Published in final edited form as:

Expert Rev Pharmacoecon Outcomes Res. 2018 October ; 18(5): 487–503. doi:
10.1080/14737167.2018.1489243.

Assessment of components included in published societal perspective or QALY outcome economic analyses for antiepileptic drug treatment in chronic epilepsy

Melissa H. Roberts, Mikiko Y. Takeda, Shannon Kindilien, Yazan K. Barqawi, and Matthew E. Borrego

Department of Pharmacy Practice and Administrative Sciences, College of Pharmacy, University of New Mexico, Albuquerque, USA

Abstract

Introduction: Antiepileptic drug (AED) treatments seek to control seizures with minimal or no adverse effects, effects which can substantially impact costs and outcomes for patients, caregivers, and third party payers. The First and Second Panel on Cost-Effectiveness in Health and Medicine recommend inclusion of a societal reference case, even in studies conducted from a healthcare sector perspective, for comparability of findings across studies. Cost and outcome evaluation components include direct medical, non-direct medical-related (e.g. patient-time and transportation costs for treatment) and non-healthcare sectors (e.g. lost productivity).

Areas covered: Guided by Second Panel recommendations, this review developed an overall impact inventory and detailed adverse effect impact inventory to assess the scope and methods in published economic evaluations of AED treatments for adults with chronic epilepsy. Societal perspective evaluations or evaluations that utilized quality-adjusted life-years (QALYs) as an outcome were reviewed. The majority of reviewed articles were healthcare sector perspective studies, methods for estimating QALYs varied widely, and a minority considered specific AED treatment adverse effects.

Expert commentary: Only considering a healthcare sector perspective fails to provide full information for patients on AED treatments. Using an impact inventory to guide study scope and design will facilitate full reporting of costs and benefits.

Keywords

Adverse effects; antiepileptic drugs; cost-effectiveness; cost-utility; economic evaluation; epilepsy; QALY; quality of life; systematic review; utility

CONTACT Melissa H. Roberts MHRoberts@salud.unm.edu Department of Pharmacy Practice and Administrative Sciences College of Pharmacy, University of New Mexico, MSC09 5360, Albuquerque, NM 87131-0001.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

1. Introduction

Epilepsy can have a substantial burden for patients and society, not only from high medical and nonmedical costs but also from high indirect costs for patients and caregivers due to lost productivity and underemployment [1]. The primary objective of antiepileptic drug (AED) therapy is to control seizures, and achievement of that objective should result in a reduced burden. Studies that provide comparative information for AED therapies on costs and benefits are of particular value to not only third party payers, but also to patients and society.

A primary concern for third party payers – insurance providers and national health systems – is direct medical costs. Estimates for the percentage of total direct medical costs due to AED therapies ranges from 20% to 50% [1,2]; however, AED therapy costs are becoming an increasingly larger proportion of direct medical costs in epilepsy due to the increased use of newer, more expensive AED therapies. Direct medical costs also increase when epilepsy is not well controlled, due not only to increased clinic visits, but also emergency department visits and inpatient care. Not as well recognized are additional direct medical costs related to comorbidities and epilepsy-related care (e.g. bone fractures due to seizures) [3,4].

Estimates for costs other than direct medical costs have varied depending on the breadth of the evaluation, but have tended to be lower when only nonmedical costs directly associated with receipt of treatment were considered (e.g. transportation to appointments, lost work time for appointments), and over 75% of total costs when long-term effects, such as productivity losses, were included [1,4–6].

Beyond greater financial costs, individuals with epilepsy often have poorer health-related quality of life (HRQoL), attributed to physical limitations and reduced vitality because of anxiety, depression, and insufficient sleep or rest [7–9]. The considerable detrimental effects epilepsy can have on individuals is shown by epilepsy's ranking in the most recent Global Burden of Disease rankings as fifth among neurological diseases as a cause of disability-adjusted life-years, a summary measure of years of life lost due to a condition and years lived with disability [10].

Economic evaluations facilitate comparisons of the relative costs and benefits of AED treatment. The value of economic evaluations in assessing pharmaceutical treatment options was brought to a wider audience in 1996 by recommendations from the Panel on Cost-Effectiveness in Health and Medicine [11–14]. Among their recommendations was that a societal perspective be taken for the reference case, a perspective that includes not only costs and outcomes relevant for a healthcare delivery system, but also those relevant for the patient, families, and caregivers [11]. The reference case analysis summarizes all areas relevant to the condition of interest that may be impacted by compared treatments. To allow comparability across differing conditions and treatments, the Panel recommended using the quality-adjusted life year (QALY), a measure combining the impacts of interventions on HRQoL as estimated by preference weights (utility values) and mortality (life-years) [11].

A review of existing economic evaluations for epilepsy treatments was published in 2000 by Langfitt with the Panel's recommendations in mind [15]. Langfitt noted that all studies reviewed had limitations in determining costs from a societal perspective [15]. In order to

better estimate societal costs associated with epilepsy, Langfitt highlighted the need for future research studies that: estimated direct nonmedical costs for patient and caregiver time, identified valid and responsive methods for valuing health states for individuals with epilepsy, and that examined health effects and leisure for the reference case analysis as recommended by the Panel [15].

Issues concerning societal perspective economic evaluations for epilepsy treatment were still identified a decade and a half later in a 2017 review by Wijnen and colleagues [16], who highlighted that many studies were characterized as being from a societal perspective, irrespective of actual analysis components. An earlier 2012 review by Bolin and Forsgren summarized the extent to which analyses included/reported guideline recommended components [17,18] and mentioned these specific issues: (1) lack of indirect costs in the form of labor markets and (2) differing sources of utility weights, the extent to which weights reflected adverse effects (AEs), and the sensitivity of results to changes in utility weights [17]. The scope of the 2012 review however did not encompass providing information on the degree to which methods of calculating QALY utility values may have differed between studies, and while the review discussed the importance of assessment setting [17], it did not discuss other important aspects of how utilities were assessed (e.g. method [direct or indirect], derivation populations, and assessment settings) [19].

A critical effectiveness measure for AED therapy is seizure control, but safety of AED use must also be considered. AED-related AEs can result not only in substantial costs but also decreased patient HRQoL [20–22]. The degree and magnitude of incorporation of AEs in economic evaluations has not been directly discussed in the majority of AED economic reviews [15,16,23–27]. Two prior reviews of economic evaluations discussed specific AEs in their review, but did not summarize AEs by AED, nor discuss potential AED AEs not included in studies [17,28].

Previous literature reviews of economic evaluations for the treatment of epilepsy have highlighted discrepancies between the stated perspective of economic evaluations and the actual components used in the analysis and have drawn attention to the inconsistencies both within and between epilepsy studies in the use of utility weights, indirect cost estimation, and QALY estimates [1,16,17,23,27–30]. However, consistency between stated perspective and QALY operationalization was not a focus of those prior reviews.

Recognition of the importance of including perspectives beyond the healthcare sector and the impact of pharmaceutical treatments on patients' HRQoL has increased since the Panel's 1996 recommendations. In 2016, the Second Panel on Cost Effectiveness in Health and Medicine (Second Panel) repeated the original Panel's recommendation that cost-effectiveness analyses (CEAs) utilize a reference case from the societal perspective that includes healthcare and non-healthcare sector components [31]. Additionally, the Second Panel recommended studies utilizing a healthcare sector perspective include both medical costs reimbursed by third-party payers and those paid out-of-pocket by patients [31]. To facilitate transparency both in and across studies, the Second Panel provided a template for their suggested 'impact inventory', a list of all potential components of the societal reference

case that would serve as an aide in study design, and provided recommendations for reporting CEA evaluations [31].

The specific objectives of this review are to utilize the recommendations of the Second Panel to (1) provide a summary of methods used to estimate costs and benefits, to include AEs, in published societal perspective economic evaluations for AED treatment of chronic epilepsy, (2) provide a summary of methodologies used to determine QALYs in published economic evaluations for AED treatment of chronic epilepsy regardless of study perspective, and (3) provide recommendations for future AED economic evaluations.

2. Methods

2.1. Search strategy

Potential studies for inclusion were identified using the search method employed by Wijnen in the most recent systematic review of epilepsy related economic evaluations [16]. The Cochrane Database of Systematic Reviews, Prospero, and the PubMed databases were searched for cost-related articles concerning AEDs or epilepsy or seizures or convulsions. All original research articles published between 1 January 1995 and 31 December 2017 that included an economic evaluation, societal perspective, (and/or) QALYs as an outcome of a pharmaceutical intervention on adults with chronic epilepsy were considered for inclusion. Specific inclusion criteria were (1) a study population that included adults (age 18 and older) with chronic epilepsy and (2) an economic evaluation in the form of a cost-benefit, cost-effectiveness, or cost-utility analysis for AED treatment, and (3) an economic evaluation with either a stated societal perspective or QALYs as an outcome. Chronic epilepsy included both established and newly diagnosed patients. Articles not primarily about chronic epilepsy, focused on status epilepticus, included nonhuman or exclusively pediatric patient groups, did not include pharmaceutical interventions, did not include an economic evaluation, were editorial, or did not use either the societal perspective or QALYs as an outcome were excluded. No restriction was placed on the study population country.

Three reviewers independently assessed titles and abstracts found via the search to ascertain which met inclusion criteria. All articles receiving at least one vote were read by all three reviewers to identify articles to be read by all authors. Final determination of individual articles was made by all authors.

2.2. Review forms

This review utilized three review forms based on recommendations from the Second Panel [31]. First, a detailed Impact Inventory of potential elements for a societal perspective economic evaluation of AED treatments was constructed using the Second Panel's impact inventory template [31]. Sources for Impact Inventory components specific to epilepsy were published literature and expert opinion of the clinician member of the team (MT) [32–35].

While the Impact Inventory includes an item related to overall assessment of AEs, to account for the substantial heterogeneity in AEs that may be associated with AED treatments, a separate Adverse Effect Impact Inventory (AEI) was developed. The AEI was initially constructed using a review of AEDs published by the Agency for Healthcare

Research and Quality in 2011 [32] and then revised to include box warnings and adverse reactions identified as occurring in 10% of patients receiving AED related drug therapies using information from Lexicomp Online® Lexi-Drugs® (Hudson, Ohio: Lexi-Comp, Inc.). Recognizing the terms adverse event or side effect are often used to describe negative impacts directly related to a drug, we use the term adverse effect since the term adverse event can also denote events that may not be associated with drug use [22].

The third review form was adapted from recommendations by the Second Panel for reporting methods used for estimating utility value weights for QALYs.

2.3. Review process

All authors participated in reviewing articles. Articles selected for inclusion were randomly assigned to two authors who independently read and completed all three review forms for each article. Authors then met to find consensus on any discrepancies noted for individual components. Any unresolved discrepancies were adjudicated by all authors. The clinical pharmacist author (MT) served as the third and adjudicating reviewer for all articles for the AEI review form.

3. Results

3.1. Included studies

The initial search yielded 479 publications for review (Figure 1). Two authors (YB, SK) conducted independent reviews of the article titles and abstracts and reached consensus on the exclusion of 403 publications. A more thorough full-text review was then conducted by 3 authors (YB, SK, MR) on the remaining 76 publications and through this process 4 other articles were identified.

Sixty-four publications were excluded in the final review, resulting in 16 articles for the final review [36–51]. Of the 16 articles, 5 societal perspectives used QALYs, 1 societal perspective study did not use QALYs, and 10 non-societal perspective studies used QALYs (Table 1). The 10 non-societal perspective studies were categorized as healthcare sector studies, though four did not explicitly state a perspective. The predominant source of study funding was the pharmaceutical industry ($n = 8$). Other funding sources were not reported ($n = 5$), were through a government agency ($n = 2$), or were unfunded ($n = 1$).

All societal perspective articles and seven of the 10 healthcare sector perspective articles were from Europe (Table 1). The remaining articles were from the United States ($n = 2$) or South Korea ($n = 1$). The most frequently used study time horizon was 1 year ($n = 5$), followed by horizons of 2 years ($n = 4$), 15 years ($n = 3$), and lifetime ($n = 3$). One article included two time horizons (3 months and 2 years). Five studies included children and/or adolescents in addition to adults [38,39,42,48]. Jentink et al. focused on teratogenic outcomes of AED treatments and included women intending to have children [41].

Five studies focused on patients newly or recently diagnosed with epilepsy (Table 1). Overall, the types of epilepsy included in studies were associated with a greater economic burden: refractory epilepsy ($n = 7$), focal or partial onset seizures ($n = 6$), generalized ($n =$

3), and Lennox–Gastaut Syndrome (LGS) ($n = 1$). Most studies estimated the economic benefit of adjunctive AED therapy ($n = 11$). The most common evaluated AEDs were lamotrigine ($n = 7$) and carbamazepine ($n = 5$).

Most studies ($n = 13$) utilized an economic simulation model: six utilized a decision tree model, four a Markov model, and three articles did not specify model type. The others were observational studies ($n = 3$).

3.2. Impact inventory

The Impact Inventory components developed from the Second Panel for studies are summarized in Table 2. Few articles discussed decisions about costs and outcomes that were included versus excluded. As a result, few also discussed the magnitude/direction excluded costs and outcomes would have on the final estimate of economic value. No articles mentioned expense of obtaining information as a reason for whether items were included or not; however, most mentioned a lack of existing information for populating models or extrapolating to longer time periods, a limitation underscored by prior economic evaluation reviews [20,30,48,50,51].

The most recent healthcare sector perspective studies utilized a 2-year time horizon, a decision based on availability of clinical data [39,43,48]. Bolin and colleagues (2010) did not discuss their 2-year time horizon choice [38]. Bolin and colleagues in 2013 justified their extrapolation of 18-week drug trials to a 2-year time horizon by stating that a ‘longer time perspective was appraised as too uncertain due the severity of the health state among included patients. Shorter time perspective would have entailed limited comparability with previous relevant studies’ [43]. Simoens et al. stated data from clinical trials following patients over 2 years was not available and that ‘2 years was a reasonable time point to catch any differences in consequences and costs of the interventions given the data available ... as well as the natural history of epilepsy’ [48]. While 2 years may be sufficient for healthcare sector studies, a 2-year time horizon may underestimate the costs or benefits of treatment from a societal perspective.

Other time horizon considerations include whether treatments are expected to result in differential survival, a topic infrequently addressed by the reviewed studies, and potential long-term AEs from AED treatments. Most economic evaluation guidelines recommend the time horizon be sufficiently long to reflect all important differences in costs and outcomes [52]. Hawkins and colleagues stated they used a 15-year time horizon to inform decision makers from a policy perspective [40] and also noted analyses were not sensitive to longer time periods [40]. Spackman and colleagues employed a 15-year time horizon based on the ‘chronic nature of epilepsy and the recommendations of clinical experts’ [49]

3.2.1. Formal healthcare sector costs and outcomes—None of the societal perspective studies provided a full examination of potential costs and outcomes. Almost all limited study scope to impacts on the individual with epilepsy. Few included treatment effects on caregivers/family as a result of changed health status for individuals with epilepsy. Two lifetime horizon societal studies specifically excluded indirect costs (e.g. productivity) and nonmedical costs [44,45].

The objective of AED therapy is to control seizure activity, and all evaluations, except for the study by Jentink et al., included frequency of seizures and/or health status defined by seizure frequency. The one societal perspective study that did not use QALYS compared cost-effectiveness for three seizure-defined outcomes: complete success (seizure-free), partial success (reduction in seizure frequency from baseline more than 50%), and failure (less than 50% seizure reduction) [42].

Inclusion of breakthrough seizures in studies was difficult to unambiguously ascertain. Nine studies were determined to incorporate breakthrough seizures [36–40,43,46,47,49], including all three observational studies [36,37,47]. All Markov model studies, with the exception of Vera-Llonch and colleagues, modeled movement of patients between states based on seizure status (seizure-free, partial success, failure), allowing for movement from seizure-free to partial success or failure [38,40,46,49]. Other models also incorporated seizures occurring after achievement of seizure freedom [38–40,43]. Analyses by Knoester et al. and by Suh and Lee modeled patients according to seizure frequency (success, partial success, failure), but did not model seizures after being seizure-free [42,50]. The lifetime horizon models used in the articles by Maltoni and Messori and by Messori et al. assumed effects of treatment at the end of the clinical trial periods (12 weeks and 6 months, respectively) remained stable over the remaining time horizon, thus breakthrough seizures were not modeled [44,45]. Seizure reduction and withdrawal due to nonresponse were modeled in the decision-analytic model by Simoens et al. but not a seizure-free state [48]. The Markov model utilized by Vera-Llonch et al. assessed seizure experience for patients on a daily basis; movement between states defined by seizure status was not explicitly modeled [51].

Inclusion of seizure-related injuries was similarly not clear. Medical costs for seizure-related injuries were explicitly included by Clements and colleagues [39]. Other studies did not discuss seizure-related injuries, but did include costs related to accidents and/or emergency events: Maltoni and Messori, Messori et al., Bolin et al. (2010), Bolin et al. (2013), Hawkins et al., Remak et al. (2004), and Simoens et al. [38,40,43–45,47,48]. These were categorized as including effects due to secondary seizure injuries.

Extra or unexpected healthcare as a result of individuals not being controlled by therapy was considered by almost all studies. Two studies did not – Vera-Llonch et al. and Jentink et al. [41,51]. Although Vera-Llonch and colleagues did consider the cost of utilization associated with therapy discontinuation and switching in sensitivity analyses [51].

Some impact due to AEs was considered by the majority of studies. Two studies stated AEs were not included because of minimal impact [39,48]. AE details are summarized in Table 4 and discussed in Section 3.2.3.

Mortality was a consideration in the lifetime comparisons of adjunctive therapies by Messori et al. and by Maltoni and Messori [44,45]. Maltoni and Messori utilized similar information to that used by Messori et al. to estimate reduced life expectancy for individuals with epilepsy, but mortality was not differential between treatments [44,45]. Jentink et al. utilized a lifetime horizon, but did not consider mortality related to AED treatments [41]. Mortality

was a consideration in the 15-year time horizon studies [40,46,49], but not in studies with a time horizon of 2 years or less. Future medical costs, a consideration when survival is differential between compared treatments, were included in the 15-year time horizon Markov model studies [40,46,49]. No studies included future unrelated medical costs.

All studies included direct medical care costs associated with treatment; however, not all reported utilization estimates or sources the estimates (See Table 1). However, most only reported one cost and did not differentiate medical care costs by who was impacted (payers vs. patients). In most studies, standard costs were assigned to units of utilized healthcare [36–38,42,43,47–49,51]. Using standard costs in models facilitates using alternative values for the costs, but it also has the disadvantage of not capturing real-world heterogeneity that may occur in costs. Messori et al. used cost and utilization data from a published study along with expert opinion [45], while the remaining studies utilized a mix of standard costs for medications and aggregated cost estimates [39–41,44,46,50].

3.2.2. Methods: preference weights—QALY measurement methods are summarized in Table 3. All QALY articles, except for Jentink et al., provided sufficient information to determine utilities were measured on a scale from 0 to 1.0. Jentink and colleagues examined ‘lifetime loss in quality’ for offspring from women using AED therapy, but did not examine HRQoL impacts from AED therapies [41].

Messori et al. conducted one of the earliest assessments of preference weights [45]. They utilized the time trade-off (TTO) technique to elicit preferences from patients with refractory epilepsy referred to an outpatient clinic in 1997 [45]. Patients were first interviewed to classify them according to five epilepsy health states and then asked TTO questions (number of years willing to give up to live in excellent health) in regard to their current state of health [45]. TTO utility values were then associated with the five health states: (1) presence of drugrelated side effects, (2) suboptimal seizure control (< 10 seizures/month), (3) suboptimal seizure control (2–9 seizures/month), (4) nearly complete seizure control (< 1/month), and (5) seizure-free (no seizure in last year) [45]. Validity and responsiveness of the utility measurement method was not discussed and it does not appear the utility measurement directly considered lost productivity. Specific AEs that may have been experienced by patients were not described; however, AED AEs were indirectly considered in the utility value associated with the first health state. The utility values were utilized in four other economic evaluations – the study by Maltoni and Messori, again evaluating AED treatment among individuals with refractory epilepsy [44]; the studies by Bolin et al. in 2010 for uncontrolled partial onset seizures [38], and 2013 for uncontrolled focal seizures [43]; and the study by Simoens et al. in 2012 for individuals with focal seizures with or without secondary generalization, which aggregated the Messori utility values into two mean values of therapy response (health states 3, 4, and 5) and lack of response (states 1 and 2) [48].

Using the generic EQ-5D instrument, an instrument widely considered to be a valid and responsive method for measuring utility values, Selai and colleagues estimated preferences in the late 1990s for 125 patients with intractable epilepsy about to start a new adjunctive AED [53–57]. The EQ-5D comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [58]. Seizure frequency status for patients was

determined using the National Hospital seizure severity and frequency scale [55]. Patients were interviewed at baseline and at 3 and 6 months posttreatment initiation, and mean utility values for patients with 10, 2–9, and 1 seizure per month [55], as well as those experiencing no seizures, or a reduction in seizure, or no longer on an AED in 6 months and at 5 years were reported [56,57]. Based on measurement methods, neither lost productivity nor AED AEs was directly considered in the utility values. Despite differences in treatment and epilepsy status, Remak and colleagues (2003) [46] utilized the Selai estimated utility values in their study comparing topiramate to carbamazepine or lamotrigine as monotherapy therapy treatment for partial seizures and comparing topiramate to sodium valproate or lamotrigine for generalized seizures over a 15-year time period [46]. In 2004, Remak, with Selai, Trimble, and Price as co-authors, conducted another economic evaluation using the earlier study by Selai and colleagues, but now reported EQ-5D values at 3 and 6 months posttreatment initiation by specific AEDs [47]. Hawkins and colleagues in comparing newer versus older monotherapy AEDs for partial and generalized seizures and adjunctive therapy for refractory patients over a 15-year time period [40] also utilized the Selai utility values [55]. Finally, Spackman and colleagues, in their 15-year comparison of zonisamide to levetiracetam for adults with uncontrolled partial epilepsy also utilized the Selai utility values [49].

Cramer and colleagues in 2007 examined AED impacts on seizure and AEs using visual analog scale (VAS) ratings of 0 to 100 scale for ‘today’s’ health state [59]. A cross-section of adults with partial-onset epilepsy (with or without secondary generalization) who had all experienced a seizure in the past year and who had been treated with at least two AEDs were surveyed [59]. Mean disutility values comprised differences between baseline patient ratings and ratings that considered actual and hypothetical seizure and AED AEs [59]. AED AEs considered included: muscle incoordination, diplopia, dizziness, fatigue, weakness, headache, nausea, sleepiness, poor concentration, and anomia [59]. Results for perceived severity of impact varied: patients with more recent seizure experiences estimated greater disutility for AED AEs compared to seizures and those with ‘remote’ seizures estimated greater disutility for seizures [59]. Based on the measurement methods, lost productivity was not directly considered in the measurement, but specific AED AEs were. Limitations noted by Cramer et al. included that ratings appeared to be influenced by prior seizure experience, and that adverse event queries were not presented as being specific to AEDs, but rather identified as being ‘symptoms’ [59]. Two studies included these utility values. Bolin and colleagues in 2013 incorporated the adverse event disutility values in addition to the utility values measured by Messori et al. [43]. Vera-Llonch, Brandenburg, and Oster, all co-authors on the Cramer 2007 study, included the Cramer utility values in their adjunctive therapy evaluation for patients with refractory partial epilepsy [51].

Three studies directly elicited utility values from study populations by employing a disease specific instrument – the 31-item Quality of Life in Epilepsy Inventory (QOLIE) [60]. Based on questions about the last 4 weeks, the QOLIE-31 is intended to measure multiple domains and in addition to one overall health question has seven subscales (number of items):(1) overall HRQoL (2), social functioning (5), medication effects (3), cognitive functioning (6), energy-fatigue (4), emotional well-being (5), and seizure worry (5) [60]. The three medication effect items concern physical and mental effects of AEDs, and overall concerns

regarding long-term use of AEDs [60]. Included in social functioning is one question concerning work limitations [60]. Based on these items, lost productivity and overall AED AEs could be considered as directly measured, but not impact of specific AED AEs. Balabanov and Zahariev used the QOLIE-31 to assess utility values at the end of their 1 year observational economic evaluation of monotherapy AEDs for adults newly diagnosed with epilepsy [36]. The later Balabanov and colleagues article, again for monotherapy for newly diagnosed adults with epilepsy, presented estimated utility values at one year stratified by AED treatment for adverse event experience (frequency <2 or ≥2), seizure occurrence (within 26 weeks of treatment, after 26 weeks), and seizure reduction (<50%, ≥50%) [37]. Suh and Lee utilized the QOLIE-31 in their 1-year economic evaluation of adjunctive therapy for adults with refractory partial epilepsy and provided estimated utility values by treatment at baseline and at 16-weeks post-initiation for the health states of: seizure freedom; not seizure-free, remain on adjunctive AED treatment; not seizure-free, change adjunctive AED treatment; not seizure-free, stop adjunctive treatment; not seizure-free on standard therapy [50]. Suh and Lee also indicated that the QOLIE-31 has demonstrated ‘good reliabilities and validities’ [50].

One study utilized utility values estimated from the general public as opposed to patients with epilepsy. Clements and colleagues examined clobazam as adjunctive therapy for LGS, and used utility values for categories of drop-seizure frequency reduction associated with LGS treatment summarized in an abstract by Verdian et al. [39,61]. The abstract states that: the utility values were obtained from the general public, 48% of whom were parents or caregivers of children; using descriptive scenarios of LGS outcomes and five health states defined by drop attack seizure frequency, disutility scores were estimated by the TTO technique for common AEs of concentration problems, weight loss, somnolence, rash, and nausea/vomiting [61]. The abstract noted that TTO scores were higher than utility values derived from the same population using EQ-5D or VAS methods [61]. The Clements study did not incorporate the utility values associated with AEs, but did utilize estimated disutility scores for the difference between an anchor state of 21–28 seizures per week, and three subsequent health states defined by seizure reductions of <50%, 50–<75%, and ≥75% [61].

3.2.3. Methods: AEI inventory—Table 4, the AEI Inventory, summarizes incorporation of AED related AEs. Jentink et al. was not included since impacts of AED treatment on individuals with epilepsy were not assessed, but rather teratogenic effects on offspring [41]. Most evaluations did not include specific details about side effects and AEs considered in their analyses, to include whether or not utility values for QALYs included impacts from AEs.

Two healthcare sector studies evaluating adjunctive AED cost-effectiveness over short time horizons specifically stated AEs were considered to have minimal impact and were not included [39,48]. Clements and colleagues reviewed clobazam as an adjunctive therapy for LGS versus adjunctive lamotrigine, rufinamide, and topiramate over short time horizons and AEs were not considered in the utility value assessment or separately considered in the study [39]. Simoons and colleagues stated AEs were not included due to low incidence rates; however, their decision tree model for seizure reduction and withdrawal due to lack of response/AEs could be considered to indirectly measure AEs [48]. Suh and Lee compared

effectiveness of levetiracetam adjunctive therapy over a 1-year time horizon and while specific AE events were not included, effects of AEs in general on HRQoL could be considered to have been included through the QOLIE-31 utility assessment [50].

Hawkins and colleagues compared newer versus older AEDs over a 15-year period and again, while ‘tolerability’ to treatment, which could include AE experience, was considered, AED-related AEs were not explicitly considered and were also not considered in HRQoL values [40].

The societal perspective study by Balabanov et al. in 2008 mentioned some AEs reported by patients (and for which any associated medical care was captured), but did not include an a priori listing of potential AEs to be tracked. However, this study and two other studies that did not specifically discuss or incorporate AEs utilized the QOLIE-31 instrument to assess HRQoL, which contains three general medication effects questions [36,37,50]. AEs were also indirectly measured through utility values for four studies that were associated with health states defined by AE experience [38,44,45,48].

Four of the healthcare sector studies incorporated specific AEs into their models and examined AE probability for each particular AED being evaluated and determined if risks were substantive or nonexistent [43,46,49,51].

Within the cosmetic grouping, alopecia was considered by Remak et al. in their 15-year assessment of topiramate, carbamazepine, lamotrigine, and valproate as part of the HRQoL assessment [46]. Valproate had the highest probability of occurrence, followed by minimal occurrences for topiramate and carbamazepine and none for lamotrigine [46]. Alopecia was noted to be a more common side effect for valproate in the 1-year time horizon study by Balabanov and Zahariev comparing carbamazepine and valproate [37].

Among dermatological-related reactions, the most severe, Stevens–Johnson syndrome (SJS) is associated with lamotrigine use [62]. SJS usually requires inpatient care with an intensive care unit stay. Seven studies included lamotrigine [39,40,42,45–47,49]. Of the 7, the 15-year time horizon study by Remak and colleagues included medical costs and HRQoL impacts from SJS [46], and the study by Spackman et al. included medical costs associated with SJS [49]. Skin rashes and associated costs were additionally considered by these two studies for all AEDs [46,49]. Two other 2-year time horizon studies included lamotrigine as a standard therapy for adjunctive AEDs [38,48], but both did not include specific AEs.

The endocrine and metabolic-related AEs concerned weight changes. The Remak et al. study considered the impact of weight changes on HRQoL [46]. Valproate had the highest probability with regard to weight gain; minimal impacts on weight gain were associated with topiramate and carbamazepine, and none with lamotrigine [46]. For weight loss, topiramate and carbamazepine had the highest probability, with minimal probability for valproate use, and none with lamotrigine [46]. Spackman and colleagues considered weight loss as part of treatment response and assessed a small probability of occurrence with zonisamide, and none with levetiracetam or lamotrigine [49].

Nausea and vomiting was the most universally considered AE. Remak and colleagues evaluated the impact on HRQoL of nausea/vomiting, with occurrences ranging from 7% for topiramate to 20% for carbamazepine [46]. Nausea was mentioned as a more common side effect for carbamazepine by Balabanov and colleagues in comparison to valproate [37]. Spackman and colleagues also indicated nausea was a common occurrence – from 8% for levetiracetam to 18% for lamotrigine – and included it as factor related to nonresponse [49]. Bolin and colleagues (2013) assessed the impact of nausea on HRQoL, utilizing percentages of approximately 8% for retigabine/ezogabine and 11% for lacosamide [43]. Vera Llonch et al. also included the impact of nausea on HRQoL and therapy continuation, estimating a 15% probability for discontinuation of pregabalin add-on therapy [51].

Kidney stones are associated with use of carbonic anhydrase inhibitors, such as topiramate and zonisamide. Six studies conducted comparative assessments of these drugs (five for topiramate and one for zonisamide), but only Remak and colleagues (2003) included costs associated with lithotripsy for kidney stone treatment [46].

Bolin and colleagues (2013) compared retigabine (ezogabine) and lacosamide as adjunctive therapy for focal/partial seizures and included negative neurological impacts on HRQoL: dizziness affected almost 30% of both drug groups, somnolence impacted 20% of retigabine (ezogabine) users and 15% of lacosamide users, fatigue impacted 18% of retigabine/ezogabine and 11% of lacosamide users, and ataxia impacted 11% of retigabine/ezogabine and 12% of lacosamide users [43]. Vera-Llonch et al. also included associated utility decrements and impacts on therapy continuation for numerous neurological AEs related to pregabalin [51].

Studies by Remak and colleagues (2003) and by Spackman and colleagues included cognitive effects [46,49]. Remak and colleagues estimated negative impacts on HRQoL with lamotrigine use [46], and while the Spackman study evaluated AED related concentration problems on HRQoL and therapy continuation, no occurrences were included for levetiracetam or zonisamide [49]. In the study by Balabanov et al. comparing carbamazepine and valproate, tremor associated with valproate, and headache, drowsiness, and restlessness associated with carbamazepine were reported with lower HRQoL [37].

No studies explicitly included psychiatric adverse reactions such as depression or suicidal ideation that might occur from the use of AEDs that were being evaluated. However, studies reviewing QALYs that used EQ-5D or QOLIE-31 utility values indirectly included depression since these instruments include domains for anxiety/depression (EQ-5D) [58] and emotional well-being (QOLIE-31) [60].

Long-term cognitive impacts may occur for substantive percentages of individuals on AED therapy [63]. Yet few reviewed studies included cognitive AEs. Significantly, no studies identified psychiatric and behavioral AEs, potentially costly reactions that have been found in epileptic patients [64,65]. Lastly, the majority of studies reviewed adjunctive therapies ($n = 11$), and included AEs specific to adjunctive therapies. None discussed potential multiplicative AE risks for AED polypharmacy. Increases in incidence and severity of side

effects from multiple AEDs use have been reported – for example, higher SJS risk when using valproic acid and lamotrigine [5,21,62].

To avoid double counting, the costs of AEs may not be specifically included in a study if utility values already include the impact of AEs, but this was never mentioned as a justification to exclude AEs. Higher treatment cost for AEs did not seem to be a driver (given the minimal inclusion of SJS and kidney stones) for including in costs.

3.3. Informal healthcare and non-healthcare sectors

Among the six societal perspective studies, half included informal healthcare sector components. Three studies included patient-time costs associated with medical care [36,37,42], but only one clearly stated inclusion of unpaid caregiver time costs [42]. Transportation costs associated with receipt of medical care were included in two observational studies [36,37].

The Second Panel found little evidence for productivity losses being reflected in QALYs, particularly in a generic measure like the EQ-5D, and recommended productivity losses due to morbidity be included as a cost [66]. Three of the six societal studies included lost productivity. The study by Knoester et al. did not assess QALYs as an outcome [42], but did include lost productivity. The studies by Balabanov and colleagues utilized the QOLIE-31 which includes a question about impact of disease on work, but costs from lost productivity were still considered in analyses [36,37].

The two lifetime societal analyses specifically excluded indirect costs (productivity), and lost productivity was also not considered in utility values for QALYs [44,45]. The two healthcare sector articles by Bolin and colleagues stated that if they had included loss in income due to sick days, the AED treatments would have been cost saving [38,43].

Studies did not include cost of uncompensated household production necessary due to a patients' worsened health status. Balabanov and colleagues (2008) included costs related to 'specific lifestyle changes' but examples were not provided [37]. None of the other non-healthcare sector components (Table 2) were specifically incorporated in societal studies.

4. Conclusion

The majority of reviewed studies were conducted from a healthcare sector perspective, and among the six societal perspective studies, only three considered costs beyond the formal healthcare sector. In order to insure comparability of findings across studies the Second Panel recommends inclusion of a societal reference case, even in studies conducted from a healthcare sector perspective. Importantly, the Second Panel drew attention to the fact that while treatments may be cost-effective for the healthcare sector, they may result in an increased burden for patients, caregivers, and families either through cost shifts or an increase in non-healthcare negative effects [66]. The societal perspective case not only increases ability to compare results with other studies, but also informs decision makers about treatment impacts across all sectors.

Half of the societal perspective studies did not include productivity costs for patients and caregivers. Lack of accounting for lost productivity was also identified in earlier reviews of AED economic evaluations [15,16]. The geographical context of studies and the intended decision-maker likely influenced components included in studies as published guidelines for economic evaluations from government agencies often make explicit requirements [67], for example, excluding productivity losses [52], and recommending use of generic HRQoL instruments like the EQ-5D over disease-specific HRQoL instruments [52,68]. For individuals with epilepsy and their families, studies have found a burden related to productivity losses equal to or greater than the healthcare costs of epilepsy [5,69]. While the First Panel recommended that productivity losses due to morbidity not be included as a cost when included as an 'effect' in the form of reduced QALYs (as inclusion would be double counting) [11], the Second Panel found little evidence for productivity losses being reflected in QALYs, particularly in a generic measure like the EQ-5D, and recommended productivity losses due to morbidity be included as a cost [66]. Among the instruments utilized by studies, only the QOLIE-31 instrument contains any mention of impact on work, and that is limited to one question. We recommend AED economic evaluations include impacts on lost productivity as a cost.

The methods for estimating QALYs varied widely, and the specific impacts of AED AEs on QALYs were infrequently considered. In this review, both generic and epilepsy-specific instruments were used to determine preference values for QALYs. The generic EQ-5D instrument is preferred by European countries [67]. In using the EQ-5D, Remak and colleagues (2004) determined that it demonstrated differences between patient groups after seizure status, neurological deficit, psychiatric morbidity, and working status but acknowledged that differences were relatively small and that a generic instrument like the EQ-5D may not be sensitive to change [47]. The epilepsy-specific QOLIE-31 instrument, while not a preference-based instrument and therefore estimated utility values cannot be directly compared to utilities estimated from a generic instrument such as the EQ-5D, does assess domains specifically of importance to individuals with epilepsy. It should be noted that efforts to map the QOLIE-31 to the EQ-5D have indicated there is low to moderate overlap between the instruments [70]. When a generic instrument is not sensitive to meaningful differences, as has been noted for the EQ-5D and epilepsy, using an epilepsy-specific instrument as a supplement to a generic instrument may be useful [70]. The Personal Impact of Epilepsy Scale (PIES), while again not a preference-based instrument, measures overall impact of seizures, medication side effects, comorbidities, and QOL, and is an example of a promising new epilepsy-specific instrument that could be used along with a generic instrument [35]. Choice of instrument however will be context driven and it is important for articles to include discussion of critical aspects of QALY measurement, to include domains included in the utility instrument and methods for utility assessment (e.g. direct or indirect elicitation, derivation populations, and assessment settings) in order to understand the appropriateness of values used and generalizability of QALY estimates.

We recommend that future evaluations consider a societal perspective and complete an impact inventory, to include an AEI inventory, to guide study scope and design. Articles summarizing evaluations should include decisions regarding inclusion/exclusion of potential components impacting treatment outcomes. In particular, AED evaluations should explicitly

state assumptions concerning impacts on AEs. For studies considering QALY outcomes, beyond considering the validity and responsiveness of the instrument used to assess utility values, we also recommend evaluating the extent to which the instrument evaluates impacts from AEs and treatment effects on productivity.

5. Expert commentary

The ultimate goal of economic evaluations is to provide an assessment of the overall costs and benefits of treatment.

Evaluations that solely consider a healthcare sector perspective without offering a societal perspective fail to provide full information on the impact AED treatments will have on patients who receive those treatments.

Paucity of data and limited longitudinal data to inform evaluations were mentioned as reasons to exclude components in analyses or use shorter time horizons. The Second Panel provides guidance for evidence synthesis to inform economic evaluation analyses, reiterates that time periods should be sufficiently long, and recommends that projections of clinical trial data incorporate several scenarios to include no maintenance of trial effects, maintenance at the same level, and diminishing trial effects [66]. Uptake of these recommendations should help to produce evidence for AED economic evaluations. In addition, efforts similar to advanced modeling simulations utilizing longitudinal information from big data will help to inform future models [71,72].

Although previous research has highlighted the importance of including at-risk groups for special consideration or sensitivity analysis when doing cost-effectiveness studies, almost all of the articles included in this review did not consider demographics, inherent susceptibility, or prior AE experience alongside their analysis of the general epileptic population [20,22]. One economic evaluation focused solely on women of childbearing age taking AEDs [41], but no other studies also considered the possibility of teratogenic effects or complications to pregnancy to women in their study [73]. There may be merit in including age and sex standardized assumptions among general population studies.

Genetic screening is being increasingly incorporated into economic evaluations of pharmaceutical treatments where genetic phenotypes may cause drug response to be differential in individuals [74]. Some gene abnormalities have been shown to be closely related to epilepsy syndromes. For example, patients diagnosed with Dravet syndrome may have sodium channel mutation [75]. Similar to other conditions, the use of genetic testing is projected to grow and as costs for genetic screening decrease, may play a substantive role in identifying appropriate AEDs, to include AEDs that should be avoided [76–78].

6. Five-year view

Simulated data will be increasingly utilized within economic evaluations in general, to include AED therapy economic evaluations. Technology is creating the opportunity to mine many large datasets of epilepsy-related information similar to [SeizureTracker.com](https://www.seizuretracker.com)®

(Alexandria, VA) to create predictive models that can help inform future economic evaluations of AED therapy [71,79].

Adoption of the Second Panel's recommendation that an impact inventory be completed for economic evaluations will serve to reinforce that costs and outcomes beyond the healthcare sector are important and should be acknowledged in studies. Greater attention to methods and populations used to estimate utility values, and to conducting assessments to determine the degree to which utility values reflect all treatment effects (e.g. AEs not already considered in the cost assessment) will insure that future evaluations are more comprehensive in scope. The AEI Inventory form developed in this review will assist in insuring that AEs are considered in AED economic evaluations. Additionally, as knowledge expands about the potential multiplicative effects on AEs when combining antiepileptic treatments, there will be greater incorporation of these effects within AED economic evaluations.

Future economic evaluations conducted from a healthcare sector perspective will progressively include a societal perspective reference case allowing for better comparison across studies. Sensitivity analyses for subgroups for whom treatment effects will be differential will be increasingly important given aging populations and greater availability of genetic phenotypes information.

Funding

This manuscript was not funded.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Strzelczyk A, Reese JP, Dodel R, et al. Cost of epilepsy-a systematic review. *Pharmacoeconomics*. 2008;26(6):463–476. [PubMed: 18489198] • This review provides a summary of studies evaluating world wide direct medical costs associated with epilepsy.
2. Begley CE, Durgin TL. The direct cost of epilepsy in the United States: a systematic review of estimates. *Epilepsia*. 2015;56(9):1376–1387. [PubMed: 26216617] • This review provides a summary of studies from the United States evaluating direct medical costs associated with epilepsy.
3. Frost FJ, Hurley JS, Petersen HV, et al. A comparison of two methods for estimating the health care costs of epilepsy. *Epilepsia*. 2000;41(8):1020–1026. [PubMed: 10961630]
4. Jennum P, Christensen J, Ibsen R, et al. Long-term socioeconomic consequences and health care costs of childhood and adolescent onset epilepsy. *Epilepsia*. 2016;57(7):1078–1085. [PubMed: 27321903]
5. De Kinderen RJA, Evers SMAA, Rinkens R, et al. Side-effects of antiepileptic drugs: the economic burden. *Seizure*. 2014;23(3):184–190. [PubMed: 24315662] •• This study provides detailed healthcare costs, patient and family costs, and productivity costs associated with common side effects of AED treatment.
6. Pugliatti M, Beghi E, Forsgren L, et al. Estimating the cost of epilepsy in Europe: a review with economic modeling. *Epilepsia*. 2007;48(12):2224–2233. [PubMed: 18088267]
7. Hesdorffer DC. Comorbidity between neurological illness and psychiatric disorders. *CNS Spectrums*. 2016;21(3):230–238. [PubMed: 26898322]
8. Collings JA. Psychosocial well-being and epilepsy: an empirical study. *Epilepsia*. 1990;31(4):418–426. [PubMed: 2369877]

9. Baker GA, Brooks J, Buck D, et al. The stigma of epilepsy: a European perspective. *Epilepsia*. 2000;41(1):98–104. [PubMed: 10643931]
10. Feigin VL, Abajobir AA, Abate KH, et al. Global, regional, and national burden of neurological disorders during 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Neurol*. 2017;16(11):877–897. [PubMed: 28931491]
11. Gold MR, Siegel JE, Russell LB, et al. Cost-effectiveness in health and medicine. New York: Oxford University Press; 1996.
12. Russell LB, Gold MR, Siegel JE, et al. The role of cost-effectiveness analysis in health and medicine. Panel on Cost-Effectiveness in Health and Medicine. *JAMA*. 1996;276(14):1172–1177. [PubMed: 8827972]
13. Weinstein MC, Siegel JE, Gold MR, et al. Recommendations of the Panel on Cost-Effectiveness in Health and Medicine. *JAMA*. 1996;276(15):1253–1258. [PubMed: 8849754]
14. Siegel JE, Weinstein MC, Russell LB, et al. Recommendations for reporting cost-effectiveness analyses. Panel on Cost-Effectiveness in Health and Medicine. *JAMA*. 1996;276(16):1339–1341. [PubMed: 8861994]
15. Langfitt JT. Cost evaluations in epilepsy: an update. *Epilepsia*. 2000;41:S62–S68. [PubMed: 10885741]
16. Wijnen BFM, Van Mastrigt GAPG, Evers SMAA, et al. A systematic review of economic evaluations of treatments for patients with epilepsy. *Epilepsia*. 2017;58(5):706–726. [PubMed: 28098939] • This article provides the most current systematic review of AED economic evaluations. It summarizes cost-effectiveness estimates and evaluates studies using the Consensus Health Economic Criteria (CHEC) and Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklists.
17. Bolin K, Forsgren L. The cost effectiveness of newer epilepsy treatments. *PharmacoEconomics*. 2012;30(10):903–923. [PubMed: 22924967]
18. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ*. 1996;313(7052):275–283. [PubMed: 8704542]
19. Weinstein MC, Torrance G, McGuire A. QALYs: the basics. *Value Health*. 2009;12(Suppl 1):S5–S9. [PubMed: 19250132]
20. Greenwood RS. Adverse effects of antiepileptic drugs. *Epilepsia*. 2000;41:S42–S52. [PubMed: 10885739]
21. Perucca E, Meador KJ. Adverse effects of antiepileptic drugs. *Acta Neurol Scand*. 2005;112:30–35.
22. Perucca P, Gilliam FG. Adverse effects of antiepileptic drugs (vol 11, pg 792, 2012). *Lancet Neurol*. 2012;11(9):746. •• This article provides a detailed summary of methods for screening adverse effects of AEDs, characterizes types of AED adverse effects, discusses the connection between adverse effects and health-related quality of life, and highlights the improved tolerability and safety profile of the newer AED treatments.
23. Levy P. Economic evaluation of antiepileptic drug therapy: a methodologic review. *Epilepsia*. 2002;43(5):550–558. [PubMed: 12027918]
24. Pillas MD, Selai C. Economic aspects of epilepsy and antiepileptic treatment: a review of the literature. *Expert Rev Pharmacoeconomics Outcomes Res*. 2005;5(3):327–338.
25. Heaney Dominic C, Begley Charles E. Economic evaluation of epilepsy treatment: a review of the literature. *Epilepsia*. 2002;43:10–16. [PubMed: 12059996]
26. O'Neill BA, Trimble MR, Bloom DS. Adjunctive therapy in epilepsy: a cost-effectiveness comparison of alternative treatment options. *Seizure*. 1995;4(1):37–44. [PubMed: 7788105]
27. Allers K, Essue BM, Hackett ML, et al. The economic impact of epilepsy: a systematic review. *BMC Neurology*. 2015;15(1):245. [PubMed: 26607561] • This review summarizes direct, patient out-of-pocket costs, productivity losses, and employment impacts in 22 articles with economic outcomes.
28. Simoens S. Lacosamide as adjunctive therapy for partial-onset epileptic seizures: a review of the clinical and economic literature. *Curr Med Res Opin*. 2011;27(7):1329–1338. [PubMed: 21561394]

29. Beghi E, Atzeni L, Garattini L. Economic analysis of newer antiepileptic drugs. *CNS Drugs*. 2008;22(10):861–875. [PubMed: 18788837]
30. Wilby J, Kainth A, Hawkins N, et al. Clinical effectiveness, tolerability and cost-effectiveness of newer drugs for epilepsy in adults: a systematic review and economic evaluation. *Health Technol Assess*. 2005;9(15).
31. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. *JAMA*. 2016;316(10):1093–1103. [PubMed: 27623463]
32. Talati R, Scholle JM, Phung OJ et al. Effectiveness and safety of antiepileptic medications in patients with epilepsy Comparative Effectiveness Review No. 40. (Prepared by the University of Connecticut/Hartford Hospital Evidence-based Practice Center under Contract No. 20-2007-10067-I.). (AHRQ Publication No. 11 (12)-EHC082-EF, Rockville, MD, Agency for Healthcare Research and Quality 12 2011 Available from www.effectivehealthcare.ahrq.gov/reports/final.cfm)
33. Theodore WH, Spencer SS, Wiebe S, et al. Epilepsy in North America: a report prepared under the auspices of the global campaign against epilepsy, the International Bureau for Epilepsy, the International League Against Epilepsy, and the World Health Organization. *Epilepsia*. 2006;47(10):1700–1722. [PubMed: 17054693]
34. Katsiki N, Mikhailidis DP, Nair DR. The effects of antiepileptic drugs on vascular risk factors: a narrative review. *Seizure*. 2014;23(9):677–684. [PubMed: 25028247]
35. Fisher RS, Nune G, Roberts SE, et al. The Personal Impact of Epilepsy Scale (PIES). *Epilepsy Behav*. 2015;42(Supplement C):140–146. [PubMed: 25450530] •• This article summarizes the development process for a new patient-reported outcome measures, PIES, that encompasses the impact of seizures, AED side effects, comorbidities, and overall quality of life into a single brief questionnaire to be used as a study endpoint.
36. Balabanov PP, Zahariev ZI. A pharmacoeconomic comparison of monotherapy with Tegretol, Finlepsin and Trileptal (preliminary data). *Folia Med (Plovdiv)*. 2006;48(2):37–43. [PubMed: 17408075]
37. Balabanov PP, Zahariev ZI, Mateva NG. Evaluation of the factors affecting the quality of life and total costs in epilepsy patients on monotherapy with carbamazepine and valproate. *Folia Med (Plovdiv)*. 2008;50(2):18–23. [PubMed: 18702221]
38. Bolin K, Berggren F, Forsgren L. Lacosamide as treatment of epileptic seizures cost utility results for Sweden. *Acta Neurol Scand*. 2010;121(6):406–412. [PubMed: 20199516]
39. Clements KM, Skornicki M, O'Sullivan AK. Cost-effectiveness analysis of antiepileptic drugs in the treatment of Lennox-Gastaut syndrome. *Epilepsy Behav*. 2013;29(1):184–189. [PubMed: 23973644]
40. Hawkins N, Epstein D, Drummond M, et al. Assessing the cost-effectiveness of new pharmaceuticals in epilepsy in adults: the results of a probabilistic decision model. *Med Decis Making*. 2005;25(5):493–510. [PubMed: 16160206]
41. Jentink J, Boersma C, De Jong-Van Den Berg LT, et al. Economic evaluation of anti-epileptic drug therapies with specific focus on teratogenic outcomes. *J Med Econ*. 2012;15(5):862–868. [PubMed: 22494266]
42. Knoester PD, Deckers CL, Termeer EH, et al. A cost-effectiveness decision model for antiepileptic drug treatment in newly diagnosed epilepsy patients. *Value Health*. 2007;10(3):173–182. [PubMed: 17532810]
43. Bolin K, Wachtmeister K, Stefan F, et al. Retigabine as add-on treatment of refractory epilepsy—a cost-utility study in a Swedish setting. *Acta Neurol Scand*. 2013;127(6):419–426. [PubMed: 23368976]
44. Maltoni S, Messori A. Lifetime cost-utility analysis of patients with refractory epilepsy treated with adjunctive topiramate therapy: cost-effectiveness in refractory epilepsy. *Clin Drug Investig*. 2003;23(4):225–232.
45. Messori A, Trippoli S, Becagli P, et al. Adjunctive lamotrigine therapy in patients with refractory seizures: a lifetime cost-utility analysis. *Eur J Clin Pharmacol*. 1998;53(6):421–427. [PubMed: 9551700]

46. Remak E, Hutton J, Price M, et al. Markov model of treatment of newly diagnosed epilepsy in the UK. An initial assessment of cost-effectiveness of topiramate. *Eur J Health Econ.* 2003;4(4):271–278. [PubMed: 15609195]
47. Remák E, Hutton J, Selai CE, et al. A cost-utility analysis of adjunctive treatment with newer antiepileptic drugs in the UK. *J Med Econ.* 2004;7(1–4):29–40.
48. Simoens S, De Naeyer L, Dedeken P. Cost effectiveness of lacosamide in the adjunctive treatment of patients with refractory focal epilepsy in Belgium. *CNS Drugs.* 2012;26(4):337–350. [PubMed: 22452528]
49. Spackman DE, Yeates A, Rentz AM, et al. The cost effectiveness of zonisamide as adjunctive therapy in adult partial seizure epilepsy. *J Med Econ.* 2007;10(4):455–473.
50. Suh GH, Lee SK. Economic evaluation of add-on levetiracetam for the treatment of refractory partial epilepsy in Korea. *Psychiatry Investig.* 2009;6(3):185–193.
51. Vera-Llonch M, Brandenburg NA, Oster G. Cost-effectiveness of add-on therapy with pregabalin in patients with refractory partial epilepsy. *Epilepsia.* 2008;49(3):431–437. [PubMed: 17822431]
52. National Institute for Clinical Excellence. Guide to the Methods of Technology Appraisal 2013. (NICE (National Institute for Health and Care Excellence), 2013)
53. Selai CE, Trimble MR. Adjunctive therapy in epilepsy with new antiepileptic drugs: is it of any value? *Seizure.* 1998;7(5):417–418. [PubMed: 9808121]
54. Selai CE, Smith K, Trimble MR. Adjunctive therapy in epilepsy: a cost-effectiveness comparison of two AEDs. *Seizure.* 1999;8(1):8–13. [PubMed: 10091841]
55. Selai C, Kaiser S, Trimble M, et al. PNP15 Evaluation of the relationship between epilepsy severity and utility. *Value Health.* 2002;5 (6):512–513.
56. Selai C, Trimble M, Kaiser S, et al. P330 New antiepileptic drugs: clinical outcome and utility scores. *Epilepsia.* 2002;43(S8):65–207. [PubMed: 12060008]
57. Selai CE, Trimble MR, Price MJ, et al. Evaluation of health status in epilepsy using the EQ-5D questionnaire: a prospective, observational, 6-month study of adjunctive therapy with anti-epileptic drugs. *Curr Med Res Opin.* 2005;21(5):733–739. [PubMed: 15969872]
58. Rabin R, Charro FD. EQ-SD: a measure of health status from the EuroQol Group. *Ann Med.* 2001;33(5):337–343. [PubMed: 11491192]
59. Cramer JA, Brandenburg NA, Xu X, et al. The impact of seizures and adverse effects on global health ratings. *Epilepsy Behav.* 2007;11 (2):179–184. [PubMed: 17681863]
60. Cramer JA, Perrine K, Devinsky O, et al. Development and cross cultural translations of a 31-item quality of life in epilepsy inventory. *Epilepsia.* 1998;39(1):81–88. [PubMed: 9578017]
61. Verdian L, Oyee Y, Heyes A, et al. Eliciting preferences for health states associated with Lennox-Gastaut syndrome (LGS) In: American Epilepsy Society 62nd Annual Meeting. (Seattle, Washington, 2008)
62. Kavitha S, Anbuchelvan T, Mahalakshmi V, et al. Stevens–Johnson syndrome induced by a combination of lamotrigine and valproic acid. *J Pharm Bioallied Sci.* 2015;7(Suppl 2):S756–S758. [PubMed: 26538961]
63. Arif H, Buchsbaum R, Weintraub D, et al. Patient-reported cognitive side effects of antiepileptic drugs: predictors and comparison of all commonly used antiepileptic drugs. *Epilepsy Behav.* 2009;14 (1):202–209. [PubMed: 19010446]
64. Chen B, Choi H, Hirsch LJ, et al. Psychiatric and behavioral side effects of antiepileptic drugs in adults with epilepsy. *Epilepsy Behav.* 2017;76(Supplement C):24–31. [PubMed: 28931473]
65. Weintraub D, Buchsbaum R, Resor SR, et al. Psychiatric and behavioral side effects of the newer antiepileptic drugs in adults with epilepsy. *Epilepsy Behav.* 2007;10(1):105–110. [PubMed: 17079191]
66. Neumann PJ, Sanders GD, Russell LB, et al. Cost-effectiveness in health and medicine. New York: Oxford University Press; 2017. •• This book summarizes recommendations of the Second Panel on Cost-effectiveness in health and medicine and provides detailed guidance for conducting economic evaluations.
67. Pharmacoeconomic guidelines around the world: Country-specific pharmacoeconomic guidelines International Society for Pharmacoeconomics and Outcomes Research (ISPOR). cited 12 15, 2017 Available from: <https://www.ispor.org/PEguidelines/index.asp>

68. Cleemput I, Neyt M, Van De Sande S, et al. Belgian guidelines for economic evaluations and budget impact analyses second ed Health Technology Assessment (HTA). Brussels: Belgian Health Care Knowledge Centre(KCE; 2012.
69. Ivanova JI, Birnbaum HG, Kidolezi Y, et al. Economic burden of epilepsy among the privately insured in the US. *Pharmacoeconomics*. 2010;28(8):675–685. [PubMed: 20623993]
70. Wijnen BFM, Mosweu I, Majoie MHJM, et al. A comparison of the responsiveness of EQ-5D-5L and the QOLIE-31P and mapping of QOLIE-31P to EQ-5D-5L in epilepsy. *Eur JHealth Econ*. 2017.
71. Tharayil JJ, Chiang S, Moss R, et al. A big data approach to the development of mixed-effects models for seizure count data. *Epilepsia*. 2017;58(5):835–844. [PubMed: 28369781]
72. Ahn JE, Plan EL, Karlsson MO, et al. Modeling longitudinal daily seizure frequency data from pregabalin add-on treatment. *J Clin Pharmacol*. 2012;52(6):880–892. [PubMed: 21646441]
73. Weston J, Bromley R, Jackson CF, et al. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. *Cochrane Database Syst Rev*. 2016;(11).
74. Berm EJ, Loeff M, Wilffert B, et al. Economic evaluations of pharmacogenetic and pharmacogenomic screening tests: a systematic review. Second update of the literature. *PloS One*. 2016;11(1): e0146262. [PubMed: 26752539]
75. Steel D, Symonds JD, Zuberi SM, et al. Dravet syndrome and its mimics: beyond SCN1A. *Epilepsia*. 2017;58(11):1807–1816. [PubMed: 28880996]
76. Phillips KA, Ann Sakowski J, Trosman J, et al. The economic value of personalized medicine tests: what we know and what we need to know. *Genet Med*. 2014;16(3):251–257. [PubMed: 24232413]
77. Poduri A, Sheidley BR, Shostak S, et al. Genetic testing in the epilepsies—developments and dilemmas. *Nat Rev Neurol*. 2014;10:293–299. [PubMed: 24733164]
78. Chen Z, Liew D, Kwan P. Real-world cost-effectiveness of pharmacogenetic screening for epilepsy treatment. *Neurology*. 2016;86(12):1086–1094. [PubMed: 26888992]
79. Deng C, Plan EL, Karlsson MO. Approaches for modeling within subject variability in pharmacometric count data analysis: dynamic inter-occasion variability and stochastic differential equations. *J Pharmacokinet Pharmacodyn*. 2016;43(3):305–314. [PubMed: 27165151]

Key issues

- Societal perspective reference cases have not been included in healthcare sector evaluations. Future evaluations should follow the recommendation of the Second Panel on Cost-Effectiveness in Health and Medicine and include a societal reference case for comparability of findings across studies.
- Future AED economic evaluations should complete an impact inventory as recommended by the Second Panel on Cost-Effectiveness in Health and Medicine.
- Articles should include justification of decisions made regarding inclusion or exclusion of impact inventory components to insure that ramifications of those decisions have been considered in model estimates.
- AEs and related costs and impact on HRQoL have not been uniformly addressed in previous AED economic evaluations
- AED economic evaluations have not sufficiently discussed methods of estimating utility values and other important aspects of how utilities were assessed (e.g. method [direct or indirect], derivation populations, and assessment settings).
- Costs related to informal healthcare sector that are incurred by patients, caregivers, and families should be considered and where possible, included in societal perspective AED economic evaluations.
- Costs related to genetic screening, teratogenic effects, and polypharmacy should be considered for incorporation into future economic evaluations.

Figure 1.
Process for article selection.

Table 1.

Summary of economic evaluations included in the review.

First author, year published	Societal studies					Health care sector studies											
	Balshaw 2006	Balshaw 2008	Jentink 2012	Knoster 2007	Malloni 2003	Messori 1998	Bolin 2010	Bolin 2013	Clement 2013	Hawkins 2005	Remak 2003	Remak 2004	Simsen 2012	Spiekman 2007	Solt 2009	Vera-Lench 2008	
Funding	NR	NR	None	Govt	Ind	NR	Ind	Ind	Ind	Govt	NR	NR	Ind	Ind	Ind	Ind	
Perspective	Soc	Soc	Soc	Soc	Soc	Soc	NR	NR	Payer	NHS	NHS	NHS	Payer	NHS	NHS	NR	
Country	BG	BG	NL	NL	IT and UK, CUA	IT	SE	SE	US	UK	UK	UK	BE	Sco	KR	US	
Type of analysis	CUA	CUA	CEA	CEA	CEA	CEA	CUA	CUA	CEA	CUA	CEA	CEA/CUA	CEA	CUA	CEA	CEA/CUA	
Analysis design	Obs	Obs	Dec Tree	Dec Tree	Model	Model	Dec Tree	Dec Tree	Model	Markov	Markov	Obs	Dec Tree	Markov	Dec Tree	Markov	
Resource Use/valuation ^a																	
Medical care use	Act	Act	NR	Act	Obs	-	NR	Pub	Pub/Data	Pub	Obs	Act	Exp	Exp	NR	Exp	
Medical care cost	Std	Std	Std/Pub	Std	Std/Obs	Exp/Pub	Std	Std	Std/Data	Std/Pub	Std/Obs	Std	Std	Std	Std/Data	Std	
Nonmedical use	Act	Act	NR	Act	-	-	-	-	-	-	-	-	-	-	-	-	
Nonmedical cost	Act	Act	Pub	Std	-	-	-	-	-	-	-	-	-	-	-	-	
Time horizon	1 yr	1 yr	Lifetime	1 yr	Lifetime	Lifetime	2 yrs	2 yrs	3 mos, 2 yrs	15 yrs	15 yrs	6 mos	2 yrs	15 yrs	1 yr	1 yr	
Study population (demographics)	Adults	Adults	Women; age 15	Age 12	Adults	Adults	Age 16	Adults	Age 2 to 54	Age 50	Adults	Adults	Age 16	Adults	Age 18	Adults	
Study population (epilepsy type)	NewDx (FOC, GEN)	NewDx (FOC, GEN)	NR	NewDx	REF	REF	FOC	FOC	LGS	NewDx (GEN, FOC, REF)	NewDx (REF, GEN)	REF	FOC	FOC	REF	REF	
Treatments compared	CBZ, OXC	CBZ, VPA	CBZ, LTG, VPA	CBZ, LTG, VPA	TPM vs	REF	phscho	phscho	LTG vs none	LAC vs none	EZG vs LAC or none	CLB vs LTG, REF, TPM	Newer vs older	TPM, CBZ, LTG	CLB, GBP	TPM, VGB	
LAC vs none	ZNS vs LEV	LEV vs none	POB vs none	POB vs none											LTG		
Adjunctive (A) or monotherapy (M)	M	M	M	M	A	A	A	A	A	A (REF/M)	M	A	A	A	A	A	

^aFor the purpose of listing sources, productivity costs (when measured) are included in the nonmedical category.

Act: actual utilization or actual cost; AED: antiepileptic drug; BE: Belgium; BG: Bulgaria; CBZ: carbamazepine; CEA: cost-effectiveness analysis; CLB: clobazam; CUA: cost-utility analysis; Data: estimates derived from external claims data; Dec Tree: decision tree model; EZG: ezogabine (retigabine); Exp: Expert opinion/panel; FOC: focal or partial onset seizures; GEN: generalized seizures; Govt: Government; ICER: incremental costeffectiveness ratio; Ind: Industry; IT: Italy; KR: Korea; LGS: Lennox-Gastaut Syndrome; LAC: lacosamide; LEV: levetiracetam; LTG: lamotrigine; Markov: Markov model; mos: months; NewDx: newly diagnosed; NHS: National Health Service; NL: Netherlands; NR: not reported; Obs: observational study; OXC: oxcarbamazepine; PGB: pregabalin; PHT: phenytoin; Pub: published literature; REF: refractory; RUF: rufinamide; Sco: Scotland; SE: Sweden; Soc: Societal; Std: standard costs applied; TPM: topiramate; UK: United Kingdom; US: United States; VGB: vigabatrin; VPA: valproate or valproic acid; yr: year; ZNS: zonisamide.

Table 2.

Impact inventory for AED treatments for adults with chronic epilepsy.

Sector	Type of impact	Societal studies						Health care sector studies						Sub 2009	Van-Louch 2008
		Balabanov 2006	Balabanov 2008	Jordink 2012	Knoester 2007	Maltoni 2013	Messeri 1998	Bolin 2010	Bolin 2013	Clements 2013	Hawkins 2005	Remak 2003	Remak 2004	Simons 2012	Spackman 2007
Formal health care sector															
Health	Health outcomes (effects)	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Health-related quality-of-life effects														
	Mortality (including SUDEP)					✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Frequency of seizures	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	^a Breakthrough seizures	✓	✓					✓	✓	✓	✓	✓	✓		
	Secondary seizure injury (e.g. fracture, laceration, head injury, aspiration, pneumonia)					✓	✓	✓	✓	✓	✓	✓	✓	✓	
	Extra/unexpected health care (e.g. office visits, ED visits, ambulance services, hospitalization)	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	^c AEs in general ¹ (see AEI for specific AEs)	✓	✓		✓	✓	✓	✓	✓			✓	✓		✓
	Medical costs														
	Paid for by third-party payers	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Paid for by patients out-of-pocket														
	Future related medical costs ^d (payers and patients)														✓
	Future unrelated medical costs ^d (payers and patients)														
Informal health care sector															
Health	Patient-time costs	✓	✓		✓										
	Unpaid caregiver-time costs	✓	✓												
	Transportation costs														
Non-health care sectors															
Productivity ^e	Labor market earnings lost ^f	✓	✓		✓										
	Cost of unpaid lost productivity due to illness ^g	✓	✓		✓										
	Cost of uncompensated household production ^h														
Consumption	Future consumption unrelated to health														
Social Services	Cost of social services as part of intervention														
	Impact on educational achievement of population														
Education	Cost of home improvements (e.g. to reduce injuries as a result of falls due to seizures)														
Housing	Loss of drivers' license														
Transport	Other impacts														
Other															

Table adapted from Impact Inventory template suggested by Second Panel on Cost-Effectiveness in Health and Medicine [31].

^a Seizure experienced by an individual after a prolonged period without seizures (controlled epilepsy condition).

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

^qShould a patient not be controlled on their current therapy.

^cAdverse effect (AE) in general (e.g. nonspecific AEs; any AE due to AED treatment).

^dFuture costs occur when treatments produce a differential in survival and patients live longer than expected.

^eCould apply to caregivers as well as patients.

^fProductive time lost in formal labor market.

^gSpecific to the patient and could include time lost in informal labor market.

^hHousehold activity that must be replaced due to an individual's health status: e.g. food preparation, cooking, and clean up; household management; shopping; obtaining services; and travel related to replacement.

ⁱStudy included 'specific lifestyle changes' (no details provided).

AE: adverse effect; AEI: Adverse Effect Impact Inventory; ED: emergency department; SUDEP: sudden and unexpected death due to epilepsy.

Table 3.

Methods for quality-of-life measurement.

	Health Care Sector Studies														
Reportable elements and recommendations within each (N/A cells shaded gray)	Balabanov 2006	Balabanov 2008	Jentink 2012	Maltoni 2003	Messori 1998	Bolin 2010	Bolin 2013	Clements 2013	Hawkins 2005	Renak 2003	Renak 2004	Simoens 2012	Spackman 2007	Suh 2009	Vera-Llonch 2008
Complete information on sources of preference weights															
Were quality weights															
preference-based, interval- scaled, and measured or transformed onto an interval scale															
where the reference point 'dead' has a score of 0.0 and the reference point 'perfect health' has a score of 1.0?	Y	Y	P	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Utility Instrument (superscript are referenced sources for utilities) ^a	QE	QE	M	TTO ⁴⁵	TTO ⁴⁵	TTO ⁴⁵	TTO ⁴⁵ VAS ⁶⁰	TTO ⁶²	EQ ⁵⁶	EQ ⁵⁷ TTO	EQ ⁵⁵⁻⁵⁴	TTO ⁴⁵	EQ ⁵⁸	QE	VAS ⁶⁰
Were community preferences (C) or were patient preferences (P) used for health states used in the Reference Case analyses? ^b	P	P	NI	P	P	P	P	c	P	P	P	P	P	P	P
If CEA from either healthcare sector or societal perspective, was a generic preference	N	N	NI	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y

Reportable elements and recommendations within each (N/A cells shaded gray)	Health Care Sector Studies														
	Balabanov 2006	Balabanov 2008	Jentink 2012	Maltoni 2003	Messori 1998	Bolin 2010	Bolin 2013	Clements 2013	Hawkins 2005	Remak 2003	Remak 2004	Simoens 2012	Spackman 2007	Suh 2009	Vera-Llonch 2008
measure used or one capable of being compared to a generic system?															
If CEA analysis from either the healthcare sector or societal perspective, and a generic preference measure was not used or one capable of being compared to a generic system, was a health-state classification system which reflects attributes (domains or dimensions) important for the particular problem under consideration used? ^c	Y	Y	NI											Y	
Degree adverse effects in general considered in utility measurement	D	D	NA	I	I	I	D	NC	NC	NC	NC	I	NC	D	D
Was lost productivity directly assessed by the measure?	Y	Y	NI	N	N	N	N	N	N	N	N	N	N	Y	N

Table developed from recommendations suggested by Second Panel on Cost-Effectiveness in Health and Medicine [31].

^aInstruments: EQ: European Quality of Life, 5-dimensions; M: multiple reference sources (references not directly linked to specific utility measures); QE: Quality of Life in Epilepsy – 31 item; TTO: time-trade off; VAS: visual analog scale.

^bIn general, generic instruments are recommended but for some questions/contexts preferences derived from patients may be preferred [ref 2nd panel].

^cMore fundamentally, a key criterion is empirical evidence on the validity and responsiveness of the instrument in that context! [ref 2nd panel].

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

AED: antiepileptic drug; CEA: cost-effectiveness analysis; D: directly as an impact of AED; I: indirectly as part of health state; ICER: incremental cost-effectiveness ratio; N: no; NA: not applicable; NC: not considered; NI: not enough information; NR: not reported; P: partially; Y: yes.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 4.

AED adverse effect impact inventory.

	Societal studies					Health care sector studies									
	Balabanov 2006	Balabanov 2008	Knoester 2007	Malfoni 2013	Messeri 1998	Bolin 2010	Bolin 2013	Clements 2013	Hawkins 2005	Remak 2003	Remak 2004	Simoens 2012	Spackman 2007	Solt 2009	Vera-Lunch 2008
Drugs compared in the study ^a															
Phenytoin (PHT) [1953]															
Carbamazepine (CBZ) [1968]	✓	✓	✓						✓	✓					
Valproate/Valproic acid (VPA) [1978]		✓	✓						✓	✓					
Gabapentin (GBP) [1993]									✓	✓	✓				
Lamotrigine (LTG) [1994]			✓		✓			✓	✓	✓	✓	✓ ^s			
Topiramate (TPM) [1996]				✓				✓	✓	✓	✓				
Tiagabine (TGB) [1997]									✓						
Levetiracetam (LEV) [1999]									✓	✓		✓		✓	
Oxcarbazepine (OXC) [2000]	✓								✓			✓			
Zonisamide (ZNS) [2000]															✓
Pregabalin (PGB) [2004]						✓		✓				✓			
Lacosamide (LAC) [2008]															
Rufinamide (RUF) [2008]															
Vigabatrin (VGB) [2009]								✓		✓	✓				
Clobazam (CLB) [2011]															
Esogabine (retigabine) (EZG) [2011]							✓								
Adverse effects by overall type, specific effect, and associated drugs (listed by abbreviation) ^b															
AE in general considered (nonspecific AEs)	✓	✓	✓	✓	✓	✓	✓			✓	✓	-	✓	-	✓
Degree AEs in general considered in utility measurement (D, directly as an impact of AED; I, indirectly as part of health state; NA, not applicable; NC, not considered)	D	D	NA	I	I	I	D	NC	NC	NC	NC	I	NC	D	D
○ Details about AEs provided	-	✓					✓	LI		✓		LI	✓	-	✓
○ Cardiovascular AE															
§ Arrhythmia, conduction abnormality															
LAC, PGB, EZG, RUF															
§ Hypertension															
LEV, VGB															
§ Edema (peripheral edema, edema)															
PGB, VPA, VGB															
§ Syncope															
LAC															
○ Cosmetic AE															
§ Gingival hyperplasia															
PHT															
§ Alopecia		✓VPA								✓All					
VPA															
§ Facial abnormality															
PHT															
○ Dermatological AE															
§ Serious skin reactions (SSS, TEN)	-									✓LTG			✓LTG		-
CBZ, CLB, GBP, LAC, LTG, LEV, OXC, PHT, PGB, RUF, TGB, VPA, ZNS															
§ Multi-organ hypersensitivity (DRESS)	-														
CBZ, GBP, LAC, LTG, OXC, PHT, RUF, VPA, ZNS															

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

	Societal studies					Health care sector studies									
	Balabanov 2006	Balabanov 2008	Krausner 2007	Maltoni 2013	Messori 1998	Bolin 2010	Bolin 2013	Clements 2013	Hawkins 2005	Remak 2003	Remak 2004	Sincoens 2012	Spackman 2007	Suh 2009	Vera-Lluch 2008
§ Skin discoloration EZG															
§ Other skin reactions C CLB, PHT, VGB															
○ Endocrinology AE															
§ Osteoporosis/osteopenia/osteomalacia/vit D deficiency PHT , TPM, ZN															
§ Weight gain PGB, VGB		✓VPA								✓AI					-
§ Weight loss TPM										✓AI			✓All		
§ Hyponatremia/low sodium level CBZ, OXC	-									-					
§ Metabolic acidosis TPM, ZNS										-					
§ Hypothyroidism oxc	-									-					
○ Gastrointestinal AE															
§ Nausea/vomiting CBZ, LAC, LTG, LEV, OXC, PHT, RUF, TGB, TPM, VPA, VGB	-	u CBZ	-	-	-	-	✓All	LI	-	✓All	-	-	✓All	-	✓
§ Hepatotoxicity/impairment/associated symptoms d CBZ, OXC, PHT, TPM, VPA	-		-	-					-	-	-				
§ Diarrhea TPM, VPA, VGB, ZNS			-	-				LI	-	-	-		-		
§ Anorexia TPM, ZNS			-	-				-	-	-	-		-		
§ Constipation PHT, VGB															
§ Abdominal pain OXC, VPA	-		-						-	-	-				
§ Others: dysgeusia/metalllic taste PHT , dyspepsia VPA , pancreatitis VPA , sialorrhea CLB , xerostomia PGB			-					-	-	-	-				-
○ Hematologic and oncologic AE															
§ Blood dyscrasias CBZ, LTG, LEV, OXC, PHT, RUF, VPA	-								-	-	-		-		
§ Anemia CBZ, LTG, PHT, VGB	-		-		-				-	-	-		-		
§ Thrombocytopenia CBZ, LEV, LTG, PHT, PGB, VPA	-		-		-				-	-	-		-		-
§ Others: leukopenia RUF , lymphadenopathy PHT			-		-			-	-	-	-		-		
○ Nephrology AE															
§ Renal calculus TPM, ZNS										✓TPM			-		
§ Urinary retention EZG	-						-								
○ Neurological AE															
§ CNS depression CBZ, CLB, GBP, LAC, LTG, LEV, OXC, PHT, PGB, EZG, RUF, TGB, TPM, VGB, ZNS	-	u ALL	-	-	-	-	✓All		-	-	-	-	-	-	✓
§ Tremor LAC, OXC, PHT, PGB, EZG, TGB, VPA, VGB	-	✓VPA	-			-			-	-	-			-	
§ Vision issue LAC, OXC, PHT, PGB, EZG, TPM, TGB, VPA, VGB			-			-			-	-	-				✓
§ Cognitive dysfunction/confusion/memory impairment CBZ, LEV, LAC, OXC, PHT, PGB, RUF, EZG, TGB, TPM, VGB, VPA, ZNS			-			-			-	✓All	-	-	✓All	-	✓
§ Somnolence: GBP, LEV, OXC, PGB, EZG, RUF, TPM, ZNS	-		-			-	✓All	LI	-	-	-		-	-	✓
§ Headaches LAC, LEV, OXC, PHT, PGB, RUF, VPA, VGB	-	u CBZ	-			-			-	-	-		-	-	✓

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

^e E.g. agranulocytosis, aplastic anemia, neutropenia, leukopenia, pancytopenia.

^f Lack of coordination, slowed or slurred speech, drowsiness, dizziness.

^g Diplopia, nystagmus, permanent vision loss, increase IOP, eye pain, retinal abnormalities, visual field defects.

^h E.g. ataxia, myasthenia, dyspraxia, hyperkinesia, psychomotor agitation, psychomotor retardation, psychomotor slowing.

ⁱ E.g. hypoaesthesia, paresthesia

^j E.g. agitation, aggression, anger, anxiety, emotional lability, hostility, irritability, nervousness, paranoia, neurosis, psychosis.

^k Rhinitis, cough, pharyngitis, bronchitis, dyspnea, epistaxis, sinusitis, nasopharyngitis.

^l Hypersensitivity reaction, angioedema.

✓ 'yes', included; '-', no, not discussed.

AE: adverse effect; ALL: all drugs included in the analysis; DRESS: drug reaction with eosinophilia and systemic symptoms; LI: identified, but determined likely insignificant in context of analysis; SJS: Stevens–Johnson syndrome; TEN: toxic epidermal necrolysis; U: unknown if included, not enough information provided.