
**Special Issue Article**

**Economic aspects of treating seizure clusters**

Edward Faught

Department of Neurology, Emory University, Atlanta, Georgia, USA

**Correspondence**
Edward Faught, Department of Neurology, Emory Brain Health Center, Emory University, 12 Executive Park Drive NE, Atlanta, GA 30329, USA. Email: rfaught@emory.edu

**Funding information**
Development of this article was funded by Neurelis, Inc.

**Abstract**
Seizure clusters may initiate a chain of events that have economic as well as clinical consequences. The potential economic consequences of seizure clusters must be weighed against the cost of medication to attenuate them. This is true both for individual patients and for society. Data needed for economic analyses include the chance that a cluster will progress to an adverse outcome, such as the need for emergency care, the costs of such an outcome, the cost of a rescue medication (RM), and the effectiveness of the RM. Indirect costs, such as lost employment for patients and caregivers, must also be considered. Several types of economic analyses can be used to determine costs and benefits of a medical intervention. There are studies comparing different RMs from an economic perspective, but there is little direct information on the costs of using an RM versus allowing clusters to run their course. However, the high expense of consequences of seizure clusters makes it likely that effective RMs will make economic as well as medical sense for many patients.

**Keywords**
acute repetitive seizures, costs and cost analysis, rescue medications, status epilepticus

**1 | Introduction**

In a world of limited resources, economic analysis is necessary to inform decisions by individual patients, physicians, and payers, including governments and insurance companies. There are several types of economic analyses of medical care.\(^1\) In the context of seizure clusters, **cost of illness** refers to the costs of clusters without treatment. A **cost-effectiveness analysis** would consider overall costs with and without rescue medication (RM) use. A **cost-utility analysis** may include an adjustment for quality-of-life (QoL) outcomes, expressed as cost per quality-adjusted life year (QALY). A more complex analysis is the **cost-benefit analysis**, which also includes costs compared to benefits of treatment, but with all benefits expressed in monetary terms.

Economic analyses of seizure clusters and their treatment require a range of data, including estimations of the cost of illness (and seizure clusters in particular), costs of RM, and effectiveness of RM. Data are available for some, but not all, of these components needed for economic analysis of seizure clusters and their treatment; in some cases, when data relating to seizure clusters are unavailable, data for epilepsy or seizures in general may serve as a surrogate until such gaps in data can be addressed. “Big data” techniques, including machine learning and natural language processing, may prove useful in analyzing ever-growing volumes of heterogeneous datasets to fill at least some of these gaps as well.\(^2\) The objective of this article is to outline the various methods of pharmacoeconomic analysis of seizure clusters, beginning with discussion of data on...
the costs of illness and RM therapy. Recommendations for future research with these methods in the context of seizure clusters will also be provided. This article is not a formal economic analysis or a systematic review, but rather an overview of approaches with various examples, primarily from the US perspective, that have been selected for illustrative purposes.

## 2 | COST OF ILLNESS: EPILEPSY

Epilepsy carries a substantial economic burden that varies by country, payer mix, and whether both direct and indirect costs are considered.\(^3\)\(^-\)\(^5\) According to a systematic review published in 2015, annual epilepsy-specific health care costs in the United States ranged from $1022–$19,749 per person.\(^3\) More recent data indicate that, for a commercially insured patient in the United States, the median costs for an epilepsy-related health care encounter were $687 for emergency transport, $1913 for emergency department (ED) care, and $22,305 (mean = $38,085) for hospitalization.\(^6\) Severe forms of epilepsy generate especially high costs; persons with Lennox–Gastaut syndrome, identified from a national insurance claims database, averaged about 1.5 ED visits or hospitalizations per year, with costs ranging from $8147–$14,759 for each of these encounters.\(^7\) Direct costs of epilepsy may represent the tip of the iceberg. Indirect costs, including loss of income by patients and caregivers, were reported to be thousands of dollars per year per patient in the United States.\(^8\) In a Polish study, indirect costs of epilepsy, mostly from loss of employment time, constituted 80% of total costs.\(^9\)

The economic burden of epilepsy is greater when seizures are not controlled. For example, in a study of approximately 10,000 adult patients from a claims database, the overall cost of epilepsy-related medical care was $55,11 per year for “stable” epilepsy and $12,399 per year for “uncontrolled” epilepsy.\(^10\) Epilepsy-related ED and hospital care averaged $1685 per year for stable patients and $4905 per year for those with uncontrolled epilepsy.

## 3 | COST OF ILLNESS: SEIZURE CLUSTERS

Costs associated with seizure clusters in particular are difficult to assess given the absence of an agreed-on definition of seizure clusters\(^11\)\(^-\)\(^13\) and uncertainty regarding the prevalence of seizure clusters in the population of patients with epilepsy. There is wide variation in the reported frequency of seizure clusters among the epilepsy population, with estimates ranging from 5% up to approximately 50%.\(^14\)\(^-\)\(^18\) In three representative studies from diary data, the frequency of seizure clusters among patients with epilepsy was reported to be 14.9%,\(^14\) 22.2%,\(^18\) and 29%.\(^17\)

Additional gaps in knowledge required to estimate the individual and population costs of seizure clusters include the average frequency of clusters for an individual patient and for the population, the likelihood that a single cluster or many clusters over a specified time interval will progress to a need for medical intervention, and the costs of likely medical interventions.

Hospital admission for status epilepticus (SE), a severe outcome of some clusters, is associated with a median cost of approximately $7000–$8000 for children and $14,000–$22,305 for adults in the United States.\(^6\)\(^,\)\(^19\)\(^,\)\(^20\) This variability may relate to differences in physician coding of SE. There are strong statistical associations between a history of clusters and a history of SE as well as between a history of clusters and hospitalization for epilepsy.\(^21\) However, it is challenging to translate these observations to the risks associated with a single cluster.

The indirect costs of seizure clusters are difficult to measure, but 53% of patients in a large survey reported that they had lost time from work because of seizure clusters.\(^22\)

## 4 | COST OF RESCUE MEDICATION

The cost of RM will vary based on drug, route of administration, and frequency of use. All approved RMs at present are benzodiazepines.\(^23\)\(^-\)\(^25\) Brand-name prepackaged products are more expensive to acquire but may be economically justifiable if they are used more readily when indicated or in more appropriate dosages, and if they prevent wastage of unused or expired drug. Frequency of use depends not only on best medical practice but also on ease

### Key Points

- Rescue medications used for seizure episodes, including clusters, have demonstrated value to reduce costs and resource utilization
- Comprehensive economic analyses of rescue medications are lacking, owing to the limited scope of retrospective datasets
- Studies that utilize electronic medical records could allow for analyses over longer durations, comparing costs before and after therapy
- Formal economic analyses are needed to determine the impact of rescue medication on total costs of care for seizure clusters
of use and patients’ willingness to use an RM. Although the indication for each of these RMs is the same, it is likely that rectal diazepam is underused because of its physical and social awkwardness and social objection. Variability in response may also lead to the increased frequency of second dose utilization to control seizure clusters, which may also impact cost of RMs. In three open-label studies evaluating the use of a second dose of approved RMs, second doses were not used to treat 77.0% of seizure cluster episodes over 12 h with diazepam rectal gel, 61.5% of seizure cluster episodes over 6 h with midazolam nasal spray, and 87.4% of seizure cluster episodes over 24 h with diazepam nasal spray. These examples of frequency of use during clinical trials cannot be translated directly to broad clinical use, and data from real-world prescription use of the newer products are needed.

The route of administration and associated pharmacokinetic characteristics of RMs must be considered. Intranasal, rectal, and inhalation routes are inherently more expensive because of the need for special formulations to ensure absorption and adequate bioavailability. Oral benzodiazepines are inexpensive but take longer to achieve effective brain concentrations than other routes of administration (e.g., intravenous). They may be appropriate for intermittent therapy, for example, as bridging agents until a maintenance oral antiseizure medication can reach an adequate steady-state level, or for some women with predictable catamenial seizures. For true clusters, oral benzodiazepines are appropriate only if the individual seizures are spaced far enough apart for an oral medication to achieve therapeutic concentrations, if that spacing is well known for that particular patient, and if the dose used produces an adequate antiseizure effect. Most isolated seizures and some clusters stop on their own, so patient and physician impressions that the medication stops them may not be reliable. Measures such as time to maximum concentration \( t_{\text{max}} \) do not translate directly to efficacy because absorption, distribution, and the brain level of drug needed for a patient and for a specific cluster vary between patients. Values for \( t_{\text{max}} \) available in older literature are of limited value because they do not include data for the newer formulations. Nevertheless, the time for a clinically effective concentration may precede \( t_{\text{max}} \). Please see Gidal and Detyniecki, Rescue Therapies for Seizure Clusters: Pharmacology and Target of Treatments in this issue for more details on time to onset of action for RMs.

## 5 | COST-EFFECTIVENESS ANALYSIS

Cost-effectiveness analysis considers illness-related costs, medication-related costs, and the potency of a drug in averting adverse medical outcomes. Data on the cost-effectiveness of RM for treating seizure clusters are sparse and mostly limited to retrospective chart reviews. In one study, charts from a cohort of 543 patients aged >18 years who had received a prescription for an RM were reviewed, and medical costs for the 12 months after the index prescription were estimated. Patients were divided into “users,” who consistently used the RM for each cluster, and “underusers,” who were not prescribed RM or who used an RM for some but not all clusters. Epilepsy-related medical costs were significantly lower for users than for underusers ($13,265 vs. $21,790, respectively; \( p = .038 \)). In addition, for clusters that include tonic–clonic seizures, injuries are certainly a risk, and associated costs should be considered. Among 626 tonic–clonic seizures observed in an epilepsy monitoring unit, 2.1% caused an injury classified as a serious adverse event.

In the absence of adequately controlled prospective trials on the cost-effectiveness of RMs, estimates may be based on extrapolated benefits from published efficacy data for RMs. RMs do not stop every cluster of seizures and do not prevent all instances of progression to ED visits, SE, or hospitalization. In one study using historical controls from patient recollection, 75.6% of episodic SE and prolonged seizures lasted >30 min in the 2 years before treatment with rectal diazepam solution compared with 3.5% of cases in the 2 years after introduction. In an open-label study, 16 of 363 clusters (4.4%) treated with rectal diazepam were followed by hospitalization. An additional consideration is that a likely high proportion of clusters would resolve on their own, even if untreated, and not result in emergency care; data on the proportion of seizure clusters resulting in ED visits or hospitalization in the absence of RM are needed to establish the effectiveness of RM for preventing these adverse outcomes.

A logical surrogate for RM efficacy is the absence of need for a second dose during a cluster. The reported use of a second dose varies from <10% to 35% depending on the regimen and time frame. Using a rough estimate of 75% efficacy for RMs in stopping a cluster and subtracting 25% of clusters that would be assumed to resolve naturally without additional medication would suggest that use of RMs might halt approximately half of clusters. The cost-effectiveness of an RM could then be estimated by dividing all cluster-related costs in half and subtracting the cost of the RM.

Figure 1 outlines an approach to a cost-effectiveness analysis of RM for treatment of seizure clusters. An example using this approach is described in Box 1. Hypothetical numbers described in this example should be viewed as illustrative, not as a formal meta-analysis of the literature for each input. The uncertainty
underlying many of the data points that would be required in such an analysis reflects gaps in knowledge and highlights the need for prospective studies to address these gaps.

### 6 | COST-UTILITY ANALYSIS

Cost-utility analysis is a specific type of cost-effectiveness analysis that states outcomes in terms of QoL, which can be subjective. An outcome can be expressed as QALYs gained (or lost) by a medical treatment, and the costs for each QALY gained can be calculated. This type of analysis is uncommon in the field of epilepsy but has been used to estimate the relative utility of initiating antiseizure medication therapy after a first seizure versus deferring treatment.\(^4^\)\(^3^\) Baile and colleagues used data inputs from retrospective clinical studies to run a “simulated clinical trial” (Markov decision model) for the comparison.\(^4^\)\(^4^\)\(^3^\) Ideally, the value of each outcome on QoL would be determined for each patient. In practice, this is sometimes determined by pooling patient answers to a questionnaire.

An example of this type of analysis is shown in Figure 2 in the form of a Markov probability chain. It incorporates the probability of transition between the starting state “in a cluster” to subsequent outcomes, such as “seizures stop,” “seizures do not stop,” and “emergency care required,” and assigns a value to each state. The conjectural values in this example were assigned by the author, but could be assigned by a group of experts, a patient, or a group of patients. In this example, we assume that the least effective pathway is “rescue medication used” to “seizures continue” to “emergency care” because it is the most expensive and the worst outcome medically.

### 7 | COST–BENEFIT ANALYSIS

This type of analysis monetizes all health outcomes and is mainly of value for informing public health policy. In the case of seizure clusters, for example, cost–benefit analysis might be necessary to determine whether Medicaid should pay for RMs. The time horizon is usually many years, not the single year often studied in a clinical trial. The point of view is societal, and the outcome is often translated into the metric of “willingness to pay” (WTP). WTP is an attempt to monetize prevention of an adverse outcome and then to extrapolate to value at an individual level.

Cost–benefit analyses have compared different RMs. For example, data from Wales and Scotland were used to compare brand-name buccal midazolam with “standard of care” (defined as 95% unlicensed use of buccal midazolam and 5% rectal diazepam), with cost–utility values assigned based on a parent-caregiver survey (62 responses) and Delphi methodology.\(^4^\)\(^2^\) This analysis employed a decision-tree model that reflected events and treatment pathways during and immediately after prolonged acute convulsive seizures;\(^4^\)\(^2^\) a simplified representation of this model was published subsequently\(^4^\)\(^3^\) and is shown in Figure 3. The authors concluded that brand-name buccal midazolam was more cost-effective because of decreased drug wastage, decreased ambulance use, and decreased hospitalizations.\(^4^\)\(^2^\) Brand-name buccal midazolam was also advantageous with regard to QALYs gained. In an Italian study, costs of buccal midazolam were compared to those of rectal diazepam in children with prolonged acute convulsive seizures.\(^4^\)\(^4^\) Despite higher acquisition costs, buccal midazolam produced cost savings based on fewer ambulance rides, hospital admissions, and intensive care unit stays. A Delphi panel of experts was also convened in this study.
to assess probabilities of seizures lasting > 10 min and further medical care events using the previously described decision-tree model (Figure 3). A European study using the same comparator RMs and decision-tree model produced similar findings.

It must be emphasized that none of these European cost–benefit studies used actual data from individual patients on probabilities of prolonged seizures, ambulance transport, ED visits, hospitalizations, or stays in an intensive care unit. All outcomes were estimated by Delphi expert panels. Neither were actual costs measured; they were derived from known average costs of these outcomes in the countries of interest. The remaining data inputs were from published sources, including the costs of medications and the efficacy of each RM in stopping seizures.

A US cost–benefit analysis was conducted by means of a meta-analysis of 24 US studies. Medication costs...
for children receiving various RMs for SE were estimated. Incremental cost per stopped seizure ranged from $13 for buccal midazolam to $2246 for rectal diazepam. Notably, data for this meta-analysis relied mostly on costs for children treated in a tertiary-care ED and did not take into account the cost of the ED visit itself or the cost and utility of translating these methods to home use.
Epilepsy therapy. Given a sufficiently large cohort, the challenge. A historical control with each patient serving as the first listed diagnosis code; and costs attributable to emergency transportation, ED care, and hospitalization. This standard historical control method assumes stability of illness severity over time, which is not always true of epilepsy. An alternative approach would be to use a contemporaneous control group not prescribed an RM, but it is difficult for such a group to be adequately matched on parameters such as illness severity; careful propensity matching could address potential differences.

An economic comparison of different RMs administered at various doses could be performed contemporaneously because the indications for each RM are the same. This approach would also require detailed matching on many parameters related to severity of illness. Even so, in a nonrandomized comparison, there always remains the possibility of unmeasured differences between groups. For example, this could be cost of prescriptions, geographic preferences, prescriber specialty, or other unforeseen differences.

### 8 | SUGGESTIONS FOR RESEARCH

A major difficulty in conducting an economic analysis of seizure clusters is selecting the time horizon. Because it is difficult to estimate costs for a single cluster lasting up to 24 h, it may be preferable to use a longer time frame. One approach would be to identify a cohort of patients prescribed RMs, to follow their course over at least 1 year, and to identify the costs they incur. A cohort can be constructed from deidentified prescription records collected in large national databases, such as those maintained by the Center for Medicaid and Medicare Services and commercial services. However, current claims databases do not allow easy identification of patients with clusters. Implementation of a diagnostic code for seizure clusters, which does not currently exist in the International Classification of Diseases, 10th edition (ICD-10), should enable researchers to track outcomes better and to relate them to RM use. There is a proposal in ICD-11 for a new code, 8A67, for “acute repetitive seizures,” defined as “multiple seizures with a distinct time of onset, with recovery between seizures, occurring within 24 h in adults, or 12 h in children.” This code was implemented in January 2022.

Selecting a control group for such a study presents a challenge. A historical control with each patient serving as their own control has been used for similar studies of epilepsy therapy. Given a sufficiently large cohort, the average costs for 1 or 2 years before the prescription for the RM could be used as baseline data. Outcomes would include all medical costs; all medical costs with epilepsy as the first listed diagnosis code; and costs attributable to emergency transportation, ED care, and hospitalization. This standard historical control method assumes stability of illness severity over time, which of course is not always true of epilepsy. An alternative approach would be to use a contemporaneous control group not prescribed an RM, but it is difficult for such a group to be adequately matched on parameters such as illness severity; careful propensity matching could address potential differences.

### 9 | DISCUSSION

Standard methods for conducting economic analyses can be applied to the issue of treating seizure clusters, but the data needed are complex and at present incomplete. Past efforts to estimate the individual and societal value of stopping seizure clusters have involved patient questionnaires and guesses by physician panels (Delphi process) of the likelihood of medical consequences, but more direct data are needed. In addition, economic analyses do not directly measure intangible benefits such as reductions in worry about seizures or reduced social isolation.

Economic analyses of treatment for seizure clusters must consider the perspective (i.e., individual vs. societal) as well as the country or society in which patients are being treated. Most of the examples presented above are from US data. The medical consequences of seizure clusters may or may not vary around the world, but the economic consequences certainly differ. For example, in the United States, 65% of the costs of hospital epilepsy care are borne by the government via Medicaid or Medicare. An economic analysis in one society will not necessarily apply to other populations.
There are strengths and weaknesses related to the different analytical approaches (Table 1), which can affect the quality of results. Costs from the societal perspective (e.g., lost employment, transportation, and other factors associated with costs calculated for all members of the care team) may be incomplete or not fully described, and incomplete data could greatly impact conclusions. Establishing the values of future costs and outcomes (i.e., discounting) along with study duration can also influence the type and magnitude of results. Methods used to establish utility weights for QALY calculations (e.g., weights associated with the severity of seizure clusters) can vary across studies, which can lead to disparate results based solely on how the QALYs were determined. Thus, whether a therapy is determined to be cost-effective could vary based on how QALYS were weighted. Cost–benefit analysis uses monetary units for both costs and benefits, which, in theory, would allow for comparisons with other studies that utilized this same type of analysis.

Future studies of rescue drugs could utilize a cost-utility approach that leverages a combination of electronic medical record types. Data types used could include diagnosis codes, emergency visits/hospitalizations, prescription information (drug codes, fill dates, quantities), electronic seizure diary data, and physician/chart notes. Although an ICD-10 code of seizure clusters is not available, the new ICD-11 code for acute repetitive seizures (8A67) will likely make it easier to identify patients once the US Department of Health and Human Services updates the clinical modification for medical diagnosis codes, which has been based on the World Health Organization ICD system. The structured and unstructured data (free text) recorded in seizure diaries allow matching the use of rescue medication to a specific seizure cluster, however, diary data may be subject to inconsistencies including recall bias.

Many patients believe that RMs are underused and would welcome having one available. In a Harris poll, patient responses identified too many ED visits and too few RMs as problems. Researchers also view underuse of RMs as a concern. Although it may seem intuitively apparent that wider use of RMs will save money, formal economic analyses are needed to evaluate this hypothesis. As with all therapies, RMs must be prescribed and used appropriately; overuse will skew the cost–benefit equation negatively. Accordingly, such analyses will be important to establish best medical practices as well as to guide allocation of financial resources.

ACKNOWLEDGMENT
The author wrote the entire article. Kirk W. Evanson, PhD, of the Curry Rockefeller Group (Tarrytown, NY), provided editorial assistance including reference searching, formatting and proofreading. This support was funded by Neurelis (San Diego, CA).

CONFLICT OF INTEREST
E.F. has been a member of scientific advisory boards for Biogen, Eisai, Neurelis, SK Life Science, Sage Pharmaceuticals, and the Centers for Disease Control and Prevention, and has received research support from UCB Pharma.

ORCID
Edward Faught https://orcid.org/0000-0001-7415-8044

REFERENCES
1. Introduction to economic evaluation in public health. Atlanta, GA: Centers for Disease Control and Prevention; 2021.
50. Kobau R, Boring M, Zack MM, Croft JB. In 2016, Medicaid and Medicare paid about 65% of all inpatient hospitalization costs for all-age persons hospitalized with epilepsy as the principal diagnosis. Epilepsia Behav. 2021;114(Pt A):107601.

How to cite this article: Faught E. Economic aspects of treating seizure clusters. Epilepsia. 2022;63(Suppl. 1):S45–S54. https://doi.org/10.1111/epi.17340