treatment. Most current SE treatment guidelines recommend a timely stepwise treatment of SE, starting with benzodiazepines (BZDs) and moving to non-BZD antiepileptic drugs (AEDs) as needed.[5,6] However, there is limited evidence on the most effective non-BZD AED for SE.[5,6]

After failure of 1 or 2 doses of BZDs to stop SE, guidelines recommend treatment with phenytoin/fosphenytoin (PHT), phenobarbital (PB), valproate (VPA), levetiracetam (LEV), or lacosamide (LAC).[5,6] PHT has been a standard treatment for SE since the 1940s, it is reportedly the most frequently used non-BZD AED for SE in surveys of clinical practice,[7,8] and it appears as the preferred initial non-BZD AED in many hospital SE protocols.[9] However, evidence-based guidelines acknowledge that there is insufficient information from individual studies to recommend PHT, PB, VPA, LEV, or LAC as the most effective second-line therapy for SE.[6] Similarly, there have not been cost-effectiveness studies comparing second-line non-BZD AEDs for SE.

This study aims to address these gaps in knowledge by comparing the effectiveness and cost-effectiveness of non-BZD AEDs for SE.

Methods

Study design

This is a systematic review, meta-analysis, and cost-effectiveness analysis.

Population of interest

We focused on patients with convulsive SE who did not respond to initial rescue treatment with BZDs. The effectiveness and cost-effectiveness of initial treatment with non-IV BZDs for SE has been previously reported.[10]

Outcome

The outcome of the meta-analysis is the effectiveness of the different non-BZD AEDs, and the outcome of the decision analysis model is the cost-effectiveness of non-BZD AEDs to stop SE. The cost was based on market prices for each non-BZD AED. Effectiveness was measured as the probability of seizures stopped (SS), that is, if a non-BZD AED had a 75% probability of stopping SE, its effectiveness would be SS = 0.75. The measure of cost-effectiveness was the incremental cost-effectiveness ratio (ICER), which is calculated as the incremental cost of a treatment divided by the incremental effectiveness (both compared to the next most cost-effective treatment). When options are not exclusive (several can be selected at the same time), the problem is classified under the category of "noncompeting choice" and cost-effectiveness should be calculated comparing each option to the "null option." In contrast, in competing-choice problems such as the present one, the alternatives are not independent: the choice of the most cost-effective alternative influences the additional effectiveness to be gained and the additional cost to be incurred by the second-most cost-effective alternative and so on. In competing-choice problems, the appropriate calculation of cost-effectiveness is the ICER, which measures the ratio of the additional cost to the additional gain in effectiveness, compared to the previous most cost-effective alternative. Treatments with a lower ICER cost fewer dollars per SS and are thus more cost-effective.

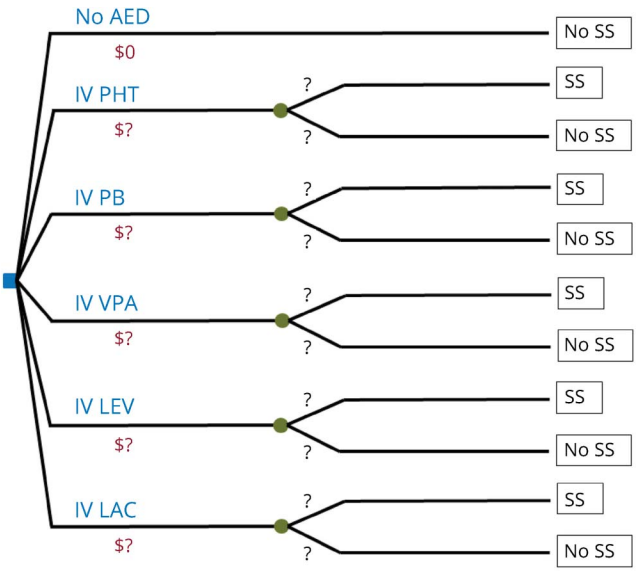
The decision model: Competing strategies

Main options for a health care provider when considering non-BZD AEDs for patients who did not respond to BZDs are PHT, PB, VPA, LEV, and LAC. The order of administration of a non-BZD AED may influence its effectiveness. Therefore, we only considered data of non-BZD AEDs when these were given as a second-line non-BZD AED, given after failure of initial BZDs and before any other non-BZD AED. Data available from github and zenodo, table e-1, github.com/IvanSanchezFernandez/CostEffectivenessAEDsforStatusEpilepticus and at zenodo.org/badge/latestdoi/154592756 specify for each study what BZDs and by what route were administered before the non-BZD AED. We could not find studies evaluating the effectiveness of fosphenytoin in which it was given as second-line non-BZD AEDs just after BZDs. Therefore, we considered the effectiveness of phenytoin as a surrogate for the effectiveness of fosphenytoin. Unless stated otherwise, we considered the cost of fosphenytoin, the most commonly used form in the United States. The decision model reflects the competing treatments and possible outcomes of each decision (figure 1).

Input parameters for the model

The input parameters for the model were extracted from the literature. The systematic search of the medical literature for effectiveness data used the following strategy in PubMed: ("phenytoin" OR "fosphenytoin" OR "phenobarbital" OR "valpro*" OR "levetiracetam" OR "lacosamide") AND "intravenous" AND "status epilepticus." Our search was

Figure 1 Decision tree



There are 6 options in this study: no AED, PHT, PB, VPA, LEV, and LAC. AED = antiepileptic drug; LAC = lacosamide; LEV = levetiracetam; PB = phenobarbital; PHT = phenytoin; SS = seizure stopped; $ = US dollars; VPA = valproate.

restricted to English-language full-length articles in humans until August 2018. In addition, we added relevant articles known to the authors and from the reference lists of the articles in the primary search (data available from github and zenodo, figure e-1, github.com/IvanSanchezFernandez/CostEffectivenessAEDsforStatusEpilepticus and at zenodo.org/badge/latestdoi/154592756). We excluded patients in whom non-BZD AEDs were given as first-line AED without prior BZDs, and also excluded patients in whom the non-BZD AED of interest was given after failure of other non-BZD AEDs. We estimated costs based on market data from a large drug database (Lexicomp, last accessed August 8, 2018), confirmed that the estimated costs were within the price ranges of retail pharmacies, a publicly available resource (drugs.com, last accessed August 8, 2018), and our own pharmacy department.

Meta-analysis

We performed a meta-analysis with the predictor being the second-line AED (or non-BZD AED) and the outcome being the proportion of SS. Because of expected heterogeneity in populations, response to treatment, and outcome definitions, we considered a priori a random-effects model. This a priori choice was supported by the finding of moderate to high between-study heterogeneity on statistical analysis as measured by the I^2 index. Publication bias was evaluated visually with a funnel plot that displayed the effect size (log-transformed proportion of SS) in the x-axis and precision (standard error) in the y-axis. We also evaluated publication bias using the Duval and Tweedie trim and fill method. For the Duval and Tweedie trim and fill method, we used a fixed-random model, which is a fixed-effect model to estimate the number of missing studies and a random-effects model to summarize the results. The fixed-random model performs better than the fixed-fixed model and no worse and marginally better in certain situations than the random-random model. We performed a subgroup analysis evaluating only prospective studies to determine whether the type of study (retrospective or prospective) contributed substantially to results and to between-study heterogeneity. We described results as proportion of SS with 95% confidence intervals (CIs). We compared the effectiveness of subgroups with the χ^2 test. We considered a conventional α level of 0.05.

Base case analysis

The base case refers to the cost-effectiveness model that uses the input parameters most likely to occur based on the literature and based on market costs, and yields outcomes that are also fixed.[11]

Sensitivity analysis

Sensitivity analyses evaluate the robustness of the base case analysis by evaluating how outcomes change when input parameters are modified.[11] In 1-way sensitivity analysis, the value of one parameter is varied over a broad range of values while keeping all other parameters constant.[11] In second-order Monte Carlo simulations, the individual input parameters are not fixed values, but they are randomly drawn from a distribution that reflects parameter uncertainty for that value.[11] Estimates based on meta-analysis or large series had distributions with little variance, whereas less-certain estimates based on limited literature or limited data have wider distributions.[11] The Monte Carlo model output is calculated with 10,000 iterations to simulate 10,000 random draws from each individual distribution as it would happen in a real clinical scenario.[11] The value of 10,000 iterations is a conventional value that yields stable estimates in repeated simulations for most cost-effectiveness studies and, in this study, we confirmed that results were stable in repeated simulations.[11] Second-order Monte Carlo simulations yield 95% CIs around the mean outcome, which reflect outcome uncertainty based on input uncertainty.[11]

Statistical software

Meta-analysis of proportions was performed in R: a language and environment for statistical computing (R Core Team [2015]. R Foundation for Statistical Computing, Vienna, Austria. R-project.org/) with RStudio and the package meta. All cost-effectiveness studies were performed in TreeAge Pro 2015 (TreeAge Software, Inc., Williamstown, MA). Interactive versions of the meta-analysis (app e-1, and as an interactive web page at ivansanchezfernandez-shinyapps.shinyapps.io/metaanalysis_aeds_se/) and of the cost-effectiveness model (app e-2, and as an interactive web page at ivansanchezfernandez-shinyapps.shinyapps.io/ce_aeds_se/) were created with the R packages ggplot2, plotly, and shiny and allow the reader to modify and update the meta-analysis and cost-effectiveness analysis with the most relevant and updated information, including local costs, in real time. Citations for the statistical analysis details and statistical packages can be found in data available from github and zenodo,

e-Statistics, github.com/IvanSanchezFernandez/CostEffectivenessAEDsforStatusEpilepticus and at zenodo.org/badge/latestdoi/154592756.

Data availability

The source data are available from the individual articles reviewed. All models, data, and results are available on request. The source code for the interactive models is available as an R script for RStudio data available from github and zenodo (apps e-1 and e-2, github.com/IvanSanchezFernandez/CostEffectivenessAEDsforStatusEpilepticus and at zenodo.org/badge/latestdoi/154592756).

Results

Systematic review and meta-analysis on effectiveness

We included 24 studies comprising a total of 1,185 SE episodes (table and data available from github and zenodo, table e-1, github.com/IvanSanchezFernandez/CostEffectivenessAEDsforStatusEpilepticus and at zenodo.org/badge/latestdoi/154592756). We could not find studies evaluating the effectiveness of fosphenytoin given as a second-line non-BZD AED after BZDs, and we therefore evaluated studies on the effectiveness of phenytoin. The most effective non-BZD AED was PB with an SS of 0.8 (95% CI: 0.69–0.88) followed by VPA 0.71 (95% CI: 0.61–0.79), LAC 0.66 (95% CI: 0.51–0.79), and LEV 0.62 (95% CI: 0.5–0.73), and the least effective non-BZD AED was PHT 0.53 (95% CI: 0.39–0.67) (figure 2). In pairwise comparisons, PB was more effective than PHT (p = 0.002), VPA was more effective than PHT (p = 0.043), PB was more effective than LEV (p = 0.018), but there were no statistically significant differences in effectiveness between PHT and LEV (p = 0.354), PHT and LAC (p = 0.216), PB and VPA (p = 0.161), PB and LAC (p = 0.104), VPA and LEV (p = 0.247), VPA and LAC (p = 0.617), and LEV and LAC (p = 0.647) (data available from github and zenodo, file e-1, github.com/IvanSanchezFernandez/CostEffectivenessAEDsforStatusEpilepticus and at zenodo.org/badge/latestdoi/154592756). The rank of effectiveness was not substantially modified after correcting for publication bias: the most effective non-BZD AED was PB with an SS of 0.79 (95% CI: 0.68–0.87), followed by LAC 0.66 (95% CI: 0.51–0.79), VPA 0.64 (95% CI: 0.53–0.74), and LEV 0.58 (95% CI: 0.46–0.7), and the least effective non-BZD AED was PHT 0.53 (95% CI: 0.39–0.67) (data available from github and zenodo, file e-2, github.com/IvanSanchezFernandez/CostEffectivenessAEDsforStatusEpilepticus and at zenodo.org/badge/latestdoi/154592756). After considering only prospective studies, the most effective non-BZD AED was PB with an SS of 0.79 (95% CI: 0.68–0.87) followed by VPA 0.71 (95% CI: 0.6–0.8), PHT 0.68 (95% CI: 0.6–0.76), and LAC 0.66 (95% CI: 0.51–0.79), and the least effective non-BZD AED was LEV 0.64 (95% CI: 0.51–0.76). After considering only prospective studies correcting for publication bias, the most effective non-BZD AED was PB with an SS of 0.79 (95% CI: 0.68–0.87)

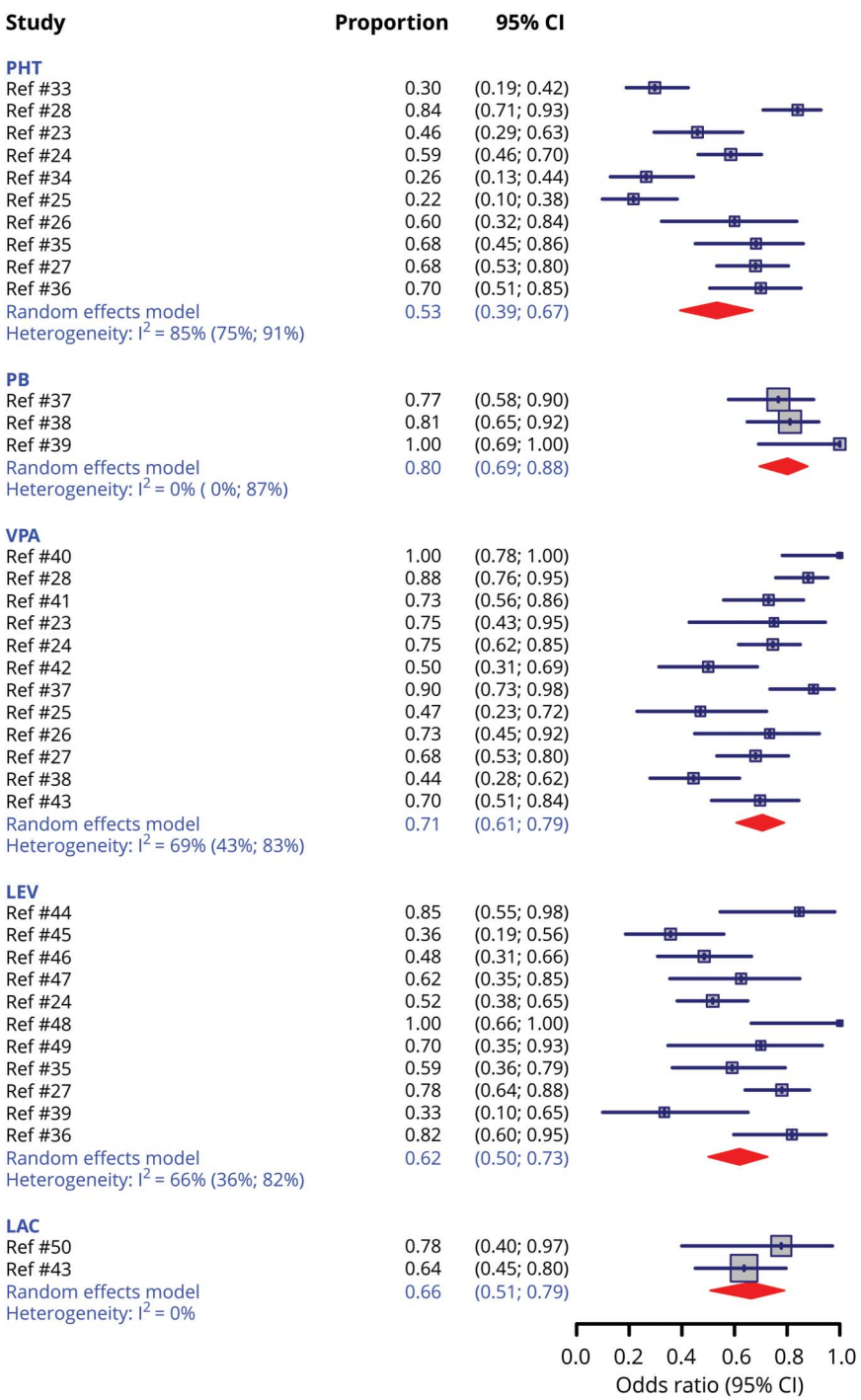
Table Inputs for the decision analysis model

Option	No. of studies and no. of patients	Base case analysis		Probabilistic distribution	
		Cost, $	Effectiveness, SS	Cost, $, triangular distribution	Effectiveness, SS, β distribution
No rescue medication		0	0	0	0
Fosphenytoin	No studies on the effectiveness of fosphenytoin	37.38	Unknown	Minimum: 14.95; likeliest: 37.38; maximum: 59.8	Unknown
Phenytoin	Effectiveness based on data from 10 studies with a total of 409 SE episodes, of which at least 114 were pediatric SE episodes	33	0.53	Minimum: 13.2; likeliest: 33; maximum: 52.8	Mean: 0.53; SD: 0.07
Phenobarbital	Effectiveness based on data from 3 studies with a total of 77 SE episodes, of which at least 40 were pediatric SE episodes	96.25	0.8	Minimum: 38.5; likeliest: 96.25; maximum: 154	Mean: 0.8; SD: 0.055
Valproate	Effectiveness based on data from 12 studies with a total of 384 SE episodes, of which at least 67 were pediatric SE episodes	20	0.71	Minimum: 8; likeliest: 20; maximum: 32	Mean: 0.71; SD: 0.05
Levetiracetam	Effectiveness based on data from 11 studies with a total of 273 SE episodes, of which at least 21 were pediatric SE episodes	11.5	0.62	Minimum: 4.6; likeliest: 11.5; maximum: 18.4	Mean: 0.62; SD: 0.06
Lacosamide	Effectiveness based on data from 2 studies with a total of 42 SE episodes, with no pediatric SE episodes	127.2	0.66	Minimum: 84.8; likeliest: 127.2; maximum: 169.6	Mean: 0.66; SD: 0.075

Abbreviations: SE = status epilepticus; SS = probability of seizure stopped.

followed by LAC 0.66 (95% CI: 0.51–0.79), VPA 0.65 (95% CI: 0.53–0.76), and PHT 0.62 (95% CI: 0.52–0.71), and the least effective non-BZD AED was LEV 0.52 (95% CI: 0.37–0.67) (data available from github and zenodo, file e-3, github.com/IvanSanchezFernandez/CostEffectivenessAEDsforStatusEpilepticus and at zenodo.org/badge/latestdoi/154592756). Inclusion of only prospective studies lacked the power to find statistically significant differences on pairwise comparisons (data available from github and zenodo, file e-4, github.com/IvanSanchezFernandez/CostEffectivenessAEDsforStatusEpilepticus and at zenodo.org/badge/latestdoi/154592756). We invite the reader to evaluate how the effectiveness varies when considering different studies in our interactive meta-analysis (app e-1 and as an interactive web page at ivansanchezfernandez-shinyapps.shinyapps.io/metaanalysis_aeds_se/).

Figure 2 Meta-analysis of the results from the literature



Effectiveness (proportion of stopped seizures) with phenytoin (PHT), phenobarbital (PB), valproate (VPA), levetiracetam (LEV), and lacosamide (LAC). CI = confidence interval.

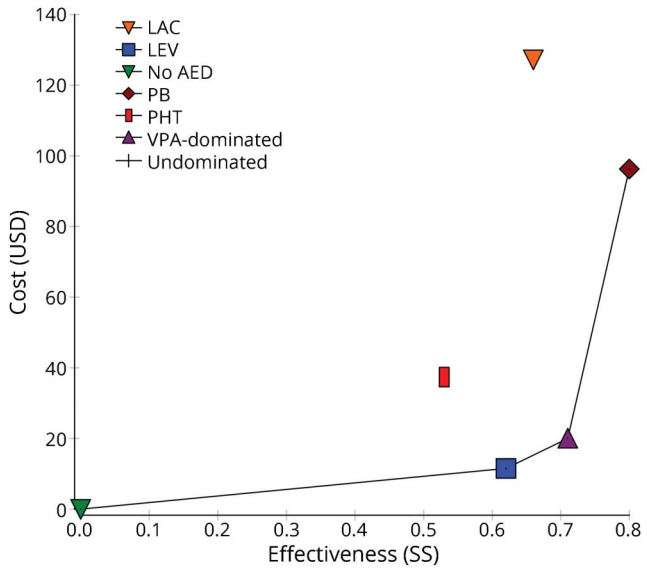
Cost data

The most expensive medication was LAC with a median bolus dose price of $127.2, followed by PB $96.25, PHT ($37.38 for fosphenytoin and $33 for phenytoin), VPA $20, and LEV $11.5 (data available from github and zenodo, table e-2, github.com/IvanSanchezFernandez/CostEffectivenessAEDsforStatusEpilepticus and at zenodo.org/badge/latestdoi/154592756). The input parameters used in the decision analysis model are summarized in the table.

Base case analysis

The ICER referencing to the next more cost-effective alternative showed that the most cost-effective alternative was LEV with an ICER of $18.55/SS followed by VPA with an ICER of $94.44/SS, and finally PB with an ICER of $847.22/SS. PHT with an incremental cost of $17.38, an incremental effectiveness of −0.18, and an ICER of −$96.56/SS, and LAC with an incremental cost of $30.95, and incremental effectiveness of −0.14, and an ICER of −$221.07 were not cost-effective compared to the other options (figure 3). Using the cost of phenytoin rather than the cost of fosphenytoin leads to similar results: the most cost-effective alternative was LEV with an ICER of $18.55/SS followed by VPA with an ICER of $94.44/SS, and finally PB with an ICER of $847.22/SS. PHT with an incremental cost of $13, an incremental effectiveness of −0.18, and an ICER of −$72.22/SS, and LAC with an incremental cost of $30.95, an incremental effectiveness of −0.14, and an ICER of −$221.07/SS were not cost-effective compared to the other options.

Figure 3 Base case analysis comparing the different AEDs for status epilepticus



The x-axis measures effectiveness as the proportion of seizures stopped and the y-axis measures cost in US dollars. An ideal non-BZD AED would have high effectiveness and low cost and would be close to the right end of the x-axis. To identify the non-BZD AED that offers the best effectiveness per dollar, the options are compared based on the ICER. The ICER is calculated as the incremental (compared to the next most cost-effective option) cost of a non-BZD AED divided by the incremental (compared to the next most cost-effective option) effectiveness. Therefore, non-BZD AEDs with a lower ICER are more cost-effective than those with a higher ICER: they cost less dollars per SS. The efficiency frontier (black line) links the most cost-effective non-BZD AEDs. Options above the efficiency frontier are less cost-effective than the options that form the efficiency frontier because they are costlier, less effective, costlier and less effective, or their increase in cost per unit of effectiveness (their ICER) is higher than the ICER of other options. Therefore, LEV, VPA, and PB are the more cost-effective strategies at different willingness to pay. PHT and LAC are dominated (above the efficiency frontier) and, therefore, not cost-effective when compared with the other options. AED = antiepileptic drug; BZD = benzodiazepine; ICER = incremental cost-effectiveness ratio; LAC = lacosamide; LEV = levetiracetam; PB = phenobarbital; PHT = phenytoin; SS = seizures stopped; USD = US dollars; VPA = valproate.

One-way sensitivity analysis

At its currently estimated effectiveness, PHT would become the most cost-effective option only if its cost was to be $9.8 or less. At its current cost, PHT would never become the most cost-effective option even with an effectiveness of 1. At its currently estimated effectiveness, LAC would become the most cost-effective option if its cost was to be $12.2 or less. At its current cost, LAC would never become the most cost-effective option even with an effectiveness of 1. We invite the reader to evaluate how cost-effectiveness varies when considering different inputs in our interactive cost-effectiveness analysis (app e-2 and as an interactive web page at ivansanchezfernandez-shinyapps.shinyapps.io/ce_aeds_se/).

Probabilistic sensitivity analysis (second-order Monte Carlo simulations)

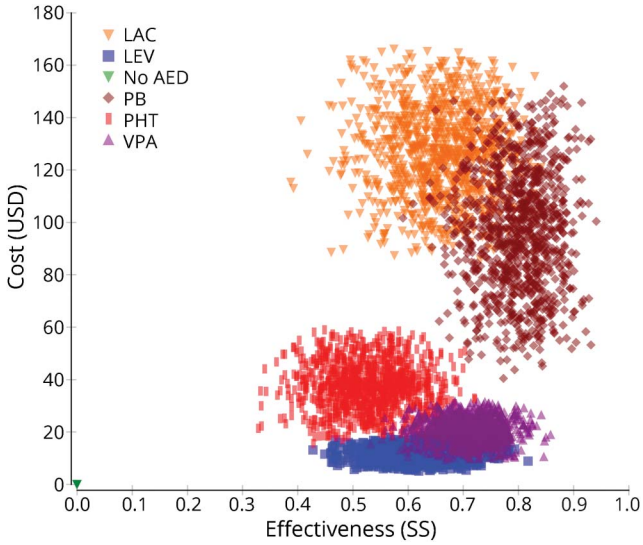
The effectiveness of non-BZD AEDs overlapped, although PHT and LAC were above the efficiency frontier in most simulations (figure 4). This fact is shown graphically also by the percentage of iterations where a strategy is cost-effective at different willingness to pay (figure 5). The more cost-effective strategy is no non-BZD AED for a willingness to pay from $0/SS to approximately $25/SS, LEV from approximately $25/SS to approximately $100/SS, VPA from approximately $100/SS to approximately $840/SS, and PB for a willingness to pay above approximately $840/SS. PHT and LAC were not the most cost-effective strategies at any willingness to pay (figure 5). We invite the reader to evaluate how cost-effectiveness varies when considering different inputs in our interactive cost-effectiveness analysis (app e-2 and as an interactive web page at ivansanchezfernandez-shinyapps.shinyapps.io/ce_aeds_se/).

Discussion

This systematic review, meta-analysis, and cost-effectiveness study of the literature on second-line non-BZD AEDs for convulsive SE shows that: (1) there are no completed studies evaluating the effectiveness of fosphenytoin as a second-line non-BZD AED, only studies on phenytoin; (2) the preeminence of PHT as second-line non-BZD AED is not supported by current evidence; and (3) there is substantial overlap in cost and effectiveness among PHT, PB, VPA, LEV, and LAC, although PHT is less effective than the other choices and less cost-effective than PB, VPA, and LEV.

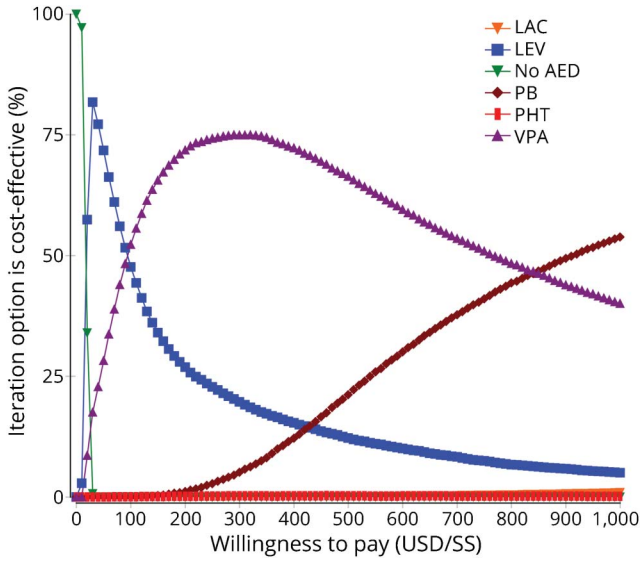
Guidelines for convulsive SE recommend a stepwise treatment with BZDs followed by non-BZD AEDs, and continuous

Figure 4 Second-order Monte Carlo simulations comparing rescue medications for status epilepticus



This figure roughly conveys the probabilistic distribution of the results. Each cloud approximately represents how results from figure 2 vary within 95% confidence intervals. The x-axis measures effectiveness as the proportion of SS and the y-axis measures cost in US dollars. An ideal rescue medication would have high effectiveness and low cost and would be close to the right end of the x-axis. There is overlap in cost-effectiveness between the non-benzodiazepine AEDs. PB is both more effective and costlier than LEV and VPA, so it is in the efficiency frontier, but its higher effectiveness also has a higher cost. Most of the distributions for PHT and LAC lies above and to the left of the distributions of LEV, VPA, and PB (above the efficiency frontier). The degree of uncertainty in the input parameters is represented by the spread of the distribution: options with more uncertain values for cost and effectiveness such as LAC have a wider distribution than options with more established values for cost and effectiveness such as VPA. AED = antiepileptic drug; LAC = lacosamide; LEV = levetiracetam; PB = phenobarbital; PHT = phenytoin; SS = seizures stopped; USD = US dollars; VPA = valproate.

Figure 5 Acceptability curve



This figure roughly conveys at what willingness to pay intervals each option is more cost-effective. The x-axis measures the willingness to pay, that is, the dollars that a payer is willing to pay per SS. The y-axis measures the percentage of second-order Monte Carlo simulations where a particular option is the most cost-effective option. When the payer is willing to pay less than approximately $25/SS, no AED is the most cost-effective strategy in most simulations. For a willingness to pay between approximately $25/SS and $100/SS, LEV is the most cost-effective strategy in most simulations. For a willingness to pay between approximately $100/SS and $840/SS, VPA is the most cost-effective strategy in most simulations. For a willingness to pay above approximately $840/SS, PB is the most cost-effective strategy in most simulations. PHT and LAC are not the most cost-effective strategies at any willingness to pay. AED = antiepileptic drug; LAC = lacosamide; LEV = levetiracetam; PB = phenobarbital; PHT = phenytoin; SS = seizures stopped; USD = US dollars; VPA = valproate.

infusions as needed.[5,6] Classically, PHT was recommended as the preferred non-BZD AED for SE. Surveys of clinical practice[7,8] and hospital protocols[9] reflect that view by selecting fosphenytoin as the first option among non-BZD AEDs. However, more recent treatment guidelines de-emphasize PHT and acknowledge that there is insufficient evidence from individual studies to recommend any of PHT, PB, VPA, LEV, or LAC as the more effective second-line non-BZD AED.[5,6] This uncertainty was reflected in a Delphi process among pediatric neurologists and emergency physicians who identified second-line management of SE as one high-priority research question.[12] Unfortunately, a meta-analysis of 2 randomized clinical trials comparing LEV with PHT and 3 randomized clinical trials comparing VPA with PHT lacked the power to show differences between these treatments.[13] The classic meta-analysis of Yasiry and Shorvon[14] included 22 studies with 727 SE episodes and showed that, among non-BZD AEDs for SE, effectiveness was highest for VPA at 75.7% (95% CI: 63.7%–84.8%), followed by PB at 73.6% (95% CI: 58.3%–84.8%), and LEV at 68.5% (95% CI: 56.2%–78.7%), and the least effective non-BZD AED was PHT at 50.2% (95% CI: 34.2%–66.1%). Although very relevant, this meta-analysis included patients in whom non-BZD AEDs were given as second line after BZD failure, but also patients in whom non-BZD AEDs were given as first line before BZDs, and patients in whom non-BZD AEDs were given after failure of other non-BZD AEDs.[14] Furthermore, this study did not compare the effectiveness of the different options with formal statistical tests.[14]

Our study adds to prior literature by carefully selecting only patients in whom non-BZD AEDs were given as second line for SE. Specifically, we considered medications given after failure of BZDs and before any other non-BZD AED. Despite the heterogeneity in populations, timelines, and outcome definitions, our study represents the combined experience of 1,185 SE episodes. One of the most surprising findings is that we could not find studies on the effectiveness of fosphenytoin as a second-line non-BZD AED. We only found studies on the effectiveness of phenytoin. It can be argued that fosphenytoin is a prodrug of phenytoin and, therefore, their effectiveness should be similar. However, although fosphenytoin can be infused faster than phenytoin, the half-life for conversion of fosphenytoin to phenytoin is 8 to 15 minutes.[15] Considering the relevance of time to treatment in the management of SE,[3] a shorter infusion time might make fosphenytoin a better non-BZD AED than phenytoin, although a longer conversion to the active drug might make fosphenytoin a worse non-BZD

AED than phenytoin. Potential infusion side effects, such as purple glove syndrome, favor fosphenytoin when peripheral IV access is utilized for administration, but unfortunately, there are no published studies on the effectiveness of fosphenytoin as a second-line non-BZD AED for SE. Another relevant finding is that the effectiveness of phenytoin appears to be inferior to the effectiveness of other non-BZD AEDs, and this difference was statistically significant for PB and VPA. It is difficult to think of another major medical emergency in which the efficacy of one of the main recommended treatments (fosphenytoin) has not been evaluated in the literature and in which the surrogate efficacy data for that treatment (from phenytoin) tends to underperform when compared with other available treatments.[14]

While our study only considered non-BZD AEDs given as second-line treatment, the literature on non-BZD AEDs given as first line before BZDs or given after another non-BZD AED shows similar results. In a series of 48 patients with SE refractory to PB, VPA stopped seizures in 87.5% of cases.[16] In a study of 35 patients, VPA given at different stages of SE stopped seizures in 77.1% of cases.[17] In a series of children, VPA stopped SE refractory to diazepam, phenytoin, and PB in 32 of 41 cases (78.1%).[18] In a study of 63 patients, VPA stopped SE in 63% of cases.[19] Furthermore, in a series of 40 children who were not controlled after diazepam and 2 boluses of 20 mg/kg of PHT, VPA stopped seizures in 80% of the cases.[20] In a different study, 68 patients were randomly assigned to VPA or PHT as first-line treatment before BZDs.[21] VPA was more effective at controlling SE in 23 of 35 cases (65.7%) vs PHT controlling 14 of 33 cases (42.4%).[21] When the first AED (VPA or PHT) failed, the other medication was given.[21] In these refractory patients, VPA controlled SE in more patients (15/19 [79%]) than PHT (3/12 [25%]).[21] The landmark Veterans Affairs Status Epilepticus Cooperative Study Group, which is frequently referred to when supporting the choice of PHT, showed that, among patients with a verified diagnosis of overt SE, the effectiveness of PHT as first-line therapy was 43.6%, while the effectiveness of PB as first-line therapy was 58.2%.[22] In summary, most studies quantify the efficacy of PHT in the range of 40% to 70%, while they quantify the efficacy of PB and VPA in the range of 60% to 80%.

A valid criticism is that patients from different populations treated in different circumstances and with a variable time to treatment may respond to treatment differently and are, therefore, not comparable. However, the studies with several arms that compared different treatments in patients in equal baseline circumstances also suggested the same trend as our global meta-analysis. A retrospective study found that PHT stopped SE in 46% of cases while VPA controlled SE in 75%.[23] A retrospective analysis of a prospective registry found the effectiveness of VPA (74.6%) superior to that of PHT (58.6%) and LEV (51.7%).[24] A retrospective study found a very low but superior efficacy for VPA (47.1%) than for PHT (21.6%).[25] A randomized prospective study found a higher efficacy for VPA (73.3%) than for PHT (60%).[26] Only 2 prospective randomized studies showed a similar effectiveness for VPA and PHT: 68% vs 68% in one study[27] and 88% vs 84% in another study.[28] In summary, most head-to-head comparisons show that PHT tends to be less effective than VPA. In the context of overlapping cost-effectiveness profiles, other considerations such as side effects or local familiarity with a particular non-BZD AED may drive the clinical decision-making among VPA, LEV, and PB. PHT tends to underperform in terms of both effectiveness and cost-effectiveness.

The main limitation of this study is the heterogeneous and limited literature on this topic. Despite heterogeneous studies in multiple countries, the definition of SE was remarkably similar. In contrast, the definition of the outcome (control of SE) varied widely and might be a major source for the measured between-studies heterogeneity, which may introduce bias. Another source of heterogeneity is the different dosing and different available market prices for non-BZD AEDs. Although different measures of the risk of bias exist, they do not effectively discriminate the quality of the studies in this meta-analysis because none of them had a large enough sample to control for confounders, but representativeness, selection, comparability, and measure of the outcome are similarly good in all studies. Therefore, instruments for the measurement of study quality did not discriminate the studies in this meta-analysis. Despite this limitation, we evaluated the robustness of our results to adjustment for publication bias and for evaluation of prospective studies only. The rank of effectiveness of the different non-BZD AEDs remained very similar.

The effectiveness of a non-BZD AED may be influenced by the order of administration in the stepwise treatment of SE. To eliminate the confounding effect of order of administration, we only considered non-BZD AEDs given as a second line, after initial BZDs and before any other non-BZD AEDs or continuous infusion, measuring effectiveness with less confounding than in prior literature. This study considers only effectiveness in terms of ability to stop SE. The current literature does not allow quantification of side effects as accurately as we have quantified effectiveness. LEV has the most favorable side-effect profile, PHT and PB have a substantial risk of respiratory depression, LAC increases the PR interval and should be carefully considered in the elderly and in patients with cardiac comorbidities, and VPA has a risk of hepatotoxicity, especially in small children and in patients with some congenital errors of metabolism. These considerations may drive decision-making in individual patients. Although adverse effects are relatively rare, they can have a major clinical and economic effect.

A limitation of this meta-analysis is that the effectiveness of PB is based on only 3 studies and the effectiveness of LAC is based on only 2 studies. Systematic reviews and meta-analysis

point toward priorities to address knowledge gaps: there are relatively numerous studies on the effectiveness of phenytoin, VPA, and LEV; therefore, studies on the effectiveness of PB, LAC, and, especially, fosphenytoin probably should take priority. There are multiple series and case reports suggesting that LAC controls approximately 60% of convulsive SE episodes.[29] However, in these cases, LAC was administered typically late in the course of SE and after failure of several other AEDs, which prevented inclusion in our study. Our study findings demonstrate the need for better evidence and guide future research by pointing out these knowledge gaps. The ongoing Established Status Epilepticus Treatment Trial (ESETT) may provide quantification of the efficacy of fosphenytoin and may contribute to further clarifying the relative efficacy of fosphenytoin, VPA, and LEV.[30] The EcLiPSE and ConSEPT studies are randomized, controlled, open-label, multicenter studies that will compare the efficacy of PHT and LEV in children.[31,32] Future studies should also better quantify the effectiveness of PB or LAC among other IV available medications. As brilliantly explained in a prior article, "It exists a paradox in the SE treatment, since practical and financial issues, and the position taken by regulatory authorities, render a prospective trial extremely difficult. A physician can choose among VPA, PHT, LEV and even other compounds, in an almost complete absence of rational evidence, but cannot collect information to determine efficacy without getting informed consent from the patient, which in an emergency condition is extremely difficult."[24] The estimated costs and effectiveness of each option should be important pieces of information on which to base clinical decisions, and might not agree with tradition-based subjective perceptions. The present study not only provides a snapshot of the current evidence on effectiveness and cost-effectiveness, but allows readers to update that information as new information becomes available to make clinical decision-making more evidence-based.

The present study quantitatively summarizes the current evidence for second-line non-BZD AED treatment of SE. The evaluation of 24 studies comprising a total of 1,185 SE episodes shows that the preeminence of PHT as second-line non-BZD AED is not supported by current evidence on its effectiveness. From a cost-effectiveness perspective, the preeminence of PHT as a second-line non-BZD AED is not supported either. There is substantial overlap in cost and effectiveness among PB, VPA, and LEV. LEV was the most cost-effective option and PHT was consistently less cost-effective than LEV, VPA, and PB.

Author contributions

I. Sánchez Fernández participated in drafting and revising the manuscript for content, including medical writing, in study concept and design, data acquisition, analysis and interpretation of data, statistical analysis, cost-effectiveness analysis, and study supervision or coordination. M. Gaínza-Lein participated in drafting and revising the manuscript for content, including medical writing, in study concept and design, data acquisition, analysis and interpretation of data, cost-effectiveness analysis, and study supervision or coordination. N. Lamb participated in revising the manuscript for content, including medical writing, in study design, data acquisition, and study supervision or coordination. T. Loddenkemper participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination.

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Meta-analysis and cost-effectiveness of second-line antiepileptic drugs for status epilepticus

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