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Value of cannabidiol as adjunctive treatment for Lennox Gastaut syndrome: cost-effectiveness and budget impact analysis

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Abstract

Background Lennox-Gastaut syndrome (LGS) is a severe encephalopathic disease that leads to a decrease in the quality of life, physical injury, psychosocial impairment, and a significant increase in treatment costs. Cannabidiol (CBD) is approved for the adjunctive treatment of tonic-colonic seizures in LGS. This study aimed to determine the cost-effectiveness of CBD compared to the usual treatment in patients with LGS syndrome.

Methods We developed a lifetime-horizon Markov model to compare the cost-effectiveness of adjunctive CBD versus usual care. Additionally, we performed a budget impact analysis over a 5-year time horizon. The findings were presented as the incremental cost-effectiveness ratio (ICER) for CEA, with a willingness to pay threshold of $18,261 per QALY gained, and as the difference in the overall budget ($) between the scenarios with and without CBD for budget impact assessment.

Results In the base case scenario, CBD was cost-effective compared with usual care $6573 per QALY. Sensitivity analyses substantiated these results. From a healthcare perspective, there is a 77% probability that CBD is cost-effective at a willingness to pay of $18,261 per quality-adjusted life-year (QALY). Overall, the market access of CBD was associated to an increased budget of about $3,459,846 (+ 33%) in the next 5 years simulated.

Conclusions Compared to usual care, CBD seems to be cost-effective in LGS patients and sustainable, with less than 34% overall budget increased in the next 5 years. Future studies need to confirm our results in the real word setting and in other countries.

Keywords CBD, Lennox-Gastaut syndrome, Cost-effectiveness, Usual care

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Background

LGS is a severe form of epilepsy that typically manifests in infancy or early childhood. It is diagnosed for the first time between the ages of 3 and 5 and continues into adulthood [1]. Affected children experience several different types of seizures, most commonly atonic, tonic, and atypical. Children with LGS may also have cognitive dysfunction, delays in reaching developmental milestones, and behavioral problems such as hyperactivity, aggression, and autism [2]. LGS can be caused by a variety of underlying diseases, but in some cases no cause

can be identified, but often the cause of LGS can be identified in 65 to 75% of patients (genetic-structural-metabolic). LGS can be difficult to treat because it is resistant to many types of anticonvulsant drugs [3].

LGS is a rare disease. With an estimated incidence rate of 0.1 to 0.28 per 100,000 overalls, with an incidence rate of 2 per 100,000 in children, it accounts for approximately 2 to 5% of all childhood epilepsies [4]. Based on a systematic literature review on global epidemiology, the prevalence of this condition in the USA is estimated to be between 5.78 and 60.8 per 100,000 people [5]. Patients with LGS have an increased risk of mortality, and approximately half of patients with LGS experience sudden falls that can lead to serious physical injury [6]. In LGS patients, the mortality rate has been confirmed to be 6.12 deaths per 1000 people per year [7].

According to the number of seizures, comorbidities, and poor prognosis, the clinical burden of disease in LGS is significant. However, there is limited information on the financial burden of service utilization and costs associated with the management of patients with LGS [3, 8].

Reaven et al. conducted a study in 2018 to investigate the cost of LGS disease in America; the results showed that patients with LGS used more than 8 times more medical services and more than 7 times more drugs than patients with other types of epilepsy [9]. Also, the length of stay of LGS patients is more than 8 days and the re-hospitalization rate of this group of patients is significant, so that approximately 0–9% of patients are re-hospitalized in 1 month and 42–45% in 1 year after discharge [10]. The average annual direct costs were 22,787 euros in Germany [11] and ranged from 28,461 dollars to 80,545 dollars in the USA among studies [12, 13].

Combinations of antiepileptic drugs have been commonly used in an attempt to achieve seizure control in patients with LGS [14]. Currently, there is no definitive treatment for LGS epilepsy. But common treatments for LGS include drug therapy (lamotrigine, topiramate, and clobazam) and surgical procedures (corpus callosotomy surgery and vagus nerve stimulation), which are usually performed once a year for some patients [4, 14].

CBD, with the brand name Epidyolex, is being used as a new treatment modality for the adjunctive treatment of seizures associated with LGS [15]. CBD has been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as a drug for the treatment of patients with LGS, as well as other types of intractable seizures, including Dravet syndrome and tuberous sclerosis complex. The approval was granted in 2018 for use in children and adolescents at least 2 years of age [16, 17].

Several mechanisms of action have been identified for the beneficial effects of CBD on LGS. CBD interacts with several GPCRs, including GPR55 and GPR18. These receptors are involved in the regulation of neuronal excitability and neurotransmitter release. By acting as an antagonist to GPR55, CBD may inhibit excitatory signaling pathways that contribute to seizure propagation. Similarly, its interaction with GPR18 is thought to modulate the endocannabinoid system, further influencing neuronal stability and reducing seizure frequency [18]. CBD has been shown to modulate T-type voltage-gated calcium channels (VGCCs), which play a crucial role in neuronal excitability. By inhibiting these channels, CBD reduces calcium influx into neurons, subsequently lowering intracellular calcium levels. This action helps prevent excessive neuronal firing, which is a hallmark of seizure activity [19]. CBD acts as a negative modulator of the CB1 and CB2 cannabinoid receptors. Unlike THC, CBD does not produce psychoactive effects, but its modulation of these receptors can lead to anti-inflammatory effects and a reduction in excitatory neurotransmission, which may contribute to its anticonvulsant effects. CBD has been found to enhance the activity of GABA (gamma-aminobutyric acid) and glycine receptors, which are critical for inhibitory neurotransmission in the central nervous system. By positively modulating these receptors, CBD promotes inhibitory signaling, counteracting the excitatory signals that can lead to seizures [17, 20]. Additionally, CBD interacts with serotonin receptors, specifically 5-HT1A and 5-HT2A. These interactions may influence mood and anxiety, which are often comorbid with epilepsy, and can indirectly impact seizure control by enhancing overall neurological stability [21].

The results of randomized, double-blind, placebo-controlled trial studies have shown that in patients with LGS, the addition of CBD to standard treatment significantly reduced overall seizure frequency compared to placebo and had an acceptable safety profile [22, 23]. Compared to other approved antiepileptic drugs, CBD has a unique structure and a potentially novel multimodal mechanism of action [24]. Studies confirm that the use of CBD improves the cognitive and behavioral domains of patients, reduces epileptic spasms, and improves the quality of life of patients [25].

Considering that CBD is added to the common treatment of LGS and the costs of treatment with CBD are significant, therefore the costs of additional treatment and the use of resources related to CBD must first be weighed against its benefits for the patient, providers, and health system. Economic evaluation is often performed to systematically examine the economic efficiency and value for money of adopting a new strategy or a new drug, along with its effects on patient care and outcomes [26]. In Iran, LGS patients have so far been receiving a various combination of levetiracetam, clobazam, lamotrigine,

and topiramate. Given that CBD is emerging as a promising treatment, it is essential to evaluate its cost-effectiveness in the pharmaceutical market for managing LGS. The purpose of the present study is to investigate the cost-effectiveness and estimate the budget impact of CBD compared to the usual treatment for patients with LGS.

Methods

Patient population

Eligible patients between the ages of 2 and 55 years with a clinical diagnosis of LGS including documented history of slow [< 3.0 Hz] spike-and-wave electroencephalograms and droplet seizures, for at least 6 months. Epilepsy treatment unresponsive (i.e., failure to respond to two to four antiepileptic drugs in previous and current treatments), and having at least two seizures per week during a period of at least 4 weeks, were included in the present study (including ketogenic diet and cervical nerve stimulation) for at least 4 weeks prior to the examination are also included. Patients who had a history of alcohol or drug abuse, and who had taken corticosteroids in the past 6 months, or who had taken felbamate less than a year before the examination, were excluded from the study for tetrahydrocannabinol through urine, and pregnant or lactating female patients are also not included [12].

Interventions

CBD in combination of clobazam, lamotrigine, and topiramate was compared with clobazam, lamotrigine, and topiramate alone. All patients received CBD treatment with an oral solution or a similar placebo solution at a daily dose of 2.5, 5, 7.5, 10, and 15 mg/kg on days 1–2, 3–4, 5–6, 7–8, and 9–10, respectively started and continued the treatment with a maintenance dose of 20 mg/kg until response. For clobazam, lamotrigine, and topiramate regimens, patients take 25 mg once a day, 10 mg once a day, and 100 mg twice a day, respectively [12].

Model structure

A Markov model was used in Tree-age software to simulate outcomes associated with CBD treatment. Markov models are powerful tools for simulating and analyzing different treatment states, especially in complex conditions such as LGS. These models allow for the precise and unambiguous definition of different patient states (such as improvement, stability, and treatment refusal). In this model, transitions between states occur with certain probabilities. This allows researcher to predict the patient's progress over time and analyze the impact of different treatments. One of the main challenges of the Markov model is that it unnecessarily simplifies complex clinical situations. In fact, the model may not fully reflect all the clinical and psychological aspects relevant to LGS patients. These models usually assume that the probability of transitions between states remains constant over time, while in reality this may not be the case. Also, we used a stationary distribution of a Markov chain, which is a probability distribution that remains unchanged as time progresses.

This model consists of four states related to the frequency of seizures compared to the basic period and includes the reduction of epileptic attacks by 75–100%, 50–75%, and 50–25% (Fig. 1). Also, patients have a treatment condition with no response to treatment, and the possibility of reducing epileptic attacks in them is less than 25%. Also, patients in all states may experience death. Patients can move between different states of response or non-response to treatment depending on the assigned transition probabilities. Patients who responded to CBD treatment (no seizures or 25–99% seizure reduction) were assumed to continue CBD in subsequent cycles. Patients whose seizures do not respond to CBD can remain refractory (less than 25% seizure reduction) for up to six cycles. After that time, it was assumed that CBD should be discontinued and patients should continue clobazam, topiramate, and lamotrigine alone (Fig. 1). A pediatric neurologist specializing in the treatment of children with LGS in Iran confirmed the applicability of the model and its inputs to clinical practice.

Model inputs

Efficacy and adverse event

In order to obtain the probability of transition between the model states for patients under treatment with CBD or common treatment, a systematic review was conducted. We found that Devi et al.'s study was published in 2022, which was a systematic review and meta-analysis that compared CBD and conventional treatment head-to-head of clinical trial studies. Considering that no new clinical trial study was published in this field after 2022, therefore, the basis for estimating the effectiveness data in our study was a Devi et al. study [27]. The side effects of the two strategies were obtained from the GWP-CARE4 clinical trial, which was conducted in the USA and included 171 patients consuming cannabidiol. Common side effects in this model include diarrhea, somnolence, pyrexia, decreased appetite, and vomiting [12].

Utility

Due to the fact that CBD is not currently consumed in Iran and the initial steps have been taken to add it to the necessary medicine list in Iran, it was not possible for us to measure the utility locally. Therefore, we used the study of Verdian and colleagues who calculated the utility values for LGS patients according to the state mentioned

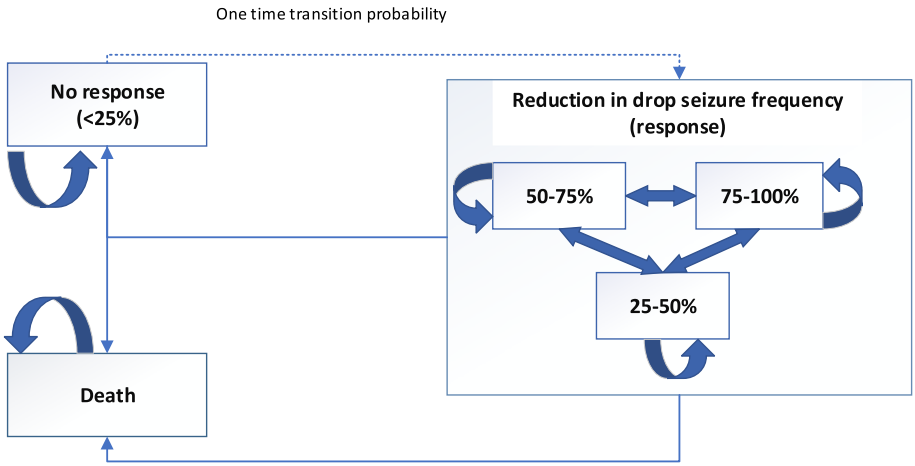

Fig. 1 Schematic of Markov model of GLS treatment. The diagram represents two main states: "response" to treatment (reduction in drop seizure frequency) and "no response" (< 25% reduction of seizure attack). "Response" state includes three levels of seizure frequency reduction: 75–100%, 50–75%, and 25–50%. Every state is a potential transition to the death state. The arrows in the diagram indicate the potential transitions between different states of seizure frequency reduction and outcomes. The dashed arrows suggest one-time transition probabilities, indicating that patients can potentially move from one state to another based on their response to treatment or other clinical factors. The direction of the arrows reflects the possible outcomes based on the treatment effectiveness, highlighting the need for personalized management strategies in epilepsy care

in the model [20]. Three percent discount rate was used to adjust the utility data in the model [28].

Cost

According to the perspective used, only indirect health costs were considered. Cost sources were identified according to the status of the study model. For this purpose, three neurologists were interviewed. The criteria for selecting neurologists were that they have with at least 5 years of experience in treating patients with the LGS. A semi-structured questionnaire was used for the interview and to collect cost data. Questionnaire dimensions included drugs, side effects, diagnostic tests, inpatient services, visits, and necessary consultations during treatment. Apart from these cases, if the doctors mentioned other services, they were included in the questionnaire. All the cases that the neurologists mentioned for identifying the treatment services for patients with the LGS were similar, and data collection reached saturation and there was no need to interview more specialists. The assumed reference case for calculating the drug dose was assumed with a body surface of 1.6 m^2 and a body weight of 35 kg with a height of 150 cm. The values of health resources and their costs are presented in Table 1. The official website of Iran Food and Drug Administration at http://irc.fda.gov.ir/nfi was used to calculate drug costs. The official tariff of medical services announced by the Ministry of Health in 2023 was used for the costs of medical services. The PPP dollar that was announced by the World Bank in 2022 as $64,529 was used for the conversion rate of rial to dollar [29] and to adjust the costs over time, we used a discount rate of 7.2% [28, 30].

Analysis

This analysis evaluated the cost-effectiveness of CBD versus usual treatment for the treatment of LGS. The perspective of the analysis was that of the Iranian health care system over a time horizon of 10 years representing patients followed up to mean age of 15 years.

Monthly cycle length was employed in the model. Future costs and benefits were discounted at 3% and 5.8%, respectively. Willingness-to-pay (WTP) threshold in Iran study is equal 18,261 PPP dollars per QALY in 2022 [30]. This is equal to one-time GDP per capita in Iran.

Uncertainty

The uncertainty of the parameter was evaluated by deterministic and probabilistic analysis. In the deterministic analysis, the ICER was calculated for different values of the variables presented in Table 1. Tornado plots were drawn for the variables that changed the ICER the most. A Monte Carlo simulation with 10,000 replications was performed for stochastic analysis. Beta probability distributions were used for utility data and probabilities, gamma distributions were used for cost data, and normal distributions for physiological variables (e.g., body surface area) were used in Monte Carlo simulations.

Table 1 Parameters for cost-effectiveness analysis

Variables	Value	Range	Distribution	Reference
Patient weight	35	32–38	Normal	(27)
Patient age	15.5	2–55	Normal	(27)
Surface of body	1.6	1.4–1.8	Normal	(27)
Clinical event	2.3	0.43–12.34	NA	(27)
OR	3.05	1.76–5.23	NA	(27,11)
> 25% reduction	4.74	1.62–13.88	NA	(27,11)
> 50% reduction	5.28	0.6–46.32	NA	(27,11)
> 75% reduction	0.382	0.3247–0.4393	Beta	(27,11)
100% reduction	0.286	0.243–0.329	Beta	(27,11)
Probability (monthly)	0.136	0.116–0.156	Beta	(27,11)
CBD	0.0188	0.017–0.022	Beta	(27,11)
> 25% reduction	0.0454	0.039–0.052	Beta	(23,11)
> 50% reduction	0.0490	0.042–0.056	Beta	(23,11)
> 75% reduction	0.0033	0.003–0.004	Beta	(27,11)
100% reduction	0.0309	0.026–0.036	Beta	(27,11)
Diarrhea	0.0239	0.02–0.03	Beta	(27,11)
Somnolence	0.132	0.11–0.15	Beta	(27,11)
Pyrexia	0.074	0.063–0.086	Beta	(27,11)
Decreased appetite	0.025	0.021–0.029	Beta	(27,11)
Vomiting	0.0033	0.003–0.004	Beta	(27,11)
Usual care	0.02390	0.022–0.033	Beta	(27,11)
> 25% reduction	0.02741	0.025–0.034	Beta	(23,11)
> 50% reduction	0.00334	0.003–0.004	Beta	
> 75% reduction	0.00402	0.003–0.005	Beta	
100% reduction	0.01695	0.014–0.019	Beta	
Diarrhea				
Somnolence				
Pyrexia				
Decreased appetite				
Vomiting				
Utility	0.46	0.39–0.53	Beta	(24)
Response (25–50%)	0.61	0.52–0.7	Beta	(20)
Response (50–75%)	0.7	0.56–0.8	Beta	(20)
Response (75–100%)	0.39	0.33–0.45	Beta	(20)
No response	−0.06	0.05–0.07	Beta	(20)
Disutility diarrhea	−0.2	0.17–0.23	Beta	(20)
Disutility somnolence	−0.1	0.09–0.12	Beta	(20)
Disutility pyrexia	−0.1	0.09–0.12	Beta	(20)
Disutility appetite	−0.04	0.03–0.054	Beta	(20)
Disutility vomiting				
Cost (PPP-adjusted USD)	$1294	1035–1552	Gamma	https://irc.fda.gov.ir/nfi https://treatment.tums.ac.ir
Emergency visit	$1952	1561–2342	Gamma	
Admission to hospital	$142	113–170	Gamma	
Laboratory tests	$688	550–825	Gamma	
Imaging	$34	27–41	Gamma	
Nutritional counseling	$65	52–78	Gamma	
Neurologist visit	$46	37–55	Gamma	
Psychiatrist visit	$25	20–30	Gamma	
Land ambulance transfer to hospital	$52	42–62	Gamma	
General practitioner visit	$4.6	4–6	Gamma	
CBD per 100 mg/ml	$0.053	0.04–0.06	Gamma	
Lamotrigine per 25 mg	$0.2	0.2–0.3	Gamma	
Topiramate per 100 mg	$0.11	0.09–0.13	Gamma	
Clobazam per 10 mg				

Budget impact analysis

The budget impact analysis was performed to assess the impact of CBD use in a cohort of GLS patients in the Iranian market. The model compared two scenarios according to CBD presence on the market: "scenario no-CBD" where the study drug was not present and "scenario CBD" which includes CBD as possible treatment on the market.

The model estimated the annual cost per patient for each type of treatment by using the parameters costs and healthcare resources consumption model included the medicine costs, diagnostic tests, inpatient services,

visits, and AEs costs. These costs were associated to the epidemiological data of GLS and market share data to estimate the 5-year overall cost of the scenario with and without CBD. The incidence of LGS is estimated to be between 0.1 and 0.28 per 100,000 population and the prevalence is about 26 per 100,000 people [31]. The budget impact of CBD in Iran, with a 5-year time horizon, was the result of the cost difference between the two scenarios.

OR, odds ratio.

Table 2 Results of base-case analysis

Strategy	Cost	Effect	Incr cost	Incr effect	ICER
Cannabidiol	57741	3.35	5661	0.86	6573
Usual Treatment	52080	2.49	-	-	-

Results

Drug costs accounted for over 80% of the total cost of treatment. CBD use yielded an incremental gain of 0.86 QALYs at an additional cost of $5661 (Table 2). The CBD was associated with an incremental cost of $6573 for each QALY gained. At a willingness to pay threshold of $18,261, CBD was the cost-effective.

Sensitivity analyses

Figure 2 shows the results of the deterministic sensitivity analysis. The ICER of the CBD group compared to the usual treatment group ranged from $ − 3859/QALY to $17,658/QALY, and the CBD price and utility of response rate of the seizure-free state in 50–75% and 25–50% states had the greatest effect on the ICER, while the other factors had little effect on the ICER. This means that if the price of CBD increases by 20%, the ICER will increase to $17,432/QALY but since the amount of ICER is below the threshold, it has no impact on the cost-effectiveness result. With a 10% increase in

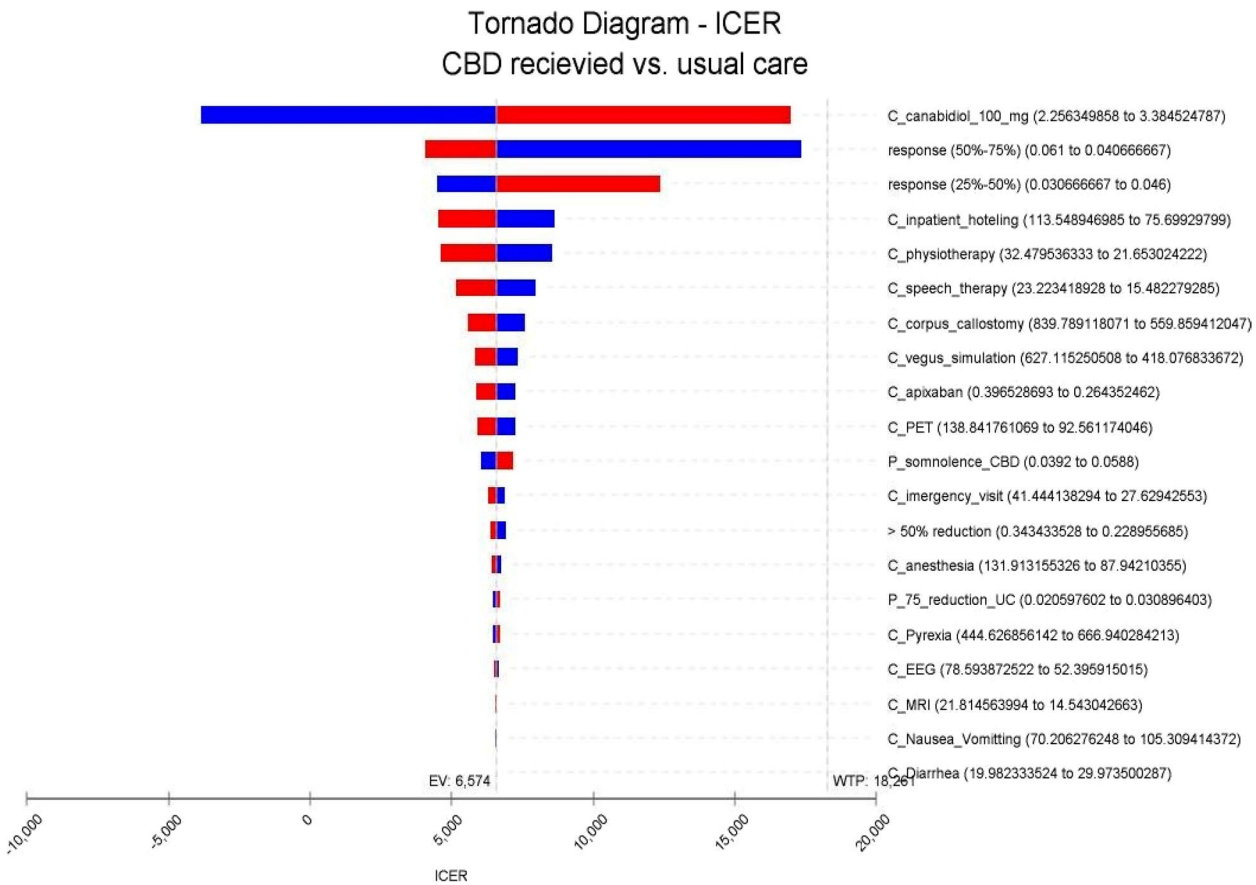

Fig. 2 Tornado diagram of the deterministic sensitivity analysis. This diagram shows a comparison of the costs of CBD treatment and usual care. Each bar represents a different cost-effectiveness ratio (ICER), clearly highlighting the strengths and weaknesses of the different treatment options. Blue bars represent cases where there were improvements in cost-effectiveness (e.g., cost reduction or effect increase). Red bars represent cases where there were higher costs or lower effects. C, cost; P, probability; response, response rate of the seizure-free; UC, usual care; CBD, cannabidiol

response rate of the seizure-free state in 50–75% and a 10% decrease in response rate of the seizure-free state in 25–50%, ICER increase to $17,982/QALY and $12,689/QALY, respectively, but ICER is still below the threshold.

The results of the probabilistic sensitivity analysis were summarized using a cost-effectiveness scatter plot (Fig. 3) and a cost-effectiveness acceptability curve (Fig. 4). In the scatter plot, the north-east quadrant included simulations in which CBD was more effective and more costly than usual care, and the south-east quadrant included simulations in which CBD was more effective and less costly than usual treatment. Compared with usual treatment, CBD has a higher QALYs at higher costs in 63% of the simulations and higher QALYs at lower costs in 32% of simulations. In different simulations, if the calculated ICERs for CBD compared with usual treatment were lower than the specified WTP threshold, situations in which CBD would be selected over usual treatment were indicated. The probability of CBD to be cost-effective versus usual treatment was estimated to be 77% at a WTP threshold of CAD 18,261.

Budget impact analysis

Based on the model assumptions, the estimated target population with GLS was composed by 16,770 patients. Figure 4 shows the number of patients treated with each DMT in the observed period. In the scenario with CBD, the number of patients potentially treated with the new treatment increased over time, from 1677 during the first year up to 8794 in the fifth year. The economic impact of CBD was estimated in an increase of 3,459,846 million dollar in 5 years simulated, with an incremental cost of 2% ($223,419) in the first year, 4% ($452,193) in the second year, 7% ($686,419) in the third year, 9% ($926,195) in the fourth year, and 11% ($1,171,621) in the last year (Table 3 and Fig. 4).

Discussion

Our study was cost-effectiveness analysis of CBD in patients with LGS seizures using Markov models. Using this approach, our base-case model with a WTP threshold of $18,261 provided evidence to aid decision-making regarding the cost-effectiveness of add-on CBD in patients with LGS aged ≥ 2 years who are refractory to current treatment.

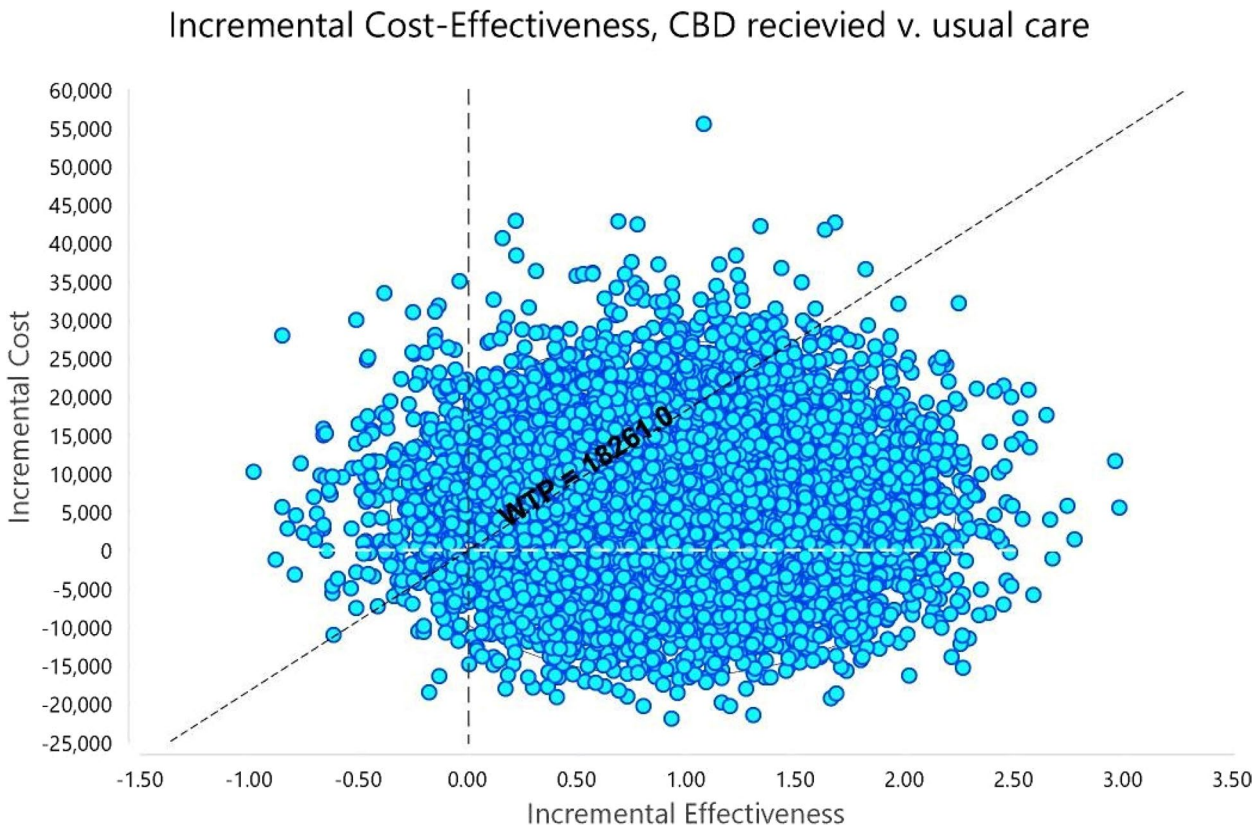

Fig. 3 Scatterplot of the cost-effectiveness plane of the probabilistic sensitivity analysis. The horizontal axis represents incremental effectiveness, while the vertical axis shows incremental costs. The blue points indicate various ICER points, and the line labeled (WTP = $18,261) represents the willingness to pay for the treatment. ICER points below WTP are considered cost-effective

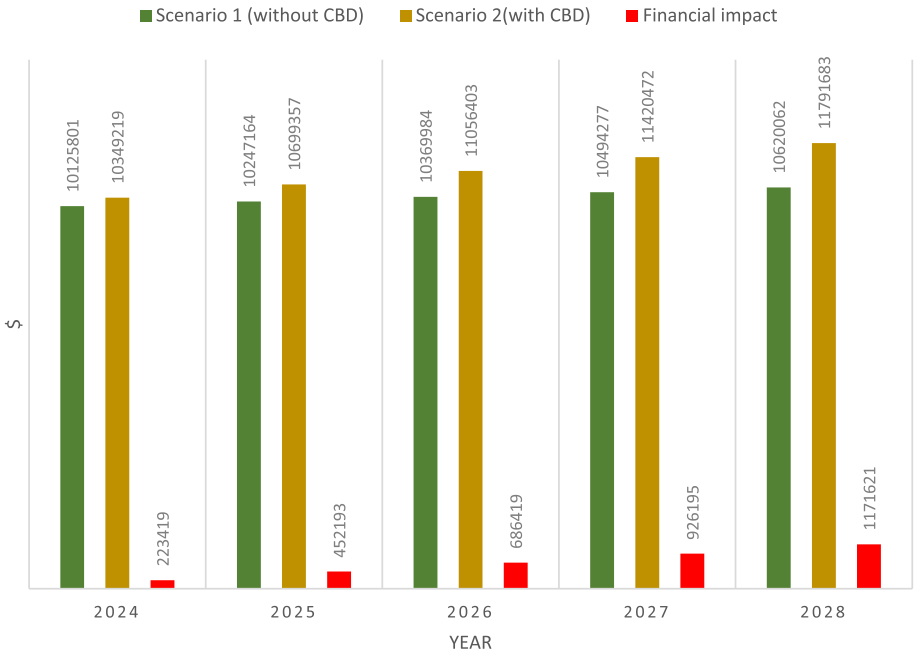

Fig. 4 Budget impact analysis of CBD in Iranian health system. This figure compares the healthcare expenditures under two scenarios: scenario 1 (without CBD) and scenario 2 (with CBD) for the years 2024 to 2028. The red bars represent the budget impact attributed to the introduction of CBD, highlighting the financial implications over time as the market share of CBD gradually increases

Table 3 The results of the budget impact analysis

Year	2024	2025	2026	2027	2028
Iran population	86369815	87406253	88455128	89516589	90590788
Population of LGS patients	16770	16971	17175	17380	17589
CBD market share	.1	0.2	.3	.4	.5
Scenario 1 (without CBD)	10125801	10247164	10369984	10494277	10620062
Scenario 2 (with CBD)	10349219	10699357	11056403	11420472	11791683
Budget impact	223419	452193	686419	926195	1171621

Compared with usual care, CBD resulted in more QALYs gained at a more cost, suggesting that CBD is more cost-effective than usual care at willingness-to-pay thresholds. Probabilistic and deterministic sensitivity analysis was used to determine the strength of the model results. Also, study findings were confirmed to all model assumptions; however, it is important to take into account the limited availability of clinical data on the efficacy of CBD in our country when interpreting the findings.

Few economic evaluations have been published investigating the cost-effectiveness of CBD in seizure treatment with contrasting conclusions. We identified only one study that had assessed the cost-effectiveness of CBD treatments for LGS. Also, we found one economic evaluation studies for the cost-effectiveness of CBD in Dravet syndrome and one study in the control of epilepsy in MS patients.

A cost-effectiveness study in LGS patients conducted in UK showed that CBD as an add-on therapy to usual care decreased the health burden (yielded 0.7 additional QALYs), but increased the drug cost ($314,900 additional healthcare cost). With the ICER of $451,800 per QALY in LGS seizures, CBD had a 0% probability of being cost-effective at a willingness-to-pay of $150,000/QALY [32].

Another study for Dravet syndrome from the perspective of the Canadian healthcare system reported the CBD to be cost-effective versus usual care over a 13-year time horizon. Seventy-six percent of replications found CBD to be the optimal treatment at a willingness-to-pay threshold of $50,000 [33]. Burke et al. reported the refractory seizures associated with tuberous sclerosis complex in patients aged 2 were treated cost-effectively

with cannabidiol. The probability that cost-effectiveness would be effective at a willingness-to-pay threshold of £20,000 or £30,000 was 30% or 52%, respectively; the disease severity modifier has a base case of 39% and 66% [34]. According to Wijnen et al. study, CBD in LGS and DS has a cost-effectiveness that is discussed by NICE (ICERs of £33,721 and £32,471, respectively) [10].

Our study, from the perspective of the Iranian health system, showed that the ICER of CBD as an add-on therapy to the usual care was $6573/QALY. Its probability of being cost-effective was 77% at a willingness-to-pay of $18,261/QALY. Different from the studies mentioned above are in methodological differences in the study design and assumptions, the price of drug and diagnostic services, clinical practice patterns in countries, and the primary source of efficacy data that we used for the meta-analysis study by Devi et al. was that others had used different clinical trial studies.

The high cost of cannabidiol was the most important factor affecting the budget impact difference for two treatment strategies. The budget impact showed that the treatment of patients with CBD causes a 33% increase cost in Iranian health system for LGS treatment. In a study in home-based care and inpatient care were major cost drivers for LGS patients, with the cost per person ranging from $24,048 to $80,545 [3].

The increased costs of CBD treatment for patients with LGS could have significant implications for health policy. Given the complex and costly nature of this condition, which requires ongoing and varied care, these additional costs need to be carefully considered. Policymakers should note that although CBD may increase treatment costs, it may also lead to reduced costs in the long term, such as hospitalization and home care services.

Indeed, adopting a comprehensive and evidence-based approach to policymaking can help identify the economic benefits of improving patients' quality of life and reducing the need for more complex care.

Also, our study demonstrating an increase of 0.86 QALYs for one patients but when all patients with the LGS are multiplied by this amount of QALY, we will have a significant increase in quality in the overall population of patients with the LGS in Iran, which can justify the increase in costs resulting from this treatment. The findings underscore the health benefits associated with CBD, which can guide clinicians in recommending treatment strategies that optimize both clinical outcomes and resource allocation.

The results of this study can be evidence for decision-making organizations to establish treatment guidelines and add CBD to the list of essential medicines in Iran. Also, these results can support decisions regarding insurance coverage and funding for CBD, promoting wider access to effective therapies for individuals suffering from LGS. Ultimately, such evidence can enhance treatment guidelines and inform stakeholder discussions, fostering an environment where patients receive the most beneficial and economically viable care options.

Based on the effectiveness of CBD for patients suffering from LGS, it is reasonable to suggest several steps for its inclusion in the Iranian reimbursement list. First, the Iranian Ministry of Health could initiate price negotiation discussions with pharmaceutical manufacturers, focusing on cost-effectiveness to align CBD pricing with its clinical benefits. This may require conducting local health economic evaluations to compare the value of CBD with existing therapies based on locally gathered efficacy data. Second, a gradual incorporation of CBD into the reimbursement system could be achieved through a tiered reimbursement approach, allowing patients suffering from LGS to access this treatment while studying its long-term effects. Engaging healthcare providers, patient advocate groups, and policymakers will be essential to raise awareness and garner support for the potential effectiveness of CBD. Additionally, ongoing monitoring and evaluation of treatment outcomes after CBD's introduction will help ensure that the therapy indeed improves patient quality of life, thereby justifying its inclusion in the reimbursement list and informing future healthcare policy.

In light of the limitations within Iran's economy, utilizing funding mechanisms such as risk-sharing agreements between the pharmaceutical industry and the Iranian government could further alleviate the costs associated with CBD therapy. By aligning reimbursement costs with the effectiveness of CBD, patient access can be achieved at a reasonable expense. Furthermore, seeking international partnerships and funds will be crucial to establish these frameworks, ensuring the sustainability of high-cost therapies like CBD within Iran's healthcare system.

Our study had some limitations. First, the efficacy data were not from Iran and transition probabilities were from a meta-analysis study in India. This may limit the generalizability of our findings to the Iranian context, as health outcomes can be influenced by regional factors such as genetics, healthcare practices, and environmental conditions. Second, we assumed that the costs of different age groups were the same. By assuming that the costs are the same across different age groups, we may overlook significant variations in healthcare usage and costs that occur as individuals age. Younger patients may experience different healthcare interactions compared to older patients, which can skew overall cost estimates. Third, due to the lack of a rate of initial distribution, we referred to the literature to get the rate of initial distribution [35]. Fourth, due to non-use of CBD medicine in Iran, we did

not able to calculate the indirect costs and lost productivity. LGS patients experience seizures associated with a risk of injury and mortality, have multiple comorbidities, and often require constant care that has a great impact on caregivers' burden. Ignoring these indirect costs may result in an underestimation of the overall burden of the condition. This oversight could lead to insufficient support and resources for families and caregivers who deal with the challenges of managing conditions like LGS, which can affect quality of life and economic stability. The last limitation is the dependence on the stationary distribution of the Markov chain, which may not accurately represent the dynamic changes in the LGS patients over time.

These limitations suggest that while our study provides valuable insights, caution should be exercised when interpreting the findings. Further research that accounts for local efficacy data, age-related cost variability, and the direct implications of treatment options is necessary to deepen understanding and improve healthcare outcomes for LGS patients in Iran. Addressing these gaps could enhance policy formulations and healthcare strategies tailored to the specific needs and conditions of the Iranian population.

Conclusions

Our study demonstrates that CBD is valuable as an add-on therapy for patients with LGS in Iran. At current list prices in Iran and assuming a WTP threshold of $18,261/QALY, CBD is cost-effective for the treatment of LGS. So CBD has a more advantage of efficacy compared with usual care and its incremental BI for health system is relatively acceptable. The present study also provides a reference for stakeholders to judge the value of cannabidiol.

Abbreviations

LGS	Lennox-Gastaut syndrome
CEA	Cost-effectiveness analysis
ICER	Incremental cost-effectiveness ratio
CBD	Cannabidiol
FDA	US Food and Drug Administration
EMA	European Medicines Agency
WTP	Willingness-to-pay
QALY	Quality-adjusted life-year

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Authors' contribution

Study design: Z.G., K.K. and F.L.; Coordination: K.K. and Z.G.; Data gathering: Z.G., R.SH., N.M. and M.T.; Data analysis: Z.G., K.K. and F.L.; Interpretation of results: Z.G., K.K. and R.SH.; Drafting the manuscript: Z.G., K.K., F.L. and N.M.; Final revision of the manuscripts: Z.G., K.K., F.L., N.M., R.SH., and M.T. All authors have read and approved the manuscript.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with International Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Shiraz University of Medical Sciences, code IR.SUMS.NUMIMG.REC.1403.061. Also considering that this study did not contain patients, there was no need to obtain consent.

Consent for publication

Not applicable.

Competing interests

None.
The authors declare no competing interests.

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References

1. Ramanathan RS, Ahluwalia T, Sharma A. Lennox-Gastaut syndrome: an overview. J Pediatr Neurosci. 2010;5(1):86–8.
2. Brigo F, Jones K, Eltze C, Matricardi S. Anti-seizure medications for Lennox-Gastaut syndrome. Cochrane Database Syst Rev. 2021;4(4):CD003277.
3. Strzelczyk A, Zuberi SM, Striano P, Rosenow F, Schubert-Bast S. The burden of illness in Lennox-Gastaut syndrome: a systematic literature review. Orphanet J Rare Dis. 2023;18(1):42.
4. Strzelczyk A, Lagae L, Wilmshurst JM, Brunklaus A, Striano P, Rosenow F, Schubert-Bast S. Dravet syndrome: a systematic literature review of the illness burden. Epilepsia Open. 2023;8(4):1256–70.
5. Sullivan J, Benítez A, Roth J, Andrews JS, Shah D, Butcher E, Jones A, Cross JH. A systematic literature review on the global epidemiology of Dravet syndrome and Lennox-Gastaut syndrome: prevalence, incidence, diagnosis, and mortality. Epilepsia. 2024;65(5):1240–63.
6. Hollenack K, Story T, Acs A, Tran O, Stockl K. Prevalence of probable Dravet syndrome, Lennox-Gastaut syndrome, and other refractory epilepsies in commercial and Medicaid populations in the United States. J Manag Care Spec Pharm. 2019;25(3-A SUPPL):S58.
7. Chin RF, Pickrell WO, Guelfucci F, Martin M, Holland R. Prevalence, healthcare resource utilization and mortality of Lennox-Gastaut syndrome: retrospective linkage cohort study. Seizure. 2021;91:159–66.
8. Cross JH, Benítez A, Roth J, Andrews JS, Shah D, Butcher E, et al. A comprehensive systematic literature review of the burden of illness of Lennox-Gastaut syndrome on patients, caregivers, and society. Epilepsia. 2024;65(5):1224–39.
9. Reaven NL, Funk SE, Montouris GD, Saurer TB, Story TJ. Burden of illness in patients with possible Lennox-Gastaut syndrome: a retrospective claims-based study. Epilepsy Behav. 2018;88:66–73.
10. Wijnen B, Armstrong N, Ramaekers B, Witlox W, Westwood M, Fayter D, et al. Cannabidiol for adjuvant treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome: an evidence review group perspective of a NICE single technology appraisal. Pharmacoeconomics. 2020;38:1043–53.
11. Devinsky O, Patel AD, Cross JH, Villanueva V, Wirrell EC, Privitera M, et al. Effect of cannabidiol on drop seizures in the Lennox-Gastaut syndrome. NEJM AI. 2018;378(20):1888–97.
12. Thiele EA, Marsh ED, French JA, Mazurkiewicz-Beldzinska M, Benbadis SR, Joshi C, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2018;391(10125):1085–96.

13. Kaplan JS, Stella N, Catterall WA, Westenbroek RE. Cannabidiol attenuates seizures and social deficits in a mouse model of Dravet syndrome. Proc Natl Acad Sci U S A. 2017;114(42):11229–34.
14. Sullivan J, Deighton AM, Vila MC, Szabo SM, Maru B, Gofshteyn JS, et al. The clinical, economic, and humanistic burden of Dravet syndrome–a systematic literature review. Epilepsy Behav. 2022;130: 108661.
15. Strzelczyk A, Schubert-Bast S, Simon A, Wyatt G, Holland R, Rosenow F. Epidemiology, healthcare resource use, and mortality in patients with probable Lennox-Gastaut syndrome: a population-based study on German health insurance data. Epilepsy Behav. 2021;115: 107647.
16. Moreira GA, Moraes R, Ribeiro RG, Crippa ACDS. Cannabidiol for the treatment of refractory epilepsy in children: a critical review of the literature. Rev Paul Pediatr. 2022;41: e2021197.
17. Rabino M, Mallia S, Castiglioni E, Rovina D, Pompilio G, Gowran A. The endocannabinoid system and cannabidiol: past, present, and prospective for cardiovascular diseases. Pharmaceuticals. 2021;14(9): 936.
18. Senn L, Cannazza G, Biagini G. Receptors and channels possibly mediating the effects of phytocannabinoids on seizures and epilepsy. Pharmaceuticals. 2020;13(8): 174.
19. Ghovanloo M-R, Shuart NG, Mezeyova J, Dean RA, Ruben PC, Goodchild SJ. Inhibitory effects of cannabidiol on voltage-dependent sodium currents. J Biol Chem. 2018;293(43):16546–58.
20. Rosenberg EC, Chamberland S, Bazelot M, Nebet ER, Wang X, McKenzie S, et al. Cannabidiol modulates excitatory-inhibitory ratio to counter hippocampal hyperactivity. Neuron. 2023;111(8):1282–300 e8.
21. De Gregorio D, McLaughlin RJ, Posa L, Ochoa-Sanchez R, Enns J, Lopez-Canul M, et al. Cannabidiol modulates serotonergic transmission and reverses both allodynia and anxiety-like behavior in a model of neuropathic pain. Pain. 2019;160(1):136–50.
22. Privitera M, Bhathal H, Wong M, Cross JH, Wirrell E, Marsh ED, et al. Time to onset of cannabidiol (CBD) treatment effect in Lennox-Gastaut syndrome: analysis from two randomized controlled trials. Epilepsia. 2021;62(5):1130–40.
23. Patel AD, Mazurkiewicz-Bełdzińska M, Chin RF, Gil-Nagel A, Gunning B, Halford JJ, et al. Long-term safety and efficacy of add-on cannabidiol in patients with Lennox-Gastaut syndrome: results of a long-term open-label extension trial. Epilepsia. 2021;62(9):2228–39.
24. Okumura H, Inoue S, Naidoo S, Holmstrom S, Akaza H. Cost-effectiveness analysis of enzalutamide for patients with chemotherapy-naïve metastatic castration-resistant prostate cancer in Japan. Jpn J Clin Oncol. 2021;51(8):1319–29.
25. Ebadi SR, Saleki K, Adl Parvar T, Rahimi N, Aghamollaii V, Ranji S, Tafakhori A. The effect of cannabidiol on seizure features and quality of life in drug-resistant frontal lobe epilepsy patients: a triple-blind controlled trial. Front Neurol. 2023;14: 1143783.
26. Chisholm D, Evans DB. Economic evaluation in health: saving money or improving care? J Med Econ. 2007;10(3):325–37.
27. Devi N, Madaan P, Ameen R, Sahu JK, Bansal D. Short-term and long-term efficacy and safety of antiseizure medications in Lennox Gastaut syndrome: a network meta-analysis. Seizure: Seizure. 2022;99:164–75.
28. Goudarzi Z, Shahtaheri RS, Najafpour Z, Hamedifar H, Ebrahimi H. Cost-effectiveness and budget impact analysis of daratumumab, lenalidomide and dexamethasone for relapsed-refractory multiple myeloma. Cost Eff Resour Alloc. 2024;22(1):17.
29. World Bank. PPP conversion factor, G.L.p.i.-l., Islamic Rep. Available from: https://data.worldbank.org/indicator/PA.NUS.PPP?locations=IR. 2023.
30. Goudarzi Z, Lotfi F, Najafpour Z, Hafezi A, Zakaria MA, Keshavarz K. Cost-effectiveness and budget impact analysis of enzalutamide in comparison to abiraterone in treatment of metastatic prostate cancer resistant to castration in Iran. BMC Urol. 2024;24(1):45.
31. Trevathan E, Murphy CC, Yeargin-Allsopp M. Prevalence and descriptive epidemiology of Lennox-Gastaut syndrome among Atlanta children. Epilepsia. 1997;38(12):1283–8.
32. Neuberger EE, Carlson JJ, Veenstra DL. Cost-effectiveness of cannabidiol adjunct therapy versus usual care for the treatment of seizures in Lennox-Gastaut syndrome. Pharmacoeconomics. 2020;38:1237–45.
33. Elliott J, McCoy B, Clifford T, Potter BK, Wells GA, Coyle D. Economic evaluation of cannabinoid oil for Dravet syndrome: a cost-utility analysis. Pharmacoeconomics. 2020;38:971–80.
34. Burke C, Crossan C, Tyas E, Hemstock M, Lee D, Bowditch S. A cost-utility analysis of add-on cannabidiol versus usual care alone for the treatment of seizures associated with tuberous sclerosis complex in England and Wales. Pharmacoecon Open. 2024:1–16.
35. Zhang D, Li X, Ding J, Ke X, Ding W, Ren Y, et al. Value of perampanel as adjunctive treatment for partial-onset seizures in epilepsy: cost-effectiveness and budget impact analysis. Front Public Health. 2021;9: 670108.

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