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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 [1]. 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's trim and fill method [2]. For the Duval and Tweedie's 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 [3]. 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 (CI). We compared the efficacy of subgroups with the chi-square test. We considered a conventional alpha 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 [4].

Sensitivity analysis. Sensitivity analyses evaluate the robustness of the base case analysis by evaluating how outcomes change when input parameters are modified [4]. In one-way sensitivity analysis, the value of one parameter is varied over a broad range of values while keeping all other parameters constant [4]. 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 [4]. 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 [4]. The 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 [4]. 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 [4]. Second-order Monte Carlo simulations yield 95% confidence intervals (CIs) around the mean outcome, which reflect outcome uncertainty based on input uncertainty [4].

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. https://www.R-project.org/) [5] with RStudio [6] and the package meta [7]. All cost-effectiveness studies were performed in TreeAge Pro 2015 (TreeAge Software, Inc., Williamstown, MA, USA) [8]. Interactive versions of the meta-analysis (App e-1, and as an interactive webpage at:

https://ivansanchezfernandez-shinyapps.shinyapps.io/metaanalysis_aeds_se/) and of the cost-effectiveness model (App e-2, and as an interactive webpage at:

https://ivansanchezfernandez-shinyapps.shinyapps.io/ce_aeds_se/) were created with the R packages ggplot2 [9], plotly [10], and shiny [11] and allow the reader to modify and update the meta-analysis and cost-effectiveness study with the most relevant and updated information, including local costs, in real time.

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