Epilepsy in Asia: Disease burden, management barriers and challenges

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Summary

This article reviews the burden of epilepsy in Asia, the challenges faced by people with epilepsy, and the management of epilepsy. Comparison is made with other parts of the world. For this narrative review, data were collected using specified search criteria. Articles investigating the epidemiology of epilepsy, diagnosis, comorbidities and associated mortality, stigmatization, and treatment were included. Epilepsy is a global healthcare issue affecting up to 70 million people worldwide. Nearly 80% of people with epilepsy live in low- and middle-income countries with limited resources. People with epilepsy are prone to physical and psychological comorbidities, including anxiety and depression, which can negatively impact their quality of life. Further, people with epilepsy are at higher risk of premature death than people without epilepsy. Discrimination or stigmatization of people with epilepsy is common in Asia and can affect their education, work, and marriage opportunities. Access to epilepsy treatment varies throughout Asia. While highly advanced treatment is available in some countries, up to 90% of people with epilepsy are not adequately treated or are not treated with conventional antiepileptic therapy in resource-limited countries. People in remote areas often do not receive any epilepsy care. First-generation antiepileptic drugs (AEDs) are available, but usually only in urban areas, while second-generation AEDs are not available in all countries. Newer AEDs tend to have more favorable safety profiles than first-generation AEDs and provide options to tailor therapy for individual patients, especially those with comorbidities. Active epilepsy surgery centers are present in some countries, although epilepsy surgery is often underutilized given the number of patients who could benefit. Further epidemiologic research is needed to provide accurate epilepsy data across the Asian region. Coordinated action is warranted to improve access to treatment and care.

Key Points

- Approximately 4 billion people (50% of the global population) live in Asia, of whom about 23 million people have epilepsy
- People with epilepsy are prone to comorbidities and stigma that can negatively impact their quality of life
- People with epilepsy are at higher risk of premature death than the general population
- The high treatment gap is the most common problem for epilepsy management in low-income regions
- Research priorities for Asia include standardized studies of epilepsy epidemiology, burden, causes, and risk factors

INTRODUCTION

Epilepsy affects 50–70 million people worldwide,[1-3] and accounts for 0.75% of the global burden of disease.[1] The annual incidence and prevalence of epilepsy worldwide are 50/100,000 and 700/100,000 population, respectively. An estimated 2.4 million people are diagnosed with epilepsy each year.[1] In 2012, approximately 20.6 million disability-adjusted life years were lost to epilepsy.[1]

Nearly 80% of people with epilepsy live in low- and middle-income countries with limited resources (South-East Asia, Latin America, sub-Saharan Africa), where the rate of new cases is up to two-fold higher than that of high-income countries.[1,4] As many as three-quarters of people with epilepsy in low-income countries do not have access to the treatment they need due to low availability and unaffordability of antiepileptic drugs (AEDs).[1,5] However, 60–70% of people with epilepsy could lead normal lives if properly treated with AEDs.[4] In many regions of the world, misconceptions, stigma, and discrimination are greater obstacles to the well being of people with epilepsy than lack of adequate healthcare.[4]

As the Asian economies grow and their populations age, the epidemiology and care of patients with epilepsy may change dramatically over the coming years. The aim of this article is to review epilepsy care in Asia. The focus is on the burden and the challenges faced by people with epilepsy in terms of comorbidity, mortality, and

stigmatization, as well as the barriers to treatment engendered by resource prioritization and cultural beliefs. Comparison is made with other parts of the world, particularly western societies.

METHODS

For this narrative review, data were collected from MEDLINE®/PubMed® and EMBASE® using specified search criteria (papers published in English from 1996 to 2016; International League Against Epilepsy classification papers published pre-1996 were allowed). The search terms were combinations of the following: 'epilepsy', 'prevalence', 'incidence', 'diagnosis', 'treatment' and treatment-specific terms such as 'surgery' and 'antiepileptic drugs', 'Asia', and individual country names. If a title or abstract described a high-quality article that was likely to be eligible for inclusion, the full article was obtained and assessed for relevance. Articles investigating the epidemiology of epilepsy, diagnosis, comorbidities and associated mortality, stigmatization, and treatment were included.

A limitation of this approach is that the selected studies are not always comparable, with diverse methodologies and endpoints. However, the intention is to provide an overview of the epilepsy situation in this diverse region.

BURDEN OF EPILEPSY

Global variation

Globally, the median lifetime prevalence of epilepsy is highest in sub-Saharan Africa (15.0/1000 population) and Latin America (17.8/1000 population), while in Asia it is similar to that of western countries at approximately 6/1000 population.[3,6] However, the rate varies throughout each region, with the lifetime prevalence rates of epilepsy being 1.5–14.0/1000 person-years in Asia, 5.1–57.0/1000 person-years in Latin America, and 5.2–74.4/1000 person-years in sub-Saharan Africa.[6-8] There is a tendency towards a higher prevalence of epilepsy in rural areas than in urban areas,[6,9] and there are differences in prevalence between high- and low-income countries.[9]

There are many reasons for the variations in the prevalence of epilepsy between high- and low-income parts of the world and between different tropical areas (Asia, Africa,

and Latin America).[2,3] These include, but are not limited to, the underlying etiology of epilepsy and the type of epilepsy studied, different definitions of epilepsy, differences in study populations, inconsistent study methods and screening tools, population-specific and environmental factors, genetic factors, diagnostic capacity, stigmatization and discrimination, cultural perceptions, and survival bias (due to the large treatment gap).[2,3,10]

Variation within Asia

Asia is the world's largest continent, with more than 40 countries that are heterogeneous in geography, population, culture, socioeconomic development, and health care systems.[11] There are vast economic differences throughout Asia, with up to 140-fold difference in gross national income per capita between the poorest and richest countries.[11] Approximately 4 billion people (50% of the global population) live in Asia, of whom about 23 million people live with epilepsy.[12] The prevalence varies among Asian countries from 1.5–14.0/1000 population (Table 1).[3,6,13-27]

The higher incidence of epilepsy in Asia than in western countries may be due to increased risk of endemic central nervous system infections: cerebral malaria, neurocysticercosis, meningitis, and encephalitis, including Japanese encephalitis, tuberculosis, and HIV infection.[3,6] Neurocysticercosis has been estimated to be the cause of epilepsy in up to 50% of patients in India[28] and 47% in Nepal.[6] Other reasons include traumatic brain injury (possibly due to the high incidence of road traffic accidents, perinatal injuries, or stroke (Table 2).[3,29-38] However, the cause of epilepsy often remains unknown (approximately 70% of all epilepsies in the US).[39]

The two peak ages for incidence of epilepsy in Asia tend to be childhood and early adulthood, which contrasts with the peaks in childhood and older ages in developed countries.[6] In Taiwan, Japan, and Thailand, the two peaks occur in childhood and old age, similar to developed countries.[14,40] The general population in Asia is relatively young compared with that in developed countries, which may influence the timing of the peak incidence ages for epilepsies.[6]

The reported distribution of seizure and epilepsy types in Asia according to the International League Against Epilepsy classification is: generalized seizures, 50–69%;

focal seizures, 31–50%; symptomatic epilepsy, 22–53%; idiopathic epilepsy, 4–42%; and cryptogenic epilepsy, 13–60%.[6,41]

Comorbidity

Patients with epilepsy are prone to psychological comorbidities that can negatively impact their quality of life (QOL).[42] Higher rates of anxiety, suicidal ideation, and depression have been reported among people with epilepsy compared with the general population,[43] with up to one-third of people with epilepsy having anxiety or depression.[42,44] QOL is generally worse in epilepsy patients with depression or anxiety than in those without these disorders,[44] and depression and anxiety may lead to suicidal ideation or self-stigmatization.[44,45]

A Canadian study found a high prevalence of suicidal ideation among epilepsy patients (25%) compared with patients without epilepsy (13.3%).[43] Anxiety disorders, suicidal thoughts, major depression, and panic disorder/agoraphobia were also higher among the group with epilepsy. In Korea, patients with epilepsy were more likely to have depression or anxiety than healthy controls, and patients with poor seizure control were more likely to have affective symptoms.[45]

In elderly Thai patients (a rapidly increasing population group), common comorbidities include mood and sleep disorders.[36] In rural India, sadness and depressive symptoms were the most common problems after seizures, and stigma was an important factor.[46] In a QOL study in Hong Kong, approximately one-third of patients with epilepsy had symptoms of anxiety, and one-third had symptoms of depression.[42] Notably, subjective anxiety, depression, and sleep disturbance had greater effects on QOL than short-term seizure control. This study implied that few patients with anxiety or depression were receiving psychiatric treatment.

Under-diagnosis, and therefore under-treatment, of psychiatric comorbidity is common, possibly because the focus is on seizure control during a clinical consultation.[42] Additionally, there is a lack of translated and validated rapid epilepsy-specific screening tests for anxiety and depression for use in busy epilepsy clinics in Asia.[44] However, guidelines for treatment of depression and anxiety in patients with epilepsy have been developed by the International League Against Epilepsy.[47]

Adoption of the guidelines within the Asian health care systems, particularly in higher income countries, will further highlight the burden of psychiatric comorbidity and the need for adequate treatment throughout the region.

People with epilepsy are also prone to have physical comorbidities, leading to increased healthcare use. In a study of patients hospitalized due to epilepsy in Hong Kong,[48] more than half of the patients had one or more physical or psychiatric comorbidities at baseline. Among patients who did not have baseline psychiatric comorbidities, 14% subsequently developed a psychiatric condition, and 15% of patients without baseline physical comorbidities developed comorbidity during follow-up (Table 2). A three-fold increased risk of stroke has been identified in Taiwanese patients with epilepsy,[49] with a hazard ratio similar to that of a UK General Practice Research Database study.[50] Stroke is also common among elderly Thai patients with epilepsy.[40]

Cognitive impairment such as memory loss, mental slowness, and attention deficits are commonly associated with epilepsy.[51] The causes of cognitive impairment in epilepsy are likely to be multifactorial, but include the underlying etiology of epilepsy, subclinical or electroencephalographic seizures, and central nervous system side effects of AEDs.[52] A Swedish study found that academic difficulties (reduced global cognition) were common in schoolchildren with active epilepsy.[53] Thus, early identification and management of cognitive impairment is important, particularly for early-onset seizures. Adult patients with drug-resistant epilepsy in Hong Kong had worse verbal recall memory than those with drug-responsive epilepsy, and there were correlations between psychological well being and cognitive performance.[54] Data from the Taiwan National Health Insurance Research Database showed a bidirectional association between epilepsy and attention deficit hyperactivity disorder[55] (Table 3[40,42,43,45,48,49,55]).

The evidence described in this, and the next, section is heterogeneous in nature. Thus, comparative studies with similar methodologies and large population-based registries would facilitate further understanding of the burden of epilepsy in the region.

Mortality

Patients with epilepsy are at higher risk of premature death than the general population, especially during the first 2 years after diagnosis.[56-59] Symptomatic epilepsies and persistent seizures are consistent risk factors for premature death in epilepsy.

A recent Hong Kong study found a standardized mortality ratio (SMR) of 5.09 among newly diagnosed patients with epilepsy.[48] The SMR was higher among patients with baseline physical and/or psychiatric comorbidity and highest for those with both physical and psychiatric comorbidities (Table 4[48,56,57,59-68]). Two studies from Taiwan found SMRs for patients with epilepsy of 2.5 and 3.47,[60,61] with the age-specific SMRs being highest for boys and young women .[60] In rural China, premature death in people with epilepsy was three times that of the general population,[62] with cause-specific SMRs being significantly elevated for drowning (39.0). Younger people (age 10–29 years) had a higher risk of premature death. Also in rural China, an SMR of 4.92 and a case fatality rate of 2.97% were observed for people with convulsive epilepsy.[63] The highest risks were for accidental death, which included drowning, and younger age.

In Laos, six (11%) of 53 patients with epilepsy died prematurely, two from drowning.[64] In Bangladesh, mortality due to injury in people with epilepsy occurred at a younger age than in the general population, and death due to drowning occurred more frequently among people with epilepsy than among the general population.[65] In Kolkata, the all-cause SMR for people with epilepsy compared with the general population was 2.58 and men were at greater risk than women.[66]

Several western studies have reported lower SMRs than in Asia. In the USA, the SMR of socioeconomically deprived patients with epilepsy was 1.8,[67] while two European studies found overall SMRs of 1.7–2.2 compared with the general population of the same geographic area.[56,57]

Seizure-related causes of death, especially non-vehicle accidents,[63] played a greater role in the higher mortality of Asian people with epilepsy than in western studies, indicating the importance of seizure control to prevent premature death. The UK National General Practice Study of Epilepsy found that most deaths were due to non-cerebral neoplasms, cardiovascular disease, or cerebrovascular disease, and only 3%

were due to epilepsy-related causes (SUDEP or status epilepticus).[59] In a European study, epilepsy etiology was the main determinant of premature death, with the risk being highest in patients with symptomatic epilepsy and lowest in those with idiopathic epilepsy or who achieved seizure freedom.[68]

There are few data on SUDEP in Asia.[69] Postmortem examinations are not often performed in low- and middle-income countries[62] and cultural customs may preclude postmortem examination.[69] Ding et al found a PMR of 1.0% for probable SUDEP in rural China, but noted that some SUDEP deaths may have been assigned to other causes,[62] whereas Mu et al reported that the PMR for SUDEP was 14% in their cohort.[63] These differences may reflect significant geographical variations in cause of death in patients with epilepsy. In Korea, disease severity, represented by uncontrolled seizures and polytherapy, was an important risk factor for SUDEP.[69] Despite scarce evidence in Asian mortality studies, frequency of recurrent generalized tonic-clonic (GTC) seizures is more important as a risk factor for SUDEP than other seizure types, and should be considered in the strategy for epilepsy management in Asia.[69] Improving training in controlling seizures, especially GTC seizures, in people with severe epilepsy, educating people with epilepsy on the risk of drowning, and treating people with epilepsy and depression or anxiety appropriately may modify the possibility of premature death.[62]

PSYCHOSOCIAL, DIAGNOSTIC AND TREATMENT CHALLENGES

Of the 23 million people with epilepsy in Asia, 15 million (65%) live without modern treatment.[13] The main challenge for people with epilepsy in Asia is access to appropriate epilepsy treatment and care.

Access to care

Epilepsy in Asia is frequently managed by primary care physicians, because of the lack of neurology specialists in many lower income countries.[70] Epilepsy specialists may only be available in sufficient numbers in Asia's wealthiest countries[6] and are often concentrated in urban areas.[70] The median number of neurologists per 100,000 population is 0.03 for low-income countries compared with 2.96 for high-income

countries, and the recommended number of neurologists in Europe or the Americas is 1–5/100,000 population.[70]

Imaging technologies are available, but their accessibility varies and may be limited to private facilities in large cities[6] so physicians often make a diagnosis based solely on clinical information.[13] The WHO reports in a survey that electroencephalography (EEG) is available in 77.8% of responding countries in South-East Asia, but long-term video EEG monitoring is available in only 21.7% of low-income countries compared with 77.1% of high-income countries.[4] Therefore, morbidity and mortality associated with epilepsy may be increased in Asia because of failure to correctly diagnose people with epilepsy in lower-income areas.

Interpretation of EEG studies can be challenging as there are fewer specialist neurologists in Asia than in western countries (0.07/100,000 population in South-East Asia vs. 4.84/100,000 in Europe).[4] This is due in part to the expense of setting up training facilities for postgraduate specialist degrees and the difficulty of retaining graduates who have completed specialist training abroad. However, efforts are being made to raise EEG skills by professional bodies in the region, for example the EEG Certification Examination conducted by the Asian Epilepsy Academy, the educational arm of the Commission on Asian and Oceanian Affairs, International League Against Epilepsy.

Stigmatization

The psychosocial impact of epilepsy may be as or more important than the physical effect, and discrimination or stigmatization of people with epilepsy is prevalent in Asia.[13,70] The stigma associated with epilepsy can affect education for children and adolescents, and work opportunities for adults. Stigma can also directly impact the family of a person with epilepsy.[68]

The chance of marriage may be reduced for people with epilepsy and, in some societies, women may be vulnerable to injury, social rejection, and abandonment. In both China and India, epilepsy is commonly viewed as a reason for prohibiting or annulling marriages.[1]

In a Malaysian study to ascertain the impact of epilepsy on employment among 250 patients with epilepsy from a neurology clinic, 20% were unemployed and 10.4% were employed part-time despite a robust economy and low social security.[71] Compared with their siblings, patients with epilepsy were more likely to be unemployed, single, have lower education level, and lower monthly income.

Even in more modern societies, stigma remains a problem.[6] In a Hong Kong study, 94.1% of respondents agreed that people with epilepsy could be married, but only 67.7% would allow their child to marry a person with epilepsy, while only 72.5% of respondents considered pregnancy to be appropriate.[72]

A systematic review found marked differences in attitudes towards epilepsy between Western and non-Western populations, with Asian and African populations having worse attitudes than those in Australia and the Americas.[73] People in rural areas with less education and lower socioeconomic status tend to have more negative attitudes towards epilepsy.[73] In Thailand, survey participants from an urban area had better knowledge, attitudes, and practices towards people with epilepsy than those from a non-urban area.[74] Related to the perception of stigma in adolescents with epilepsy, a Korean survey showed that low knowledge level and maternal concealment behavior were important predictors of higher stigma perception.[75]

Despite different attitudes between Asian and western countries, stigmatization still occurs in the west. In a European survey, 10% of participants had negative attitudes towards epilepsy, which mostly occurred in people with low socioeconomic background, low theoretical knowledge of epilepsy, misconceptions of epilepsy as a form of insanity, and no personal contact with a person with epilepsy.[76]

Epilepsy and driving

People with active epilepsy are often restricted from driving due to concern over seizure-related car accidents.[77] However, driving restriction is a concern for people with epilepsy as it hampers their ability to work and negatively impacts their QOL.

There is inconsistency between countries in the seizure-free period needed by people with epilepsy to be able to obtain a driving license, and many people with epilepsy

continue to drive.[77] Table 5 shows the driving restrictions for patients with epilepsy in Asian countries and the UK.[77-85] While driving restrictions for patients with uncontrolled epilepsy may be needed to ensure patient and public safety, these must be balanced with a patient's independence and QOL.[82]

Treatment gap

In low-income countries, the treatment gap (defined as the difference between the number of people with active epilepsy and the number whose seizures are being appropriately treated[46]) varies by region. The random effects mean of the treatment gap is 64.0% (95% CI, 24.3–100) in Asia, 55.4% (95% CI, 39.0–78.6) in Latin America, 49.0% (95% CI, 14.0–100) in Africa, and 56.0% (95% CI for true prevalence, 31.1–100) overall.[5] The mean of the treatment gap prevalence in urban and rural areas is 46.8/100 (95% CI, 34.1-64.8) and 73.3/100 (95% CI, 49.5-100), respectively. The treatment gap is the most common problem for epilepsy management in the low-income regions of Asia (Table 6[86-96]).

Reasons for the treatment gap include accessibility of adequate healthcare provision, availability of specialist care, obtainability of pharmacological treatment, lack of affordable treatment, distance to healthcare facilities, awareness of epilepsy and health-seeking behavior, stigmatization, cultural beliefs, and trust in traditional medicine.[11]

In a Global Campaign Against Epilepsy demonstration project, Wang et al conducted two epidemiological surveys before and after treatment intervention in an educational program in six provinces in China.[91] The treatment gap decreased from 62.6% to 49.8% (12.8 percentage points, 95% CI: 4.0–21.4), suggesting that the treatment of patients with active epilepsy can be improved.

Treatment challenges

In some countries and areas of Asia, treatment may be equal to that in modern cities anywhere in the world, but many people in remote areas do not receive any epilepsy care. Factors affecting healthcare provision in general, and epilepsy specifically, throughout Asia are manifold and include prioritization of resources and funding,

access to healthcare facilities, underlying etiology of epilepsy, expertise and diagnostic capacity of healthcare personnel, treatment options, sociocultural attitudes towards epilepsy, stigmatization, and treatment-seeking behavior.[2,11] Thus, large differences exist in the level of epilepsy management between countries.[97] To standardize the level of care, several countries/areas in Asia have published management guidelines, including China, Hong Kong, India, and Malaysia.[98-101]

Even when patients with epilepsy are diagnosed and prescribed AEDs, they may discontinue treatment,[102] as they are often unaware of the consequences of non-compliance.[64] In a study in rural Laos, only 10 of 46 people (22%) with active epilepsy were fully compliant with treatment.[64] However, community-based rehabilitation may help to improve compliance.[46]

Pharmacological treatment

Most drugs that have been licensed in Europe or North America also become available in Asia. Licensing of a new drug is done by each individual country rather than a continent-wide regulatory body, thus slowing the availability of newer treatments.[6,46] First-generation AEDs are more widely available in Asia, but prices vary and they may only be available in urban areas.[6] Although phenobarbital is an essential medicine for a basic health care system, some countries list it as a controlled drug, limiting its routine use for epilepsy.[103] Second-generation AEDs are not available in all countries and can be expensive in some areas.

Traditionally, new drugs have been studied in select groups of patients to satisfy regulatory requirements in Europe and the USA.[11] Given the genetic variation and ethnic heterogeneity in Asia, population-based pharmacogenetic studies are needed to determine responses to new AED therapy.[11] Studies conducted in Asian populations can identify factors such as the association between carbamazepine- or phenytoin-induced severe cutaneous adverse drug reactions (SCADRs) and HLA-B*15:02 or cytochrome P450 2C (CYP2C).[104-111]

In a Hong Kong study, mandatory pre-treatment screening for HLA-B*15:02 was found to be as efficient as accepted cancer screening programs,[110] and reduced the incidence of SCADRs induced by carbamazepine from 0.24% to 0% ($p = 0.027$) after

implementation at a system-wide level.[105] However, SCADRs induced by phenytoin increased from 0.15% to 0.26% (p = 0.058) and the overall incidence of SCADRs induced by AEDs remained unchanged (p = 0.238), suggesting a preference for AEDs that do not require genetic screening. A significant association has been found for HLA-B*15:02 and carbamazepine-induced Stevens–Johnson syndrome–toxic epidermal necrolysis (SJS–TEN) in Singapore Chinese and Malays, prompting the decision to make HLA-B*15:02 testing the standard of care prior to first use of carbamazepine in Singapore.[106] In a systematic review and meta-analysis, Tangamornsuksan et al found a strong relationship between HLA-B*15:02 and carbamazepine-induced SJS–TEN in Han Chinese, Thai, and Malaysian populations, warranting screening of these populations before starting treatment with carbamazepine.[107] A Thai modeling study found that screening for HLA-B*1502 before giving carbamazepine is cost-effective. Additionally, wider availability of the HLA-B*15:02 test will reduce the cost of screening,[108] although screening may be less beneficial in populations with low HLA-B*15:02 allele frequency.[109] The Hong Kong study also demonstrated that changes in prescription practice might render the screening policy uneconomical in the real-world setting.[110] These results indicate the importance of a comprehensive strategy for adapting the scientific knowledge into practice for useful outcomes at a national level.[105]

Newer AEDs tend to have more favorable safety profiles compared with first-generation AEDs so may help physicians to better tailor therapy to a patient's needs and comorbidities.[112] For example, some newer AEDs such as lamotrigine or levetiracetam may be preferred for women of childbearing age[112] as pregnancy data for other newer AEDs are scarce. In HIV-endemic areas, use of enzyme-inducing drugs (first-generation AEDs) may lessen the effects of anti-retroviral drugs, in which case non-enzyme-inducing AEDs should be used.[113] Convenience of once-daily oral dosing of newer AEDs helps with compliance. A recent population-based study from Germany indicates that compliance is significantly improved with once daily administration compared with twice daily dosing.[114]

There is evidence to suggest that access to newer AEDs and epilepsy specialists can result in improved seizure control.[115] Data from the US showed that use of second-generation AEDs decreased epilepsy-related hospital admissions compared with first-

generation AEDs (relative risk reduction [RRR] 31%; $p < 0.01$) and had a greater impact on epilepsy-related hospital encounters of the sickest patients with more comorbidities.[115] Interestingly, neurologists prescribed second-generation AEDs more often than primary care physicians.[115] Studies from Asia show that the older drugs such as carbamazepine and valproic acid are still more commonly prescribed than second-generation AEDs, although the use of newer AEDs is increasing in some areas.[116,117]

Epilepsy surgery

Epilepsy surgery is an important therapeutic measure for patients with refractory epilepsy. A recent US study has shown that successful surgery (defined as either seizure free or <2 GTCS per year) was associated with significantly lower mortality compared with non-surgically treated patients,[118] which has important implications for epilepsy surgery in Asia.

The use of epilepsy surgery varies throughout Asia, being well developed in some countries and less so in others.[46] Higher income countries such as Hong Kong, Japan, Korea, and Taiwan each have several active epilepsy surgery centers, with favorable results (Table 7[119-131]). However, the services are likely underutilized given the number of patients who could benefit from epilepsy surgery, while changing trends in epilepsy management and newer therapeutic procedures require ongoing training programs.[119-122]

Malaysia is considered to be a middle-income country. There is one epilepsy surgery service that treats both adults and children. The results compare favorably with more developed countries. The service is underutilized, which could be due to insufficient numbers of epileptologists, neurologists, and neuroradiologists. Sociocultural reasons and economic factors do not appear to have a role in the low uptake.[123] In China, epilepsy surgery is mainly available in the larger cities.[124] The specialty of epilepsy surgery is developing rapidly and specialized training courses are held regularly.

There are fewer epilepsy surgery centers in the lower income countries, resulting in a 'surgical gap',[125] although the situation is improving, with countries such as India, Nepal, Thailand, and Indonesia now having epilepsy surgery services.[125-128] The

groundwork has been prepared for future development of epilepsy surgery, and it is intended that it will become an acceptable and cost-effective treatment for intractable seizures.[126] In the Philippines, most of the surgeries are done for lesional epilepsy.[129] Surgery for drug-resistant epilepsy is underutilized as patients are often reluctant to undergo cranial surgery for a condition that is not considered immediately life threatening. It is hoped that with continuing education, surgery will become an accepted treatment option.[129]

Ketogenic diet

The high fat, low carbohydrate ketogenic diet has recently increased in use as an epilepsy treatment worldwide.[132] In Asia, countries offering the ketogenic diet include Japan, India, Hong Kong, Korea, Philippines, Taiwan, and Thailand. Challenges to take up of the ketogenic diet in Asia is that the traditional Asian diet is low in fat and high in carbohydrate, and there is a lack of dieticians to support patients using the diet. The efficacy of the ketogenic diet in Asian populations is thought to be similar to that in western countries, with some patients attaining seizure freedom. Positive outcomes are likely to convince more Asian patients to try this diet.

THE FUTURE

Asia is a large heterogeneous group of countries with disparate socioeconomic and cultural norms. Standardized epidemiologic and surveillance studies are needed to provide more widespread accurate data. The Research Task Force of the Commission on Asian and Oceanian Affairs of the International League Against Epilepsy has developed research priorities for the region, including studies to: increase knowledge of the burden of epilepsy in the region, with the aim of improving access to care and reducing the treatment gap; improve understanding of the causes and risk factors of epilepsy, including pathologic, genetic, and lifestyle factors; alleviate the consequences of epilepsy by reducing stigma and discrimination and improving QOL; develop improved therapies and treatment delivery to improve therapeutic outcomes; and improve the research infrastructure and capacity.[133]

In 2015, the WHO passed the Epilepsy Resolution (EB136.R8) to promote coordinated action against the treatment gap, which may provide an important

opportunity to prioritize epilepsy in Asia.[97] Evidence-based epilepsy care guidelines have been developed for use in low- and middle-income countries.[2] Guideline implementation in primary healthcare could help to reduce the treatment gap and improve management of epilepsy in low- and middle-income countries.

ETHICAL PUBLICATION

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DISCLOSURE

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All authors made substantial contributions to the concept of this review, the literature search or interpretation of data, and drafting or revising the manuscript; and all authors approved the final version for publication.

REFERENCES

1. World Health Organization. Epilepsy. Fact sheet. No. 999. 2012. Updated February 2016. Available at: http://www.who.int/mediacentre/factsheets/fs999/en/. Accessed March 12, 2016.
2. Katchanov J, Birbeck GL. Epilepsy care guidelines for low- and middle-income countries: From WHO mental health GAP to national programs. BMC Medicine 2012; 10: 107.
3. Yemadje LP, Houinato D, Quet F, et al. Understanding the differences in prevalence of epilepsy in tropical regions. Epilepsia 2011; 52: 1376-1381.
4. World Health Organization. Atlas: epilepsy care in the world. 2005. Available at: www.who.int/mental_health/publications/atlas_epilepsy_care_2005/en/. Accessed April 28, 2016.
5. Mbuba CK, Ngugi AK, Newton CR, et al. The epilepsy treatment gap in developing countries: a systematic review of the magnitude, causes, and intervention strategies. Epilepsia 2008; 49: 1491-1503.
6. Mac TL, Tran DS, Quet F, et al. Epidemiology, aetiology, and clinical management of epilepsy in Asia: a systematic review. Lancet Neurol 2007; 6: 533-543.
7. Burneo JG, Tellez-Zenteno J, Wiebe S. Understanding the burden of epilepsy in Latin America: a systematic review of its prevalence and incidence. Epilepsy Res 2005; 66: 63-74.
8. Preux PM, Druet-Cabanac M. Epidemiology and etiology of epilepsy in sub-Saharan Africa. Lancet Neurol 2005; 4: 21-31.
9. Ngugi AK, Bottomley C, Kleinschmidt I, et al. Estimation of the burden of active and life-time epilepsy: A meta-analytic approach. Epilepsia 2010; 51: 883-890.

10. Thurman DJ, Beghi E, Begley CE, et al for the ILAE Commission on Epidemiology. Standards for epidemiologic studies and surveillance of epilepsy. Epilepsia 2011; 52 (Suppl 7): 2-26.
11. Kwan P. Antiepileptic drug research in Asia: Where do we go from here? Neurol J Southeast Asia 2003; 8: 81-85.
12. World Health Organization. Epilepsy in the WHO South-East Asian Region. 2005. Available at: www.who.int/mental_health/neurology/epilepsy/searo_report.pdf. Accessed April 28, 2016.
13. Bhalla D, Tchalla AE, Marin B, et al. Epilepsy: Asia versus Africa. Epilepsia 2014; 55: 1317-1321.
14. Chen CC, Chen LS, Yen MF, et al. Geographic variation in the age- and gender-specific prevalence and incidence of epilepsy: analysis of Taiwanese National Health Insurance-based data. Epilepsia 2012; 53: 283-290.
15. Fong GC, Kwan P, Hui AC, et al. An epidemiological study of epilepsy in Hong Kong SAR, China. Seizure 2008; 17: 457-464.
16. Wang W, Wu J, Dai X, et al. Global campaign against epilepsy: assessment of a demonstration project in rural China. Bulletin World Health Organ 2008; 86: 964-969.
17. Jung J, Seo HY, Kim YA, et al. The economic burden of epilepsy in Korea, 2010. J Prev Med Public Health 2013; 46: 293-299.
18. Preux PM, Chea K, Chamroeun H, et al. First-ever, door-to-door cross-sectional representative study in Prey Veng province (Cambodia). Epilepsia 2011; 52: 1382-1387.
19. Tuan NA, Cuong le Q, Allebeck P, et al. The prevalence of epilepsy in a rural district of Vietnam: a population-based study from the EPIBAVI project. Epilepsia 2008; 49: 1634-1637.
20. Cuong LQ, Doanh NV, Jallon P. Prevalence of epilepsy in Thai Bao-Bac Ninh, a region in Vietnam affected by neurocysticercosis. Epilepsia 2005; 46 (Suppl 6): 132.
21. Tran DS, Odermatt P, Le TO, et al. Prevalence of epilepsy in a rural district of central Lao PDR. Neuroepidemiology 2006; 26: 199-206.

22. Asawavichienjinda T, Sitthi-Amorn C, Tanyanont W. Prevalence of epilepsy in rural Thailand: a population-based study. J Med Assoc Thai 2002; 85: 1066-1073.
23. Fong GC, Mak W, Cheng TS, et al. A prevalence study of epilepsy in Hong Kong. Hong Kong Med J 2003; 9: 252-257.
24. Wang WZ, Wu JZ, Wang DS, et al. The prevalence and treatment gap in epilepsy in China: an ILAE/IBE/WHO study. Neurology 2003; 60: 1544-1545.
25. Gourie-Devi M, Gururaj G, Satishchandra P, et al. Prevalence of neurological disorders in Bangalore, India: A community-based study with a comparison between urban and rural areas. Neuroepidemiology 2004; 23: 261-268.
26. Amudhan S, Gururaj G, Satishchandra P. Epilepsy in India I: Epidemiology and public health. Ann Indian Acad Neurol 2015; 18: 263-277.
27. Rajbhandari KC. Epilepsy in Nepal. Can J Neurol Sci 2004; 31: 257-260.
28. Rajshekhar V, Joshi DD, Doanh NQ, et al. Taenia solium taeniosis/cysticercosis in Asia: epidemiology, impact and issues. Acta Tropica 2003; 87: 53-60.
29. Hui AC, Kwan P. Epidemiology and management of epilepsy in Hong Kong: an overview. Seizure 2004; 13: 244-246.
30. Hui AC, Kwan P. Epilepsy in Hong Kong: a literature review. Hong Kong Med J 2004; 10: 185-189.
31. Rajbhandari KC. Epilepsy in Nepal. Neurol J Southeast Asia 2003; 8: 1–4.
32. Kim DW, Lee SY, Chung SE, et al; Korean Epilepsy Society. Clinical characteristics of patients with treated epilepsy in Korea: a nationwide epidemiologic study. Epilepsia 2014; 55: 67-75.
33. Li S, Wang X, Wang J, et al. Cerebrovascular disease and posttraumatic epilepsy. Neurol Asia 2004; 9 (Suppl): 12–13.
34. Chen CC, Chen TF, Hwang YC, et al. Population-based survey on prevalence of adult patients with epilepsy in Taiwan (Keelung community-based integrated screening no. 12). Epilepsy Res 2006; 72: 67-74.
35. Chen TC, Chen YY, Cheng PY, et al. The incidence rate of post-stroke epilepsy: a 5-year follow-up study in Taiwan. Epilepsy Res 2012; 102: 188-194.
36. Wright J, Pickard N, Whitfield A, et al. A population-based study of the prevalence, clinical characteristics and effect of ethnicity in epilepsy. Seizure 2000; 9: 309-313.

37. Kariuki SM, Matuja W, Akpalu A, et al. Clinical features, proximate causes, and consequences of active convulsive epilepsy in Africa. Epilepsia 2014; 55: 76-85.
38. Kestel D, Acevedo C, Medina MC, et al. Epilepsy in Latin America Technical document based on presentations at the international workshop held in Santiago, Chile, in August 2013, plus subsequent contributions. Washington: Pan American Health Organization; 2016.
39. Annegers JF, Rocca WA, Hauser WA. Causes of epilepsy: contributions of the Rochester epidemiology project. Mayo Clin Proc 1996; 71: 570-575.
40. Phabphal K, Geater A, Limapichat K, et al. Risk factors of recurrent seizure, co-morbidities, and mortality in new onset seizure in elderly. Seizure 2013; 22: 577-580.
41. Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia 1989; 30: 389-399.
42. Kwan P, Yu E, Leung H, et al. Association of subjective anxiety, depression, and sleep disturbance with quality-of-life ratings in adults with epilepsy. Epilepsia 2009; 50: 1059-1066.
43. Tellez-Zenteno JF, Patten SB, Jette N, et al. Psychiatric comorbidity in epilepsy: a population-based analysis. Epilepsia 2007; 48: 2336-2344.
44. Kwon OY, Park SP. Depression and anxiety in people with epilepsy. J Clin Neurol 2014; 10: 175-188.
45. Kwon OY, Park SP. Frequency of affective symptoms and their psychosocial impact in Korean people with epilepsy: a survey at two tertiary care hospitals. Epilepsy Behav 2013; 26: 51-56.
46. Meinardi H, Scott RA, Reis R, et al; ILAE Commission on the Developing World. The treatment gap in epilepsy: the current situation and ways forward. Epilepsia 2001; 42: 136-149.
47. Kerr MP, Mensah S, Besag F, et al; International League of Epilepsy (ILAE) Commission on the Neuropsychiatric Aspects of Epilepsy. International consensus clinical practice statements for the treatment of neuropsychiatric conditions associated with epilepsy. Epilepsia 2011; 52: 2133-2138.
48. Chen Z, Liew D, Kwan P. Excess mortality and hospitalized morbidity in newly treated epilepsy patients. Neurology 2016; 87: 718-725.

49. Chang CS, Liao CH, Lin CC, et al. Patients with epilepsy are at an increased risk of subsequent stroke: a population-based cohort study. Seizure 2014; 23: 377-381.
50. Cleary P, Shorvon S, Tallis R. Late-onset seizures as a predictor of subsequent stroke. Lancet 2004; 363: 1184-1186.
51. Kim EH, Ko TS. Cognitive impairment in childhood onset epilepsy: up-to-date information about its causes. Korean J Pediatr 2016; 59: 155-164.
52. Kwan P, Brodie MJ. Neuropsychological effects of epilepsy and antiepileptic drugs. Lancet 2001; 357: 216-222.
53. Reilly C, Atkinson P, Das KB, et al. Academic achievement in school-aged children with active epilepsy: a population-based study. Epilepsia 2014; 55: 1910-1917.
54. Tang V, Kwan P, Poon WS. Neurocognitive and psychological profiles of adult patients with epilepsy in Hong Kong. Epilepsy Behav 2013; 29: 337-343.
55. Chou IC, Chang YT, Chin ZN, et al. Correlation between epilepsy and attention deficit hyperactivity disorder: a population-based cohort study. PLoS One 2013; 8: e57926.
56. Trinka E, Bauer G, Oberaigner W, et al. Cause-specific mortality among patients with epilepsy: results from a 30-year cohort study. Epilepsia 2013; 54: 495-501.
57. Granbichler CA, Oberaigner W, Kuchukhidze G, et al. Cause-specific mortality in adult epilepsy patients from Tyrol, Austria: hospital-based study. J Neurol 2015; 262: 126-133.
58. Nilsson L, Tomson T, Farahmand BY, et al. Cause-specific mortality in epilepsy: a cohort study of more than 9,000 patients once hospitalized for epilepsy. Epilepsia 1997; 38: 1062-1068.
59. Keezer MR, Bell GS, Neligan A, et al. Cause of death and predictors of mortality in a community-based cohort of people with epilepsy. Neurology 2016; 86: 704-712.
60. Chang YH, Ho WC, Tsai JJ, et al. Risk of mortality among patients with epilepsy in southern Taiwan. Seizure. 2012; 21: 254-259.
61. Chen RC, Chang YC, Chen TH, et al. Mortality in adult patients with epilepsy in Taiwan. Epileptic Disord 2005; 7: 213-219.
62. Ding D, Wang W, Wu J, et al. Premature mortality risk in people with convulsive epilepsy: long follow-up of a cohort in rural China. Epilepsia 2013; 54: 512-517.

63. Mu J, Liu L, Zhang Q, et al. Causes of death among people with convulsive epilepsy in rural West China: a prospective study. Neurology 2011; 77: 132-137.
64. Tran DS, Zen J, Strobel M, et al. The challenge of epilepsy control in deprived settings: Low compliance and high fatality rates during a community-based phenobarbital program in rural Laos. Epilepsia 2008; 49: 539-540.
65. Mateen FJ, Shinohara RT, Alam N, et al. Injury deaths among people with epilepsy in rural Bangladesh: a retrospective population-based study. Epilepsy Behav 2012; 23: 291-293.
66. Banerjee TK, Ray BK, Das SK, et al. A longitudinal study of epilepsy in Kolkata, India. Epilepsia 2010; 51: 2384-2391.
67. Kaiboriboon K, Schiltz NK, Bakaki PM, et al. Premature mortality in poor health and low income adults with epilepsy. Epilepsia 2014; 55: 1781-1788.
68. Nevalainen O, Ansakorpi H, Simola M, et al. Epilepsy-related clinical characteristics and mortality: a systematic review and meta-analysis. Neurology 2014; 83: 1968-1977.
69. Ryu HU, Hong JP, Han SH, et al. Seizure frequencies and number of anti-epileptic drugs as risk factors for sudden unexpected death in epilepsy. J Korean Med Sci 2015; 30: 788-792.
70. World Health Organization. Atlas: country resources for neurological disorders. 2004. Available at: www.who.int/mental_health/neurology/epidemiology/en/. Accessed April 28, 2016.
71. Lim KS, Wo SW, Wong MH, et al. Impact of epilepsy on employment in Malaysia. Epilepsy Behav 2013; 27: 130-134.
72. Fong CY, Hung A. Public awareness, attitude, and understanding of epilepsy in Hong Kong Special Administrative Region, China. Epilepsia 2002; 43: 311-316.
73. Lim KS, Lim CH, Tan CT. Attitudes toward epilepsy, a systematic review. Neurology Asia 2011; 16: 269-280.
74. Tiamkao S, Sawanyawisuth K, Singhpoo K, et al; Integrated Epilepsy Research Group. Differences of knowledge, attitudes, and behaviors towards epilepsy between populations in municipal and nonmunicipal areas. Psychol Res Behav Manag 2013; 6: 111-116.
75. Ryu HU, Lee SA, Eom S, et al; Korean QoL in Epilepsy Study Group. Perceived stigma in Korean adolescents with epilepsy: Effects of knowledge about epilepsy and maternal perception of stigma. Seizure 2015; 24: 38-43.

76. Spatt J, Bauer G, Baumgartner C, et al; Austrian Section of the International League Against Epilepsy. Predictors for negative attitudes toward subjects with epilepsy: a representative survey in the general public in Austria. Epilepsia 2005; 46: 736-742.
77. No YJ, Lee SJ, Park HK, et al. Factors contributing to driving by people with uncontrolled seizures. Seizure 2011; 20: 491-493.
78. Epilepsy Action. Driving. Available from: https://www.epilepsy.org.uk/info/driving Accessed April 27, 2016.
79. Inoue Y, Ito M, Kurihara M, et al; Commission on Legal Affairs, Japan Epilepsy Society (Japan chapter of ILAE). Epilepsy and driving in Japan. Epilepsia 2004; 45: 1630-1635.
80. Ooi WW, Gutrecht JA. International regulations for automobile driving and epilepsy. J Travel Med 2000; 7: 1-4.
81. Singapore Epilepsy Foundation. Epilepsy factsheets. Available at: http://www.epilepsy.com.sg/factsheets.html. Accessed April 27, 2016.
82. Chen J, Yan B, Lu H, et al. Driving among patients with epilepsy in West China. Epilepsy Behav 2014; 33: 1-6.
83. Transport Department. The Government of the Hong Kong Special Administrative Region. Last review date: 31 Aug 2015. Available at: http://www.td.gov.hk/en/public_services/licences_and_permits/vehicle_and_driving_licences/how_to_apply_for_a_driving_licence/appendix_a/index.html. Accessed April 27, 2016.
84. Saengsuwan J, Laohasiriwong W, Boonyaleepan S, et al; Integrated Epilepsy Research Group. Seizure-related vehicular crashes and falls with injuries for people with epilepsy (PWE) in northeastern Thailand. Epilepsy Behav 2014; 32: 49-54.
85. Indian Epilepsy Centre. Frequently asked questions on epilepsy. Driving. Available at: http://www.indianepilepsycentre.com/faqs-driving.html. Accessed April 27, 2016.
86. Huang DH, Zheng JO, Chen J, et al. Treatment gaps of epilepsy and retention rates of sodium valproate in rural Guangxi, China. Genet Mol Res 2014; 13: 6202-6212.

87. Bhalla D, Chea K, Hun C, et al. Population-based study of epilepsy in Cambodia associated factors, measures of impact, stigma, quality of life, knowledge-attitude-practice, and treatment gap. PLoS One 2012; 7: e46296.
88. Barennes H, Sengkhamyong K, Sambany EM, et al. Children's access to treatment for epilepsy: experience from the Lao People's Democratic Republic. Arch Dis Child 2011; 96: 309-313.
89. Tuan NA, Tomson T, Allebeck P, et al. The treatment gap of epilepsy in a rural district of Vietnam: a study from the EPIBAVI project. Epilepsia 2009; 50: 2320-2323.
90. Nizamie SH, Akthar S, Banerjee I, et al. Health care delivery model in epilepsy to reduce treatment gap: World Health Organization study from a rural tribal population of India. Epilepsy Res 2009; 84: 146-152.
91. Wang W, Wu J, Dai X, et al. Global campaign against epilepsy: assessment of a demonstration project in rural China. Bull World Health Organ 2008; 86: 964-969.
92. Zhao Y, Zhang Q, Tsering T, et al. Prevalence of convulsive epilepsy and health-related quality of life of the population with convulsive epilepsy in rural areas of Tibet Autonomous Region in China: an initial survey. Epilepsy Behav 2008; 12: 373-381.
93. Rajbhandari KC. Epilepsy in Nepal. Can J Neurol Sci 2004; 31: 257-260.
94. Ray BK, Bhattacharya S, Kundu TN, et al. Epidemiology of epilepsy--Indian perspective. J Indian Med Assoc 2002; 100: 322-326.
95. San Luis AM. Seizure treatment gap estimate in the Philippines (year 2004). UERMMMC J Health Sciences 2007;10. Available from: http://ejournals.ph/article.php?id=6999 Accessed 9 June 2016.
96. Kun LN, Ling LW, Wah YW, et al. Epidemiologic study of epilepsy in young Singaporean men. Epilepsia 1999; 40: 1384-1387.
97. World Health Organization. EB136.R8. Global burden of epilepsy and the need for coordinated action at the country level to address its health, social and public knowledge implications. Available at: apps.who.int/gb/ebwha/pdf_files/EB136/B136_R8-en.pdf. Accessed April 29, 2016.

98. Epilepsy syndrome and clinical guidelines [translation]. 2nd Ed (Chinese Edition). Available from: http://www.abebooks.co.uk/Epilepsy-syndrome-clinical-guidelines-translations-2nd/10566338793/bd. Accessed August 17, 2016.
99. Guideline Development Group, Hong Kong Epilepsy Society. The Hong Kong epilepsy guideline 2009. Hong Kong Med J 2009; 15 Suppl 5: 6-28.
100. Roy MK, Das D. Indian Guidelines on Epilepsy. 2013. Available from: www.apiindia.org/medicine_update_2013/chap116.pdf. Accessed August 17, 2016.
101. Epilepsy Council, Malaysian Society of Neurosciences. Consensus Guidelines on the Management of Epilepsy. 2010. Available from: http://www.neuro.org.my/?page_id=958. Accessed August 17, 2016.
102. Radhakrishnan K. Challenges in the management of epilepsy in resource-poor countries. Nat Rev Neurol 2009; 5: 323-330.
103. Newton CR, Garcia HH. Epilepsy in poor regions of the world. Lancet 2012; 380(9848): 1193-1201.
104. Kwan PK, Ng MH, Lo SV. Association between HLA-B*15:02 allele and antiepileptic drug-induced severe cutaneous reactions in Hong Kong Chinese: a population-based study. Hong Kong Med J 2014; 20 (Suppl 7): 16-8.
105. Chen Z, Liew D, Kwan P. Effects of a HLA-B*15:02 screening policy on antiepileptic drug use and severe skin reactions. Neurology 2014; 83: 2077-2084.
106. Toh DS, Tan LL, Aw DC, et al. Building pharmacogenetics into a pharmacovigilance program in Singapore: using serious skin rash as a pilot study. Pharmacogenomics J 2014; 14: 316-321.
107. Tangamornsuksan W, Chaiyakunapruk N, Somkrua R, et al. Relationship between the HLA-B*1502 allele and carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. JAMA Dermatol 2013; 149: 1025-1032.
108. Tiamkao S, Jitpimolmard J, Sawanyawisuth K, et al. Cost minimization of HLA-B*1502 screening before prescribing carbamazepine in Thailand. Int J Clin Pharm 2013; 35: 608-612.
109. Locharernkul C, Shotelersuk V, Hirankarn N. Pharmacogenetic screening of carbamazepine-induced severe cutaneous allergic reactions. J Clin Neurosci 2011; 18: 1289-1294.

110. Chen Z, Liew D, Kwan P. Real-world efficiency of pharmacogenetic screening for carbamazepine-induced severe cutaneous adverse reactions. PLoS One 2014; 9: e96990.
111. Chen Z, Liew D, Kwan P. Real-world cost-effectiveness of pharmacogenetic screening for epilepsy treatment. Neurology 2016; 86: 1086-1094.
112. Reimers A. New antiepileptic drugs and women. Seizure 2014; 23: 585-591.
113. Birbeck GL, French JA, Perucca E, et al; Quality Standards Subcommittee Of The American Academy Of Neurology; Ad Hoc Task Force Of The Commission On Therapeutic Strategies Of The International League Against Epilepsy. Antiepileptic drug selection for people with HIV/AIDS: evidence-based guidelines from the ILAE and AAN. Epilepsia 2012; 53: 207-214.
114. Gollwitzer S, Kostev K, Hagge M, et al. Nonadherence to antiepileptic drugs in Germany: A retrospective, population-based study. Neurology 2016; 87: 466-472.
115. Faught E, Helmers SL, Begley CE, et al. Newer antiepileptic drug use and other factors decreasing hospital encounters. Epilepsy Behav 2015; 45: 169-175.
116. Tan WW, Kong ST, Chan DW, et al. A retrospective study on the usage of antiepileptic drugs in Asian children from 2000 to 2009 in the largest pediatric hospital in Singapore. Pharmacoepidemiol Drug Saf 2012; 21: 1074-1080.
117. Kwong KL, Tsui KW, Wu SP, et al. Utilization of antiepileptic drugs in Hong Kong children. Pediatr Neurol 2012; 46: 281-286.
118. Sperling MR, Barshow S, Nei M, et al. A reappraisal of mortality after epilepsy surgery. Neurology 2016; 86: 1938-1944.
119. Kwan P, Chan DT, Lui C, et al. Epilepsy surgery program in Hong Kong. Neurology Asia 2007; 12: 5-8.
120. Otsuki T. Status of epilepsy surgery in Japan: Results of 2004 national survey. Neurology Asia 2007; 12: 9-12.
121. Phi JH, Chung CK. Development and future of epilepsy surgery in Korea. Neurology Asia 2007; 12: 13-16.
122. Wong TT, Shih YH, Chang CN, et al. Epilepsy surgery programs in Taiwan. Neurology Asia 2007; 12: 17-22.
123. Selladurai BM. Epilepsy surgery service in Malaysia. Neurology Asia 2007; 12: 39-42.

124. Luan G, Li Y. Epilepsy surgery in China: The history and current development. Neurology Asia 2007; 12: 1-3.
125. Sanyal SK. Relieving the burden of intractable epilepsy in India and other developing countries: the case for two tier epilepsy centers. Neurology Asia 2007; 12: 23-26.
126. Pant B, Shrestha P, Dhakal S, et al. Current status of epilepsy surgery in Nepal. Neurology Asia 2007; 12: 29-34.
127. Visudtibhan A, Khongkhatithum C, Boongird A, The Ramathibodi Epilepsy Surgery Group. Development of epilepsy surgery in children in Thailand: Experiences in Ramathibodi Hospital. Neurology Asia 2007; 12: 47-50.
128. Gunadharma S. The need for epilepsy surgery services in Indonesia. Neurology Asia 2007; 12: 35-38.
129. Chua A. Epilepsy surgery in the Philippines. Neurology Asia 2007; 12: 43-46.
130. Xu L, Xu M. Epilepsy surgery in China: past, present, and future. Eur J Neurol 2010; 17: 189-93.
131. Muttaqin Z. Epilepsy surgery in Indonesia: achieving a better result with limited resources. Bali Med J 2012; 1: 57-63.
132. Seo JH, Kim HD. Cultural challenges in using the ketogenic diet in Asian countries. Epilepsia 2008; 49 Suppl 8: 50-52.
133. Kwan P, Cabral-Lim L, D'Souza W, et al; CAOA Research Task Force. Research priorities in epilepsy for the Asia-Oceanian region. Epilepsia 2015; 56: 667-673.

Table 1. Prevalence and incidence of epilepsy in Asia[3,6,13-27]

Country	Prevalence	Incidence
Vietnam	4.4–14.0/1000	
India	3.0–11.9/1000	38.0–60.0/100,000
Rural areas	5.5–11.9/1000	
Urban areas	5.1–5.8/1000	
Pakistan	10.0/1000	
Laos	7.7/1000	
Nepal	7.3/1000	
Thailand	7.2/1000	
Cambodia	5.8/1000	
China	4.6–7.0/1000	28.8–35.0/100,000
Singapore	3.5–5.0/1000	
Japan	2.7-40/1000	24-53/100,000,
Taiwan	2.4–5.85/1000	97/100,000
Korea	2.28/1000	
Hong Kong	1.5–3.94/1000	

Table 2. Causes of epilepsy in Asia and comparison with western data[3,29-38]

Epilepsy cause	Nepal	China	Korea	Hong Kong	Taiwan	UK	US	Africa	South America
Traumatic brain injury	2%	8–20%	10%	11.4%	13.5%	11.4%	4%	11.8%	3.0–13.3%
Perinatal injury	–	–	–	9.7%	5.4%	–	–	10.8%	6.6–11.1%
Stroke	4%	8.7%	9.6%	26.2%	2.6–5.4%	10%	11%	0.8%	2–13.3%
Central nervous system infection	47%	–	5.7%	26.0%	8.1%	2.3%	3%	9.6%[a]	13.9–37.0%[b]

[a] Acute encephalopathy

[b] Neurocysticercosis

Table 3. Comorbidities associated with epilepsy[40,42,43,45,48,49,55]

Country	Study design	Population	Comorbidity	Prevalence (95% CI)
Korea	Hospital questionnaire-based survey	568 with epilepsy	Depression	Epilepsy: 27.8% Non-epilepsy: 8.8%
			Anxiety	Epilepsy: 15.3% Non-epilepsy: 3.2%
			Affective symptoms	Epilepsy: 30.5%
Thailand	Hospital-based case control study	278 with first seizure >65 years	Mood disorder (anxiety) Depression Sleep disorder	32.5% 23.1% 16.9%
			Stroke	9.7%
Hong Kong	Hospital-based QOL study	247 with epilepsy	Anxiety Depression	75 (30.3%) 94 (38.1%)
Hong Kong	Population-based study	7461 with epilepsy	≥1 physical or psychiatric comorbidity at baseline Newly developed[a] psychiatric comorbidity Newly developed[a] physical comorbidity: Stroke	58% 14% 15% SIR 4.96 (4.19–5.84)

			Cancer (among men) Ischemic heart disease	SIR 2.30 (1.75–2.97) SIR 4.18 (3.54–4.91)
Taiwan	Population-based study	812 newly diagnosed with epilepsy 15,248 without epilepsy	Stroke	Epilepsy: 24.08/1000 person-years Non-epilepsy: 7.96/1000 person-years HR 2.92 (2.58–3.30)
Taiwan	National Health Insurance Research Database	2468 with epilepsy 9810 without epilepsy 3664 with ADHD 14,522 without ADHD	ADHD in patients with epilepsy Epilepsy in patients with ADHD	HR 2.54 (2.02-3.18) HR 3.94 (2.58-6.03)
Canada	Canadian Community Health Survey	36,984 253 with epilepsy	Suicidal ideation Anxiety disorders Suicidal thoughts Major depression	Epilepsy: 25% (17.4–32.5) Non-epilepsy: 13.3% (12.8–13.8) OR 2.4 (1.5–3.8) OR 2.2 (1.4–3.3) OR 1.8 (1.0–3.1)

			Panic disorder/agoraphobia	OR 1.9 (1.0–3.7)

[a] Developed during follow-up since epilepsy diagnosis.

ADHD, attention deficit hyperactivity disorder; HR, hazard ratio; SIR, standardized incidence ratio.

Table 4. Mortality associated with epilepsy[48,56,57,59-68]

Country	Study design	Population	Patients	SMR (95% CI)
Hong Kong	Hospital data	7461 with newly treated epilepsy	All newly diagnosed	5.09 (4.88-5.31)
			With baseline physical or psychiatric comorbidity	5.46 (5.22-5.71)
			Without baseline physical or psychiatric comorbidity	3.28 (2.87-3.73)
Taiwan	Hospital data (general population controls)	2180 with epilepsy	All epilepsy	2.5 (2.2-2.8)
			Age specific	
			Boys age 0–9 years	51.8 (6.2-187.2)
			Women age 20–29 years	8.6 (4.4-14.9)
			Cause specific	
			Brain tumor	21.4 (9.23-23.1)
			Accidental drowning	8.8 (3.5-9.6)
			Falls	5.7 (2.2-6.1)
Taiwan	Outpatients department	263 with epilepsy	All epilepsy	3.47 (2.46-4.91)
			Case-fatality rate	12.2%
China	Longitudinal prospective survey	1,986 with epilepsy	All epilepsy	2.9 (2.6–3.4)
			Age specific	
			10–29 years	27.7–36.6
			Cause specific	
			Drowning	39.0 (26.4–55.5)
			Carbon monoxide and pesticide toxicity	17.0 (6.9–35.7)
			Falls	9.8 (3.6–21.7)
			Suicide	8.2 (4.5–14.0)
			Traffic accidents	6.0 (2.8–11.4)

			Myocardial infarction Digestive system disease Pneumonia Cerebrovascular disease	3.6 (1.6–7.2) 4.4 (2.3–7.7) 2.9 (0.7–7.8) 2.2 (1.5–3.1)
China	Primary care management program	3568 with epilepsy	All epilepsy Case fatality Age specific 5–20 years Cause specific Accidental death Drowning Fall from height Suicide Traffic accident Neoplasm SUDEP	4.92 (4.0-6.1) 2.97% 55–97 34.84 (23.81–50.96) 82.4 (46.40-146.44) 20.8 (7.22–59.7) 5.92 (1.72–20.57) 34.84 (23.81–50.96) 1.94 (0.90–4.18) PMR 14.7
Laos	Community-based phenobarbital program	53 with epilepsy	Case fatality Cause specific Drowning	11% 18.2%
Bangladesh	Population-based surveillance system	223,886 population	Cause specific Drowning: With epilepsy Without epilepsy	 83% 7% RR 12.6 (7.7–20.7)
India, Kolkarta	Population-based survey		All epilepsy Men Women	2.58 (1.50–4.13) 3.67 (1.83–6.57) 1.77 (0.65–3.85)
USA	Open cohort analysis of	68,785 with epilepsy	All epilepsy	1.8 (1.8-1.9)

	Medicaid beneficiaries		Case fatality Drowning Other unintentional injuries	18.4% 3.79 (2.74 – 4.84) 1.68 (1.57 – 1.79)
Austria	Epilepsy outpatient clinic	3334 with epilepsy	All epilepsy Age 26-45 years Symptomatic epilepsies Cryptogenic causes Persistent seizures	2.2 (2.0-2.4) 6.8 (3.8-11.2) 3.1 (2.3-4.9) 2.2 (1.6-3.1) 3.3 (2.6-4.4)
Austria	Epilepsy outpatient clinic	4295 with epilepsy	All epilepsy Cause-specific Congenital anomalies suicide Alcohol dependence syndrome Malignant esophageal neoplasm Pneumonia	1.7 (95 % CI 1.6-1.9) 7.1 (2.3-16.6) 4.2 (2.0-8.1) 3.9 (1.8-7.4) 3.1 (1.2-6.4) 2.7 (1.6-4.2)
UK	National General Practice Study of Epilepsy	558 with epilepsy	Case fatality Noncerebral neoplasm, cardiovascular, cerebrovascular disease Epilepsy-related causes	 59% 3%
Finland	Systematic review	165,879 with epilepsy	All epilepsy Cause specific Cryptogenic epilepsy Symptomatic epilepsy Epilepsy due to congenital or developmental causes	RR 3.33 (2.83-3.92) RR 1.75 (1.20-2.54) RR 4.73 (3.27-6.83) RR 10.3 (4.03-26.2)

HR, hazard ratio; PMR, proportional mortality ratio; RR, relative risk; SMR, standardized mortality ratio; SUDEP, sudden unexpected death in epilepsy.

Table 5. Driving restrictions for patients with epilepsy in Asian countries and the UK[77-85]

Country	Driving restriction for private motor vehicles
UK	Seizure free for ≥12 months
Korea	Seizure free for 2 years
Japan	Seizure free for 2 years
Malaysia	Seizure free for 2 years
Singapore	No structural brain lesion Normal EEG Seizure free for 3 years Not taken AEDs for ≥1 year
China	Permanent ban Many people continue to drive despite uncontrolled seizures
Hong Kong	Not eligible to drive without stated allowance for seizure-free duration
India	No restriction Advised not to drive during the first 2 years of treatment
Thailand	No restriction

AED, antiepileptic drug; EEG, electroencephalogram.

Table 6. Treatment gap in Asia by country*[86-96]

Country	Treatment gap
China	
Tibet Autonomous Region	97%
Hunan	93.4%
Guangxi	79.1%
Sichuan	66.3%
5 provinces[†]	62.6%[‡]
India	73.7–78%
Jharkhand	95%
Laos	~90%
Pakistan	88%
Vietnam	84.7%
Nepal	>70%
Philippines	50–77%
Cambodia	65.8%
Singapore	6%

* Countries for which information is available.

[†] Heilongjiang, Ningxia, Henan, Shanxi, and Jiangsu.

[‡] Reducing to 49.8% after community-level interventions.

Table 7. Epilepsy surgery in Asia by country[119-131]

Country	Number of epilepsy surgery centers	Number of surgeries and potential candidates
Hong Kong	3	~150 ~3500 surgical candidates
Japan	43 5 reference centers (performing >25 surgeries/year)	436/year ~2000 surgical candidates
Korea	17	300–400/year
Taiwan	3	>800
Malaysia	1	12
China	5 specialist centers 32 hospitals (one in each province) provides epilepsy surgical services	2500/year
India	2	1200
Nepal	1	11
Thailand	3	7*
Indonesia	1	35–47 in 2007–2009
Philippines	4	NA

NA, not available.

*Since reactivation of the surgical treatment program in 2005.