

A comprehensive review of the literature on epilepsy in selected countries in emerging markets

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Aims: To perform a systematic literature review of studies in peer reviewed journals on the epidemiology, economics, and treatment patterns of epilepsy in selected countries in emerging markets.

Methods: A literature search was performed using relevant search terms to identify articles published from 1999 to 2000 on the epidemiology, economics, and treatment patterns of epilepsy. Studies were identified through electronic Embase®, Cochrane®, MEDLINE®, and PubMed® databases. Manual review of bibliographies allowed for the detection of additional articles.

Results: Our search yielded 65 articles. These articles contained information relevant to epidemiology (n = 16), treatment guidelines (n = 4), treatment patterns (n = 33), unmet needs (n = 4), and economics (n = 8). From a patient perspective, patients with less than or equal to two adverse events (AEs) while taking anti-epileptic drugs (AEDs) had significantly lower annual costs than those having greater than or equal to three AEs, as did patients with fewer seizures. The overall mean annual cost for epilepsy per patient ranged from US\$773 in China to US\$2646 in Mexico. Prevalence data varied widely and were found for countries including Arab League Members, China, India, and Taiwan. In Turkey, active prevalence rates ranged from 0.08/1000 to 8.5/1000, and in Arab countries, active prevalence ranged from 0.9/1000 in Sudan to 6.5/1000 in Saudi Arabia. Seventeen different AEDs were used in the identified studies. The most common AEDs utilized were phenobarbital (21.7%), valproate (17.5%), and tiagabine (16.4%). In all studies, the use of AEDs resulted in an increase of patients who became seizure free and a reduction in seizure frequency and severity.

Conclusion: Few studies have examined the prevalence and incidence of epilepsy in emerging markets and study limitations tend to underestimate these rates at all times. More cost-effectiveness, cost-minimization, and cost-benefit analyses must be performed to enhance the data on the economics of epilepsy and its therapy in regions with insufficient resources and those emerging markets which contain the majority of the world's population. And finally, the study found that generic AEDs are frequently used to successfully treat patients with epilepsy in emerging markets.

Keywords: emerging markets, epilepsy, seizures, epidemiology, treatment patterns, guidelines, economics

Introduction

Epilepsy is recognized as a collection of heterogeneous syndromes characterized by additional conditions that coexist with seizures and impacts over 50 million people worldwide.¹ Cognitive, emotional, and behavioral comorbidities are common.

Seizures are typically divided into two main categories: partial (focal) and generalized. Generalized seizures affect both cerebral hemispheres from the onset of

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the seizure. Seizures produce loss of consciousness, either for long periods of time or temporarily, and are sub-categorized into generalized tonic-clonic, myoclonic, absence, or atonic subtypes.² Partial seizures affect an area within one cerebral hemisphere of the brain and are the most recurring type of seizure experienced by patients with epilepsy.³ Partial seizures are further subdivided into simple partial seizures, where consciousness is retained; and complex partial seizures, where consciousness is diminished or lost.³

In the treatment of epilepsy, no one anti-epileptic drug (AED) has been shown to be the most effective, and all AEDs have published side effects. AEDs are selected following consideration of side effects, ease of use, cost, and physician knowledge. Patients with newly diagnosed epilepsy who require treatment can be started on standard, first-line AEDs such as carbamazepine, phenytoin, valproic acid, or phenobarbital. Alternatively, newer AEDs introduced in the past decade may be used. These include gabapentin, lamotrigine, oxcarbazepine, or topiramate.⁴ Between 70% and 80% of individuals are successfully treated with one of the AEDs now available and success rates primarily depend on the etiology of the seizure disorder.⁴ However, the remaining 20%–30% of patients have either intractable or uncontrolled seizures or suffer significant adverse side effects to medication.⁴ As with the selection of first-line therapy, choosing the appropriate drug for the treatment of refractory epilepsy must be based on the appreciation of each drug's characteristics and risks for each individual patient.

An emerging market economy is defined as an economy with low-to-middle per capita income.⁵ Such countries constitute approximately 80% of the global population, are often rapidly-growing and represent about 20% of the world's economies.⁵ Although the term emerging market is loosely defined, countries that fall into this category, range from big to small, and are often considered emerging because of development and reform programs that have been put in place to launch their markets globally.⁵ Consequently, although China is considered one of the world's foremost economic leaders, it is grouped into the emerging market category together with much smaller economies with fewer resources, such as Sudan or Bulgaria.

Epilepsy is common in patients admitted to hospitals in emerging markets.⁶ However, there are reported differences in the epidemiology, economic burden, and outcome of epilepsy in these regions compared to high-income countries; although few data from the former regions exist.⁶ Applying the International League Against Epilepsy definition of epilepsy is problematic in these areas, as patients often arrive

at health facilities without adequate documentation of the seizure duration.⁷

The goal of treatment for patients with epilepsy is no seizures with little to no side effects. However, due to variabilities in clinical presentation and available resources, treatments are highly individualized and vary widely. The objective of this study is to systematically review the literature on epilepsy to identify incidence and prevalence rates, economic data, unmet needs, and treatment patterns in those emerging markets which contain the majority of the world's population.

Methods

To ensure an extensive examination of the literature, this study included all published randomized clinical trials and observational peer-reviewed studies that examined factors associated with epilepsy in emerging markets. A comprehensive search of the literature was performed using PubMed, EMBASE, and Cochrane Review databases on the following topics concerning epilepsy in emerging markets: epidemiology, including prevalence and incidence; economics, including burden of disease, effects on productivity, and other economic issues; guidelines for treatment; treatment patterns; drug usage patterns; and unmet needs.

Search strategy and study selection

The initial search strategy was developed in the PubMed/MEDLINE database (Table 1). A search string was constructed utilizing varied approaches to identify the most comprehensive and effective method for retrieving studies specific to the study objective. Methods were explored using MeSH, (PubMed/MEDLINE's controlled vocabulary indexing hierarchy), as well as a detailed examination of key terminology that would afford the best retrieval. Provisions were made to include varied constructs of search terms with the use of the asterisk as a truncation tool (Example: epidemiolog* to ensure retrieval of epidemiological, epidemiology, etc.) Additional constraints were also placed upon the final search strategy to limit the retrieval to English, humans, and studies published in the past 10 years at the time of the search (between 1999 and 2010).

Following completion of the PubMed/MEDLINE search on January 4, 2011, the EMBASE and Cochrane databases were searched with comparable search strings on January 14, 2011 and January 18, 2011 respectively; duplicate citations, if present, were identified and removed. Figure 1 illustrates the various steps in the study selection

Table I Prevalence of epilepsy in emerging markets

Region	Age group	Time period	Prevalence/1000 inhabitants		Citation
			Lifetime	Active	
Saudi Arabia	Adults and children	1989	NR	6.54	Al Rajeh et al ¹¹
Members of the Arab League (Mauritania, Morocco, Algeria, Tunisia, Libya, Egypt, Sudan, Djibouti, Comoros, Somalia, Eritrea, Lebanon, Jordan, Syria, Iraq, Saudi Arabia, Qatar, Kuwait, United Arab Emirates, Oman, Bahrain, and Yemen) and The Palestine territory (Gaza strip and West Bank)	Adults and children	1950–2008	Libya 2.3 Tunisia 4.0 Saudi Arabia 6.5 Sudan 0.9–2.1	NR	Benamer and Grosset ¹²
Argentina	Children	1991	3.2	2.6	Somoza et al ⁸
Argentina	Adults and children	1991	6.2	3.8	Melcon et al ⁹
Argentina	Children	1994	71.9	64.8	Somoza et al ¹⁰
China/Hong Kong	Children	1997	NR	1.52	Kwong et al ¹³
China/Hong Kong	Adults	2002	NR	1.54	Fong et al ¹⁴
China/Hong Kong	Adults and children	1982–2002	NR	4.5	Hui et al ¹⁵
Colombia	Adults and children	1995–1996	11.3	10.1	Velez and Eslava-Cobos ¹⁷
India	Children	1991	NR	2.33	Shah et al ¹⁸
Russia	Adults and children	2003–2008	NR	3.4	Halász et al ¹⁹
Taiwan	Adults	2001	3.14	2.77	Chen et al ¹⁶
Turkey	Adults and children	1999–2000	0.08	NR	Onal et al ²⁰
Turkey	Children	1996	0.08	NR	Serdaroğlu et al ²¹
Turkey	Adults and children	2004–2005	12.2	8.5	Calisir et al ²²
Turkey	Adults and children	2000	6.0	5.0	Velioglu et al ²³

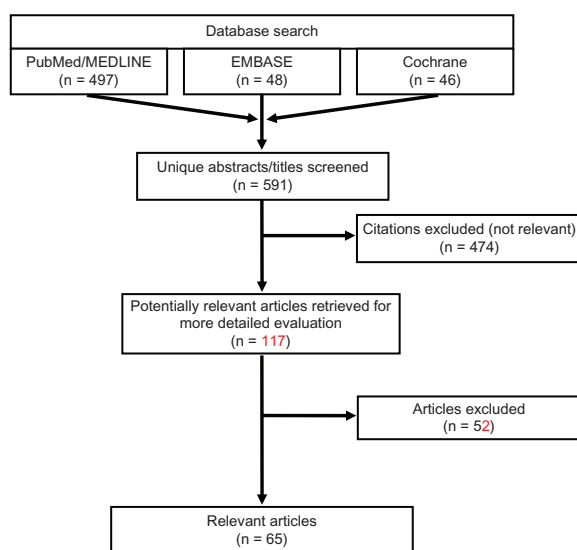
Abbreviation: NR, not reported.

process via a flow diagram. All citations were initially screened for relevancy and included where appropriate. Each abstract and, if needed, full-text article was reviewed for eligibility prior to inclusion in the current analysis. Reference lists of relevant studies identified by searching the three databases (PubMed/MEDLINE, EMBASE, and

Cochrane) were further searched manually to identify any additional publications of interest. Articles were excluded if they did not focus on epilepsy, if they did not provide information about the outcomes of interest, if the sample size was <50, or if they pertained to infantile or pediatric populations <12 years old. Articles were excluded from this review if the articles were not published in English or if the subjects studied were not humans. Reviews, letters/comments, and case studies were also excluded from the review, but associated primary references were examined to verify they were identified by our search strategy. After abstracts were screened, full texts of the selected articles were reviewed to ensure relevance and presence of desired information.

Data abstraction

A structured abstraction table consisting of descriptive characteristics of the studies such as study objective/hypothesis; data collection methods (study design and analytics); study population characteristics (sample size, subject inclusion and exclusion criteria); treatments; outcomes; and limitations was used to extract the data from all relevant articles.

**Figure I** Literature review flow diagram.

Results

Our comprehensive search yielded a total of 65 articles (Figure 1). There were 16 articles found to have information relevant to epidemiology, four treatment guidelines, 33 articles which discussed treatment patterns, four articles discussing unmet needs, and eight economic articles. No articles were found addressing the topic of drug usage trends. Since many of the studies included in this review evaluated multiple topics, there was overlap between the categories. Therefore, many of the articles summarized below have been cross-categorized and, when totaled, the numbers of articles cited in each category add up to more than the 65 indicated.

Epidemiology of epilepsy

Prevalence

Studies were found describing the prevalence in Algeria, Argentina, Bahrain, China, Colombia, Comoros, Djibouti, Egypt, Eritrea, Gaza strip, India, Iraq, Jordan, Lebanon, Kuwait, Libya, Mauritania, Morocco, Oman, Qatar, Russia, Saudi Arabia, Somalia, Sudan, Syria, Taiwan, Tunisia, Turkey, United Arab Emirates, West Bank, and Yemen. These data are summarized in Table 1. Studies may provide data for lifetime prevalence, which approximate cumulative incidence, and/or active prevalence, which measures current seizures or current use of anti-epileptic drugs.

In the literature identified for this review, the prevalence of epilepsy in emerging markets varied according to the population studied. For example, three studies discussed the prevalence of epilepsy in Argentina. In the primary school children population, the lifetime and active prevalence rates were determined to be 3.2/1000 and 2.6/1000, respectively in one report, while lifetime and active prevalence was estimated to be 6.2/1000 and 3.8/1000 in another.^{8,9} Another examination found a lifetime prevalence of 71.9/1000 and an active prevalence of 64.8/1000 in the special schools of Buenos Aires that contain student populations with physical or mental disorders and learning problems.¹⁰

The prevalence rate for active epilepsy in Saudi Arabia was reported in two separate studies. In the first, prevalence was found to be 6.54/1000 inhabitants.¹¹ A second study reported prevalence rates for several Arab countries. In this study, epilepsy prevalence ranged between 0.9/1000 in Sudan and 6.5/1000 in Saudi Arabia, reporting a median of 2.3/1000 inhabitants.¹²

Three studies addressed the epidemiology of epilepsy in China. The prevalence of active epilepsy in China was estimated to be 1.52/1000 in one study and 1.54 per 1000 inhabitants in another.^{13,14} Hui and Kwan estimated that approximately 4.5/1000 individuals in Hong Kong have active epilepsy.¹⁵ The lifetime and active prevalence rates of adult patients with epilepsy in Taiwan was estimated to be 3.14/1000 and 2.77/1000, respectively.¹⁶

In Colombia, the general prevalence of epilepsy was determined to be 11.3/1000.¹⁷ In India, they found that the age-specific prevalence of epilepsy in school-going children was 3.44/1000 for those aged 11–14 years and 2.33/1000 for those age 15–18 years.¹⁸ In the Russian Federation, an age-adjusted prevalence of epilepsy of 3.40/1000 was reported.¹⁹

Four studies examined the prevalence of epilepsy in Turkey with active rates ranging from 0.8/1000 to 8.5/1000 and lifetime rates from 5/1000 to 12.2/1000. Two separate studies found the active prevalence rate to be 0.08/1000, while in Bursa a prevalence rate for active epilepsy was 8.5/1000, and lifetime prevalence was reported to be 12.2/1000.^{20–22} Lastly, a lifetime prevalence of 6/1000 and an active epilepsy prevalence of 5/1000 was also reported.²³

Incidence

Only one study was identified that studied the incidence of epilepsy in emerging markets and it reported an annual incidence of 174 per 100,000 persons in Qatar in 2001.¹²

Economics of epilepsy

Articles from Bulgaria, China, India, Korea and Mexico were identified. These data are summarized in Tables 2 and 3.

Table 2 Societal perspective – economic data

Year	Country	Patient population	Costs of epilepsy	Cost burden	Reference
2008	China	Adults and children	↓103¥ (16 USD) ↓12¥ (2 USD) ↑10¥ (1.5 USD)	Shanghai-mean costs of health care contact with town doctors Ningxia-health care costs to town doctors Ningxia-time costs to town doctors	Ding et al ²⁸
2009	China	Adults and children	1968¥ (289 USD)	Loss of productivity	Hong et al ²⁴
2001	India	Adults	147 rupees (3 USD) 22 rupees (0.50 USD)	Drug monitoring service to hospital Drug monitoring service to hospital per seizure prevented	Rane et al ²⁵

Abbreviations: ¥, Chinese yuan, renminbi; USD, United States dollar; ↑, increased; ↓, decreased.

Table 3 Patient perspective – economic data

Year	Country	Patient population	Outcome measure	Mean cost (USD)	Reference
2008	Bulgaria	Adults	≤2 AEs	339€ (\$487)	Balabanov et al ²⁷
			≥2 AEs	806€ (\$1158)	
			CBZ patients >26 weeks between seizures	386€ (\$555)	
			<26 weeks between seizures	810€ (\$1164)	
			CBZ ≥ 50% seizure reduction	403€ (\$579)	
			CBZ ≤ 50% seizure reduction	931€ (\$1338)	
2008	China	Adults and children	Shanghai: 1-year expenses per PB treated patient	1494¥ decreased to 92¥ at 1 year (\$234 to \$14)	Ding et al ²⁸
			Ningxia: 1-year expenses per PB treated patient	213¥ decreased to 46¥ at 1 year (\$33 to \$7)	
2009	China	Adults and children	Direct medical care costs	2529¥ (\$395)	Hong et al ²⁴
			Antiepileptic drugs	1651¥ (\$258)	
			Non-medical direct costs	756¥ (\$118)	
			Annual cost for epilepsy/patient	5253¥ (\$821)	
2001	India	Adults	TDM cost per patient	147₹ (\$114)	Rane et al ²⁵
			TDM cost patient charged	30₹ (\$0.65)	
			TDM cost to hospital per seizure prevented	22₹ (\$0.48)	
			TDM cost to patient per seizure prevented	5₹ (\$0.10)	
2005	India	Adults	Cost of drug at entry – monotherapy	2276₹ (\$49)	Thomas et al ²⁹
			Cost of drug at entry – polytherapy	3629₹ (\$79)	
			Cost of drug at last follow-up – monotherapy	1898₹ (\$41)	
			Cost of drug at last follow-up – polytherapy	4929₹ (\$107)	
2006	Mexico	Adults and children	Annual healthcare cost per patient	2646 USD	Garcia-Contreras et al ³⁰

Note: USD conversion rates as at August 21, 2011.

Abbreviations: ¥, Chinese yuan, renminbi; USD, United States dollar; €, euro; PB, phenobarbital; TDM, therapeutic drug monitoring.

Societal perspective

From a societal perspective, costs due to loss of productivity averaged US\$289 per patient per year in China (Table 2).²⁴ In India, the direct costs were calculated to be 147 rupees (US\$3.26) to hospitals per epileptic patient, while the cost of monitoring therapeutic drugs to the hospital, per seizure prevented, was 22.35 rupees (US\$0.50).²⁵

Payer perspective

In Korea, from the payer's perspective, adjunctive therapy led to the incremental cost-effectiveness ratios being estimated at US\$44 per seizure-free day per adult patient and US\$11,084 per quality-adjusted life years gained.²⁶

Patient perspective

From a patient perspective, Bulgarian patients with one or two adverse events (AEs) had significantly lower annual costs (mean €338.73) than those with more than two AEs (mean €806.03) while taking AED monotherapy (Table 3). Monotherapy patients with fewer seizures also showed significantly lower costs (mean €85.97), compared with patients with more frequent seizures (mean €810.43). Patients on AED therapy, with 50% or more seizure reduction

compared with baseline, showed significantly lower costs (mean 402.67€) than those with worse control (mean €931.30).²⁷

In rural Shanghai and Ningxia, China, the total 1-year expenses per patient before AED treatment were 1494.30¥ (US\$229) and 213.09¥ (US\$33), respectively, and these expenses decreased to 91.52¥ (US\$14) and 45.90¥ (US\$7), respectively ($P < 0.05$) following treatment for 1 year.²⁸ In another study from China, direct medical care costs were 2529¥ (US\$372) per year per patient, of which anti-epileptic drugs (1651¥ or US\$243) accounted for the major cost component.²⁴ Nonmedical direct costs were much less than direct health care costs, averaging approximately 756¥ (US\$111). The overall mean annual cost for epilepsy per patient in this series was approximately 5253¥ (US\$773), and these costs accounted for more than half of the mean annual income.²⁴

In India, direct costs were calculated, including cost to the hospital of providing the therapeutic drug monitoring (TDM) service, cost to the hospital per seizure prevented, and cost to the patient per seizure prevented.²⁵ The cost per patient of the TDM service to the hospital was 147 rupees (US\$3.26), while each patient was charged only 30 rupees

(US\$0.67) per sample, reflecting the cost of the consumables only. The cost of TDM to the hospital per seizure prevented was 22.35 rupees (US\$0.50) while the cost to the patient was 4.50 rupees (US\$0.10). A second study found that the cost of drug therapy for patients at entry ranged from 2276 rupees (US\$50.46) to 3629 rupees (US\$80.46). At the time of last follow-up, it ranged from 1898 rupees (US\$42.08) to 4929 rupees (US\$109.28).²⁹

Lastly, in Mexico, the annual mean health care cost per treated patient was found to be US\$2646. Ambulatory health care contributed to 76% of the total, and hospital health care contributed 24%.³⁰

Treatment guidelines

The goal of epilepsy treatment is to maintain a normal lifestyle, ideally, by complete seizure control with minimal side effects. For the majority of patients with epilepsy, AED therapy is used. The quality of care and therapeutic outcome may differ across countries because of numerous variations in medical systems. Few additional studies were identified that addressed ways by which care providers could more effectively identify patients with epilepsy or determine an appropriate therapy.

In China, age-varying differences between the effectiveness of carbamazepine and valproate for the treatment of generalized onset and partial onset seizures were reported in a study that suggested valproate may be more effective at treating epilepsy in younger patients, while carbamazepine may be more effective at treating patients older than 30.³¹ An electroencephalography screening process by which high-risk patients can be better screened was described as well as a method used to aid health care providers in the identification of patients with generalized tonic-clonic seizures.^{32,33}

Treatment patterns

In the articles identified, data on the treatment patterns of 12,317 patients with generalized or partial onset epilepsy were found for countries including Argentina, Brazil, China, Czech Republic, India, Korea, Poland, Russia, and Taiwan. These data are summarized in Table 4. Seventeen different AEDs were used in these studies. The proportion of patients receiving each AED was phenobarbital (21.7%), valproate (17.5%), tiagabine (16.4%), oxcarbazepine (8.3%), levetiracetam (8.1%), topiramate (7.2%), eslicarbazepine acetate (5.8%), lacosamide (3.9%), lamotrigine (2.1%), pregabalin (1.9%), and clobazam (1.6%). Zonisamide, primidone, clonazepam, phenytoin, gabapentin, and carbamazepine

were used in <1% of the population each. In all studies, the use of these AEDs resulted in an increase of patients who became seizure free and a reduction of seizure frequency and severity.

Unmet needs

The literature review identified five articles discussing the unmet needs of patients with epilepsy in emerging markets. There were two studies of the Indian population and one study found for each of the countries of Bahrain, the Czech Republic, and Kuwait. In general, the articles identified the need for developing treatment strategies, counseling therapies, and social support for people with epilepsy to improve their quality of life.^{34,35} As the mean delay in diagnosis is 1.5 ± 4 years in parts of India, facilities for epilepsy surgery, therapeutic drug monitoring, and services of clinical psychologist or medical social workers are also needed.³⁶ In Kuwait, objections to shaking hands with, working with, marrying, and employing patients with epilepsy were reported by 16.0%, 24.8%, 71.6%, and 45.2%, of the general population, respectively.³⁷ Therefore, continuing effective educational interventions are needed to improve the understanding of epilepsy and to diminish social discrimination and misconceptions against these patients.³⁷

Discussion

This review is a thorough study of epilepsy in emerging markets summarizing the available literature on epidemiology, economics, unmet needs, treatment and drug usage patterns, and guidelines for the treatment of epilepsy in emerging markets. To more fully grasp the information found in this review concerning epilepsy and its treatment in emerging markets, it is useful to compare these findings to data from developed countries with higher per capita incomes.

Because it is often less complicated to obtain information regarding prevalence than incidence, many more prevalence studies of epilepsy from diverse populations were found. In general, prevalence rates per 1000 individuals varied widely in this review. In Argentina and China, rates ranged from 2.6–3.8 and 1.5–4.5 respectively.^{8,9,13,15} In India, prevalence was reported to be 2.3 and in Turkey, rates ranged from 0.08 to 8.5 individuals.^{18,20,22} Studies from Argentina reported a wide range of per 1000 population rates of 3.2, 6.2, and 71.9 in the general school, general, and the special school populations, respectively. The prevalence study from southern Sudan was based on a population estimate

Table 4 Clinical trials of therapies for epilepsy

Country	Therapeutic agent(s)	Patient population	Trial design	Key findings	Reference
Brazil	Clobazam	Partial onset patients with refractory epilepsy	Retrospective	Following treatment, 7% of patients were seizure free, 49% had $\geq 50\%$ of improvement in seizure control, 40% had $< 50\%$ of improvement in seizure control.	Montenegro et al ⁵⁰
Brazil	Clobazam as add-on agent	Generalized	Retrospective	Following treatment, 20% of patients were seizure-free, 25% had more than 75% improvement in seizure control, 10% had more than 50% and 26% were non responders to treatment.	Montenegro et al ⁵¹
China	Phenobarbital	Generalized	Prospective observational	Following treatment, 78% of the patients had a 50% or greater reduction in seizure frequency and 43% were seizure free.	Liu et al ⁵²
China	Topiramate monotherapy vs add-on agent	Generalized and Partial onset	Prospective observational	The rate of AEs was significantly higher with use of topiramate as monotherapy than as adjunctive therapy.	Lu et al ⁵³
China	Zonisamide as add-on agent	Partial onset refractory epilepsy	RCT	Zonisamide showed significantly greater efficacy compared with placebo.	Lu et al ⁵⁴
China	Topiramate monotherapy vs add-on agent	Generalized	Retrospective	The percentage of seizure-free patients was 69% in the topiramate monotherapy group and 42% in the topiramate add-on group.	Lu et al ⁵⁵
China	Valproate and Primidone	Partial onset patients unresponsive to carbamazepine	Prospective observational	Significantly more patients on Valproate (51%) achieved a greater than 50% seizure reduction than on Primidone (34%).	Sun et al ⁵⁶
China	Levetiracetam as add-on agent	Partial onset	RCT	Levetiracetam significantly decreased weekly partial-onset seizure frequency over placebo by 27%.	Wu et al ⁵⁷
China	Levetiracetam as add-on agent	Partial onset	RCT	The proportion of patients with a minimum of 50% reduction in partial seizure frequency occurred in 46% of the treatment group, compared with 39% of the placebo group.	Xiao et al ⁵⁸
Czech Republic	Levetiracetam	Generalized and partial onset	Retrospective	A significant decrease in the number of seizures occurred after 6 months of treatment.	Tlusta et al ⁵⁹
India	Phenobarbital Carbamazepine Phenytoin Valproate Clobazam Clonazepam Lamotrigine Oxcarbazepine	Generalized and partial onset elderly population	Retrospective	One year remission rate was 56%.	Tran et al ⁵⁹
India	Phenobarbital or phenytoin	Generalized and partial onset	Prospective observational	The proportion with remission at each of four successive years of follow-up ranged from 58% to 66% for patients who were drug compliant and who had a lifetime total of 30 or fewer generalized tonic-clonic seizures.	Mani et al ⁴⁹
India	Gabapentin or Lamotrigine	Partial onset patients refractory to carbamazepine	RCT	The average frequency of partial seizures decreased significantly in both groups. The responder rate was 78% and 92% for gabapentin and lamotrigine respectively.	Sethi et al ⁶⁰
Multiple	Lacosamide	Partial onset	RCT	The median percent reduction in seizure frequency was 21% for placebo, 35% for lacosamide 200 mg/day, and 36% for 400 mg/day.	Halász et al ⁶¹

(Continued)

Table 4 (Continued)

Country	Therapeutic agent(s)	Patient population	Trial design	Key findings	Reference
Multiple	Eslicarbazepine acetate	Partial onset patients refractory to treatment with one or two concomitant AEDs	RCT	Seizure frequency was significantly lower in the treatment groups as compared to placebo.	Elger et al ⁶²
Multiple	Eslicarbazepine acetate	Partial onset	Prospective observational	Seizure frequency decreased by 39% during the first 4 weeks and between 48% and 56% thereafter.	Halász et al ¹⁹
Multiple	Valproate	Generalized and partial onset	Prospective observational	At 6 months, 77% of subjects were seizure free.	Jedrzejczak et al ⁶³
Multiple	Valproate	Partial onset	Prospective observational	At 6 months, 87% of patients became seizure free.	Deleu et al ⁶⁴
Multiple	Levetiracetam as add-on agent	Partial onset	Prospective observational	44% of patients had a $\geq 50\%$ reduction in seizure frequency, with a median reduction of 46%. 18% became seizure free during treatment.	Kwan et al ⁶⁵
Multiple	Oxcarbazepine	Partial onset	RCT	The median reduction in seizure frequency was 26%, 40%, 50%, or 8% for patients receiving 600, 1200, or 2400 mg/d treatment or placebo, respectively. Of patients in the 600, 1200, or 2400 mg/d treatment groups, 27%, 42%, and 50% respectively, had more than 50% reduction in seizure frequency compared with 13% for placebo.	Barcs et al ⁶⁶
Poland	Tiagabine as add-on agent	Generalized and partial onset	Prospective observational	The mean initial seizure rate per patient decreased following treatment. The percent of responders with $\geq 50\%$ reduction of seizure rate reached 52% after 8 weeks and 77% after 16 weeks.	Chmielewska and Stelmasiak ⁶⁷
Poland	Tiagabine as add-on agent	Generalized and partial onset	Prospective observational	71% patients had a $\geq 50\%$ decrease in seizure frequency compared with baseline. The beneficial effect of treatment on seizure reduction was most marked in patients with partial seizures.	Jedrzejczak ⁶⁸
Poland	Topiramate as add-on agent with Carbamazepine	Partial onset	Retrospective	Most AEs with adjunctive therapy were transient.	Majkowski et al ⁶⁹
Poland	Lamotrigine vs Valproate	Generalized	Retrospective	Valproate showed comparable efficacy in all syndromes where lamotrigine showed better efficacy in childhood epilepsy.	Mazurkiewicz-Beldzinska et al ⁷⁰
Russia	Pregabalin as add-on agent	Partial onset	Prospective observational	The patients receiving treatment showed a significant reduction at the end of the first month in the number of seizures.	Bondarenko II ⁷¹
Russia	Oxcarbazepine monotherapy and as add-on agent	Generalized and partial onset	Non randomized clinical trial	52% of patients had 50% less seizures; 35% of patients had a reduced number of seizures by 75%; 18% of patients had full control. In patients who never received AED therapy, full treatment control was achieved in 74% and among patients who had received AED treatment full control was reached in 44%. Monotherapy or combined therapy also led to decreased seizure duration.	Burd et al ⁷²

(Continued)

Table 4 (Continued)

Country	Therapeutic agent(s)	Patient population	Trial design	Key findings	Reference
Russia	Topiramate anticonvulsant monotherapy	Generalized and partial onset	Prospective observational	9.2% of patients had an increase in and duration of remission. Patients treated with other drug therapy had much lower rates of remission (4.6% for carbamazepine; 3.0% valproate; 1.5% phenobarbital). Depression and anxiety developed twice as frequently in women than men.	Zheleznova et al ⁷³
South Korea	Topiramate as add-on therapy	Partial onset refractory	Retrospective	The median seizure frequency reduction rate was 69% in the treatment population. Cumulative seizure-free rate was 30% and the 1-year seizure-free rate was 13% at five-year follow-up.	Cho et al ⁷⁴
South Korea	Levetiracetam	Partial onset refractory	Prospective observational	The median percent reduction in weekly seizure frequency over the treatment period was 43.2%. The $\geq 50\%$ and $\geq 75\%$ responder rates were 45.4% and 36.1%, respectively.	Heo et al ⁷⁵
South Korea	AED drug tapering	Generalized	Retrospective	75% of patients achieved complete seizure freedom for ≥ 1 year. AED discontinuation was attempted in 91% of patients with a successful outcome.	Kim et al ⁷⁶
South Korea	Pregabalin as add-on therapy	Partial onset refractory	RCT	There was a significant seizure reduction (52.7%) with pregabalin compared to placebo (37.7%).	Lee et al ⁷⁷
Taiwan	Levetiracetam and topiramate as add-on agents	Partial onset	Prospective observational	Seizure frequency and epilepsy duration were not significantly different between the two groups compared to baseline.	Huang et al ⁷⁸
Taiwan	Levetiracetam	Treatment-resistant partial onset patients	RCT	Levetiracetam reduced weekly partial-seizure frequency by 24% relative to placebo. Significantly more levetiracetam than placebo patients experienced a response of a $\geq 50\%$ decrease from baseline in weekly frequency of partial seizures.	Tsai et al ⁷⁹

Abbreviations: RCT, randomized controlled trial; AE, adverse event; AED, anti-epileptic drug.

of '50–100,000' making comparisons to other countries impractical.¹² Yet, the general prevalence of epilepsy in Colombia was determined to be 11.3/1000 which was reported to be similar to prevalence rates found in nations with comparable developmental status.¹⁷

In developed countries, prevalence rates for epilepsy have been reported to range from 0.027–0.1 per 1000 individuals.^{38,39} It is generally accepted that the prevalence rate in developing countries is approximately double that of developed countries, at approximately 0.15/1000.⁴⁰ Variation in rates, between and within studies, may be attributable to differences in definitions of epilepsy and prevalence. For example, in the study by Banerjee and colleagues,³⁸ the reported age-adjusted prevalence was based on medical records, whereas Onal and colleagues, used self-reported prevalence which was

not confirmed by medical diagnoses.²⁰ Yet, as prevalence is also a measure of the interaction of additional factors such as death, incidence, remission of illness, population migration, or access to appropriate medical care, it is likely that numerous factors account for the differences found between world populations, and not just differing methodologies. Population screening is needed to reveal the true epilepsy prevalence. Until broader, countrywide studies are performed, epidemiological rates will tend to be underestimated.

Incidence rates for North America and Europe have been reported to range from 16–51 per 100,000 people.^{38,39,41} These rates are at the lower end of global annual incidence estimates of 50–70 cases per 100,000.⁴² Only one study was identified in our review reporting an incidence of 174 per 100,000 persons in Qatar.¹² However, this incidence study

was regional, retrospective, hospital-based, and did not have a clear definition of epilepsy. Interpretation of the differences in incidence and prevalence rates will require additional awareness of the role of economic, cultural, and social factors effecting epilepsy and its care in these markets.

The primary focus of care for patients with epilepsy is the prevention of further seizures which may lead to additional morbidity or mortality.⁴³ The goal of treatment is the maintenance of a normal lifestyle, ideally by complete seizure control without, or with, minimal side effects. If seizures are provoked by external factors, avoidance might be sufficient to prevent attacks. However, for the majority of patients, AED therapy is used. In addition to seizure control, patients with epilepsy may have psychosocial symptoms requiring treatment. But the quality of care and therapeutic outcome may differ across countries because of variations in medical systems. The Commission of European Affairs of the International League Against Epilepsy has defined standards for appropriate care,⁴⁴ which have not yet been met by some European countries.⁴⁵ As such, the situation in many developing countries is frequently less adequate. Few studies were identified that addressed ways by which care providers could more effectively identify patients with epilepsy or suggest an appropriate therapy, but in the studies reviewed for this report, the use of AEDs resulted in an increase of patients who had a decreased seizure burden.

In 2005, Garcia-Contreras et al reported the annual health care cost per treated patient in Mexico to be US\$2646.³⁰ In the US, this number has been reported to be in the range of US\$2600–9400 per person.^{46,47} It should be noted, however, that these values from the year 2000 provide an outdated estimate of the direct costs of epilepsy, and it is reasonable to assume that in current monetary terms this burden is greater. Again, the differences between regions may be due to multiple factors including an underestimation of the affected population due to limited resources or, perhaps, the use of less expensive generic drugs over branded products. In 1999, phenytoin (dilantin) had a 42% market share of all AED prescriptions in the US.⁴⁸ The introduction of new AEDs over the past decade, including gabapentin, felbamate, lamotrigine, tiagabine, and topiramate, has increased the options available for adjunctive treatment when first-line therapy is ineffective. Many of these newer medications, however, often have increased tolerability and are beginning to replace their preceding agents as first-line therapy.⁴⁸ In fact, in 2004, phenytoin's US market share had dropped to 33%.⁴⁸ Yet, while the newer, branded medications are available in many emerging markets, resources are often limited

and the inexpensive, effective generic AEDs are often used out of necessity. For example, Mani et al demonstrated successful treatment of epilepsy in a rural area of India using a combination of trained physicians and health workers, generic AEDs, drug compliance, health education, and follow-up.⁴⁹ Further analyses considering cost-minimization, cost-effectiveness, and cost-benefit must be done in the future to further understand the cost of epilepsy therapy to resource-poor regions.

Epilepsy care in developing countries lags behind care in developed countries. Precise data on delivery of neurological services for epilepsy is vital to optimize medical services for patients with limited resources. This review additionally highlighted the need for the development of treatment strategies, counseling therapies, and social support services for people with epilepsy.³⁴ Facilities for epilepsy surgery, therapeutic drug monitoring, and clinical psychologist or medical social worker services are also needed, as are educational interventions to improve the awareness of epilepsy misconceptions, and to end social discrimination against patients with epilepsy.^{36,37}

Other limitations must be considered when evaluating the literature described in this review. One limitation of some of the literature included in this review is study design. Most of the evidence was derived from retrospective analyses of observational, uncontrolled studies. These study designs cannot lead to conclusions regarding causality, but rather provide correlative evidence. Sample sizes were generally large, however, the lack of statistical differences in certain factors found in some studies may have been due to an insufficient number of subjects in treatment groups. Additionally, selection and treatment bias towards individuals residing in a particular geographical region was inherent to some studies. Another limitation of this literature review was that results were limited to English. Some of the objectives (eg, treatment patterns, epidemiology) might have been explored in more detail in older literature and therefore would not have been captured in our search. Our search strategy also focused on peer-reviewed publications and did not capture information from abstracts, posters, or dissertations, which may have limited the amount of information assessed for this review. Lastly, all literature reviews are limited by publication bias with regard to the articles that are available.

Conclusion

This paper is an exhaustive examination of published literature describing many aspects of epilepsy in emerging

markets. Overall, the reported incidence of epilepsy is low in the general population and, overall, treating patients with epilepsy is inexpensive and decreases the use of health care resources.

However, the identified clinical studies generally lacked standardized diagnosis criteria and used ineffectual methods with which to grade symptoms. Standards of care and baseline medications varied greatly between populations and adjunctive medications were often arbitrarily examined. Studies with longer follow-up periods and larger patient populations are needed to document the long-term effectiveness of several AEDs. Many of the observations discussed in this review need to be further confirmed in larger prospective trials, and, looking for specific characteristics of patients responding to certain drugs may lead to useful guidelines for drug choice in treating epilepsy. Knowledge gained in these areas will enable improvement to the care of people with epilepsy both in emerging markets and elsewhere.

Disclosure

The authors declare no conflicts of interest in this work.

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