

Implementing WHO's Intersectoral Global Action Plan for epilepsy and other neurological disorders in Southeast Asia: a proposal



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Summary

The World Health Assembly approved the Intersectoral Global Action Plan for epilepsy and neurological disorders. Member states, including those in Southeast Asia, must now prepare to achieve IGAP's strategic targets by embracing novel approaches and strengthening existing policies and practices. We propose and present evidence to support four such processes. The opening course should engage all stakeholders to develop people-centric instead of outcome-centric approaches. Rather than caring for convulsive epilepsy alone, as currently done, primary care providers should also be skilled in diagnosing and treating focal and non-motor seizures. This could reduce the diagnostic gap as over half of epilepsies present with focal seizures. Currently, primary care providers lack knowledge and skills to manage focal seizures. Technology-enabled aids can help overcome this limitation. Lastly, there is need to add newer "easy to use" epilepsy medicines to Essential Medicines lists in light of emerging evidence for better tolerability, safety and user-friendliness.

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Introduction

The World Health Assembly approved the Intersectoral Global Action Plan (IGAP) for Epilepsy and other Neurological Disorders.¹ This represents the culmination of a long journey, started in 2002, when World Health Organization (WHO), International League Against Epilepsy (ILAE) and International Bureau for Epilepsy (IBE) partnered for a Global Campaign Against Epilepsy known as "Out of the Shadows".² The global campaign aimed to reduce the treatment gap, economic burden, and stigma associated with epilepsy through several regionally focused initiatives.³ An assessment of epilepsy care worldwide, the "Atlas of Epilepsy Care" was a historical by-product.⁴ In 2015, the World Health

Assembly approved a resolution on the global epilepsy burden recognising the need for coordinated action at country level.⁵ The resolution prescribed the involvement of primary care health providers in regions where specialists were lacking, developing community approaches and emphasising preventive strategies when possible. More demonstration projects followed in Ghana, Myanmar, Vietnam and Mozambique with reasonable successes.⁶ Epilepsy was declared as a public health imperative, and WHO, ILAE and IBE jointly produced the first-ever global report on epilepsy. In parallel, regional declarations, e.g., from the Pan-American Health and Southeast Asian Regional Organizations, were made to expand the reach of the global epilepsy campaign. Subsequently, the World Health Assembly approved a resolution to develop a draft of a ten-year global epilepsy action plan and other neurological disorders.⁷ It was envisaged to identify and bridge gaps in care, prevention and research through a series of ambitious accomplishments. It was produced and refined through a series of steps and eventually passed by the World Health Assembly.¹ The IGAP adopted epilepsy as an indicator condition to pursue its

Abbreviations: IGAP, Intersectoral Global Action Plan; WHO, World Health Organization; ILAE, International League Against Epilepsy; IBE, International Bureau for Epilepsy; NLEM, National list of essential medicines

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Box 1.

Epilepsy: some fundamental facts and tenets.

- Roughly 50 million people worldwide have epilepsy.⁸
- Epilepsy is fifth commonest neurological cause for disability adjusted life years (DALYs), and in some regions it is the second commonest cause.⁸
- Epilepsy is beset with considerable premature mortality, which is at least three-folds compared to the general population.^{9,10}
- Epilepsy burden is not limited to years lived with or lost to the condition but includes intangible burdens due to stigma, social discrimination and caregiver liabilities.¹¹
- Epilepsy can be managed with uncomplicated and cost-effective regimens comprising safe medications in nearly 70% cases.
- Roughly 80% of the world's people with epilepsy live in resource-limited settings of low- and low-middle income countries.⁸
- Over 2/3rds of the world's people with epilepsy are unable to access the treatment that they require; many of them remain undiagnosed.¹²
- The epilepsy treatment gap is seven times higher in LMICs when compared to high income countries.¹³
- There are inequities in care provision for epilepsies, for example, among the poor and those living in rural and remote areas but also women with epilepsies, transgenders, migrants and refugees.¹⁴
- Epilepsy should preeminently be managed by specialists; however, specialists are either absent or few and far apart in LMICs and other resource-limited settings including rural and remote areas.³

objectives based on critical premises, assumptions and facts (Box 1). It seeks commitment from member states to implement the goals, gather data on epilepsy services, and include epilepsy service provision in national health plans and budgets. Furthermore, it construes epilepsy as an entry point to a concerted effort to diminish the disease burden associated with many other neurological disorders, if only because of synergies involved in prevention and management. Consistent with the IGAP objectives, the ILAE proposes a 90%–80%–70% target-oriented strategy, which entails that at least 90% of people with epilepsy worldwide are appropriately diagnosed, at least 80% are on appropriate and affordable treatment/s, and at least 70% of those treated attain complete seizure remission without experiencing side effects.¹⁵ The targets, though desirable, are challenging. Hence, realistic plans for implementing the strategy require strengthening existing policies, provisions and practices and adopting novel approaches.

The Southeast Asian region is home to 15 million people with epilepsy, representing nearly a third of the world's burden (Fig. 1). The majority of those with epilepsy cannot access the treatments they require. Furthermore, WHO estimates that there are only three neurologists for one million people in Southeast Asia compared to 90 in Europe. Ostensibly, while epilepsy medicines on Essential Medicines Lists are generally available in urban and tertiary care settings in many countries, the availability in rural and remote regions is restricted to urban and tertiary care settings.

We propose four crucial approaches to epilepsy care, particularly in resource-limited settings in the Southeast Asian region, and present evidence supporting them (Fig. 2).¹⁶ The first relates to recognising fully that communities in general and people with epilepsy, their families and care providers are crucial stakeholders in reducing the epilepsy burden. Without co-opting and working with them, efforts may not produce the desired results. The second pertains to scaling up the capacity of

primary health care providers to diagnose and treat all epilepsies, particularly in recognising focal non-motor seizures. We propose accomplishing this through developing and integrating technology-enabled service delivery models in primary health care. Lastly, we suggest expanding the WHO Model and National Essential Medicines Lists (NMEs) for epilepsy. Notably, these apply mainly to low- and middle-income countries (LMICs) in the Southeast Asian region, where nearly 70% of the people with epilepsy remain untreated.^{8,12,13} The methods and search strategy used to develop these suggestions are detailed in [Search Strategy section](#) and [Supplementary Materials](#).

1. Make communities epilepsy-literate

Epilepsy is not just a medical condition but a complex social construct fuelled by ignorance, discrimination, poverty, patriarchy, stigma and much more.¹⁸ Efforts to improve epilepsy care and the quality of life of people with epilepsy are traditionally led by governments, health care organisations, non-governmental organisations and media, which indisputably are vital to making people epilepsy-literate. The objectives, however, can be better advanced through engaging with communities and their grassroot representatives. These may include health workers, local leaders, administrators, religious leaders, and school teachers.¹⁹ Understanding epilepsy as a medical condition and not an evil, contagious scourge by entire communities rather than select individuals is required for people with epilepsy to live dignified lives, be accepted in communities and be treated with empathy.¹¹ To be acceptable, resilient and sustainable, epilepsy intervention programs should be accompanied by active engagement with communities at every possible level. Evidence to support the participation of community-based stakeholders in epilepsy care is building up.²⁰ Initiatives that inform communities, consult, partner and collaborate with them and,

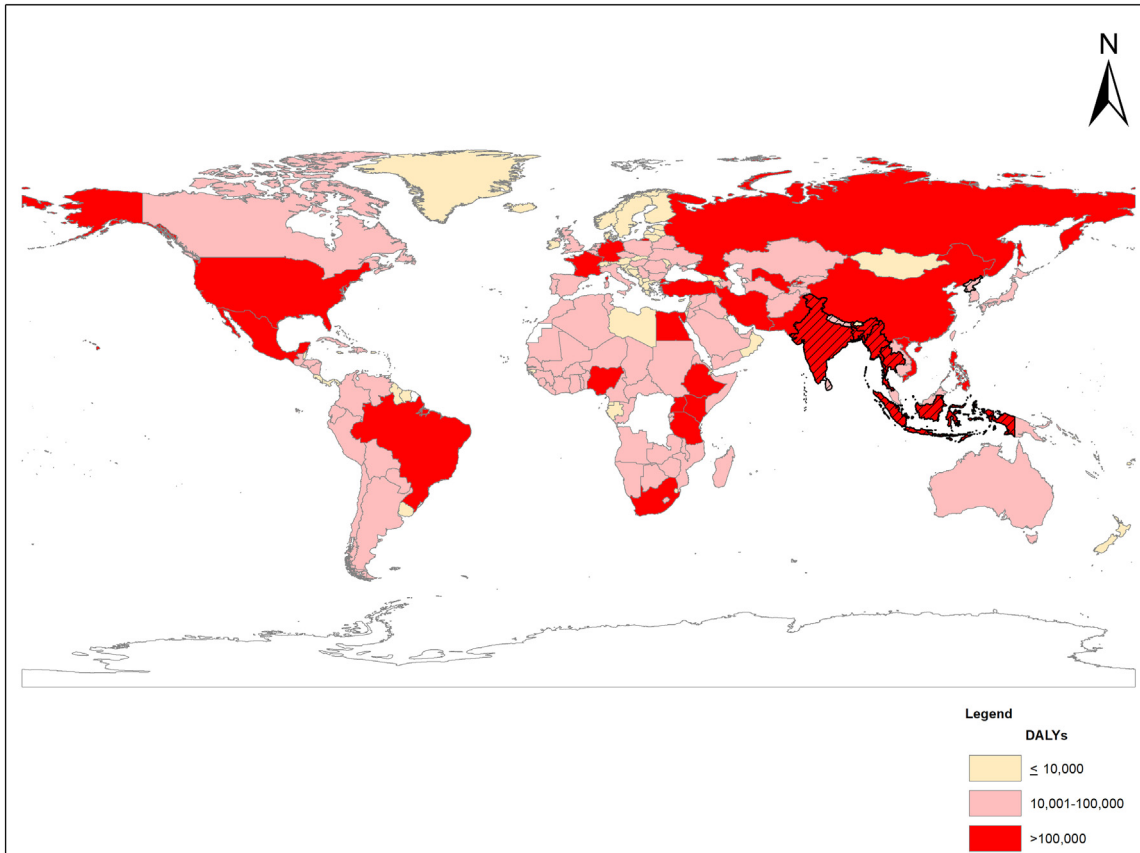


Fig. 1: World map depicting DALYs due to epilepsy across countries in the world and the Southeast Asian region in particular. Adapted from Ref. ⁸

in due course, are delegated to and owned by communities form the backbone of a people-centric approach to epilepsy care.²¹ It is not by coincidence, therefore, that

the IBE, which represents people with epilepsy, is a signatory to the global epilepsy report and a key stakeholder in IGAP.

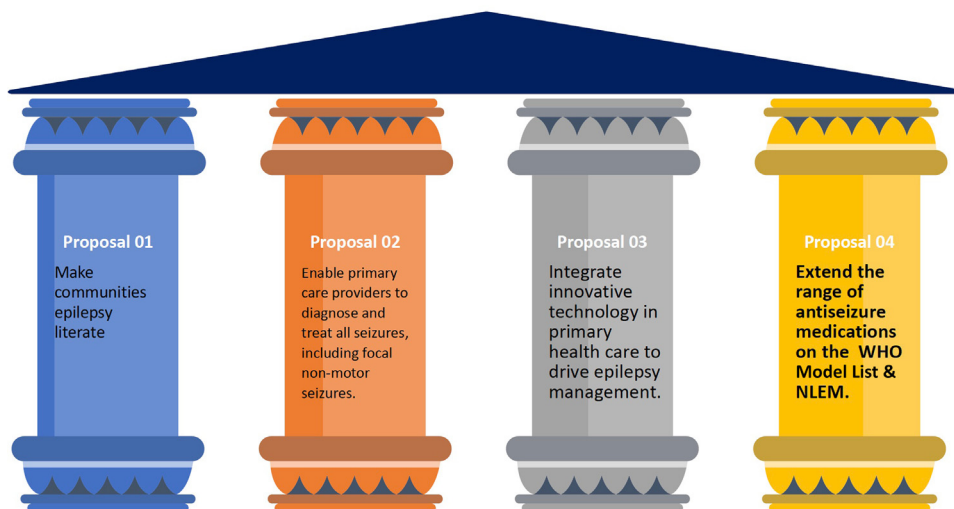


Fig. 2: Cartoon depicting the four approaches proposed in this Review.

Search strategy

For this review, we systematically searched PubMed to determine the proportion of focal epilepsies among population-based samples of new-onset or newly-diagnosed epilepsy (see [Appendix S1](#) for more details). We also searched PubMed for studies reporting diagnostic delay among samples of newly-diagnosed epilepsies using the search terms “Epilepsy” AND diagnostic delay OR diagnostic gap in the title or abstracts of articles. A third search comprised of population-based studies from LMICs reporting long-term use of conventional antiseizure medications, for which the search terms, Enzyme-inducing antiepileptic drugs or antiseizure medication and side effects or adverse effects were used. Lastly, we examined studies reporting the involvement of primary and community health care providers in delivering adherence monitoring and counselling, stigma- and self-management guidance to people with epilepsy in LMICs. This was based on a systematic review performed earlier by some of the authors (G.S. & L.S.).¹⁷ Searches were made between July 15 & August 22. Bibliographies of full papers were perused as well for relevant publications.

2. Primary health care providers should be enabled to diagnose and treat all seizures, including focal non-motor seizures

Most population-based assessments of epilepsy and field interventions have been limited to active convulsive epilepsies denoting convulsions (bilateral tonic-clonic seizures, as part of focal or generalised epilepsies).^{11,17,22} These studies often use a 1 year period to characterise active epilepsy. This represents a departure from the ILAE Epidemiology Commission recommendations, which proposed 5 years as the time criteria for active epilepsy.²³ These pragmatic operational criteria stand well as convulsions (now termed motor seizures) are unmissable and usually unmistakable, especially in settings with modest expertise and busy primary care practices. Moreover, they impact the quality of life more than focal and non-motor seizures. In line with this, the WHO mental health Gap action program (WHO mhGAP) has formulated diagnostic and treatment algorithms for active convulsive epilepsy.^{24,25}

Tackling only active convulsive epilepsies is an appealing approach which has provided rewards but has a downside. A review of population-based studies of new-onset epilepsy suggests that 55% (95% CIs, 48–61%; range 20–92%) of seizures in new-onset epilepsies are focal ([Fig. 3](#)). Addressing convulsive epilepsies will include focal to bilateral tonic-clonic seizures but exclude focal seizures with or without impaired awareness and other non-motor seizures. As a result, nearly one-half of all epilepsies will remain undiagnosed and untreated for long periods.

Recent evidence, albeit in resource-rich settings, have emphasised delays in diagnosing epilepsy among frontline health care services.^{26–30} The delays could vary from 1 month to several years. Most of these delays have been on account of focal and/or non-motor seizures. One study reported a substantially high rate of motor vehicle accidents among those experiencing diagnostic delays because of focal and/or non-motor seizures.²⁸ Some of these diagnostic delays could undoubtedly be due to an inability of people with epilepsy to recognise focal and/or non-motor events as seizures.³¹ Additional diagnostic delays at levels of frontline health care providers have also been documented. Reducing this diagnostic delay and gap is a public health challenge, all the more relevant to the realisation of ILAE target 1, which is to reduce the diagnostic gap to 10% by 2031.

Primary care providers' perspective

Relevant to the engagement of primary health care providers in managing focal seizures is determining if they have the requisite capacity to diagnose focal seizures. Only limited evidence is available in this regard, and when existing, it is in the form of epilepsy knowledge, attitudes, and practice surveys among healthcare workers in LMICs.^{32,33} Whilst these do not substitute for knowledge and skills assessments, they provide some insights. A Zambian survey presented different clinical scenarios spanning 2–3 sentences to assess knowledge about epilepsy among trained non-physician healthcare workers.³⁴ Nearly 80% correctly identified focal seizures with impaired awareness from the clinical descriptions. Surveys from other settings and parts of the world, however, suggest that knowledge and understanding of the manifestations of focal epilepsies are generally poor among medical students, physicians and nurses in LMICs.^{32,35}

Systematic baseline assessments of the knowledge and skills at the primary care level and the feasibility, acceptability and adaptability of primary care participation in recognising and treating focal and non-motor seizures, alongside convulsive epilepsies are urgently required. Plausibly, these might guide the development and refinement of primary healthcare epilepsy educational packages. There are existing packages to consider, e.g., the Paediatric Epilepsy Training (PET) courses initiated by the British Paediatric Neurology Association, the Practical Approach to Care Kit (PACK) epilepsy folio, and the Latin American epilepsy e-learning initiative.^{36–38} Of note, PET courses have been held in India, Singapore and New Zealand but not in any other Southeast Asian country. Further development of packages should ideally be technology-enabled, self-paced or blended and incorporate assessment tools. The ILAE Epilepsy Primary Care Curriculum could form the starting point for such initiatives.³⁹

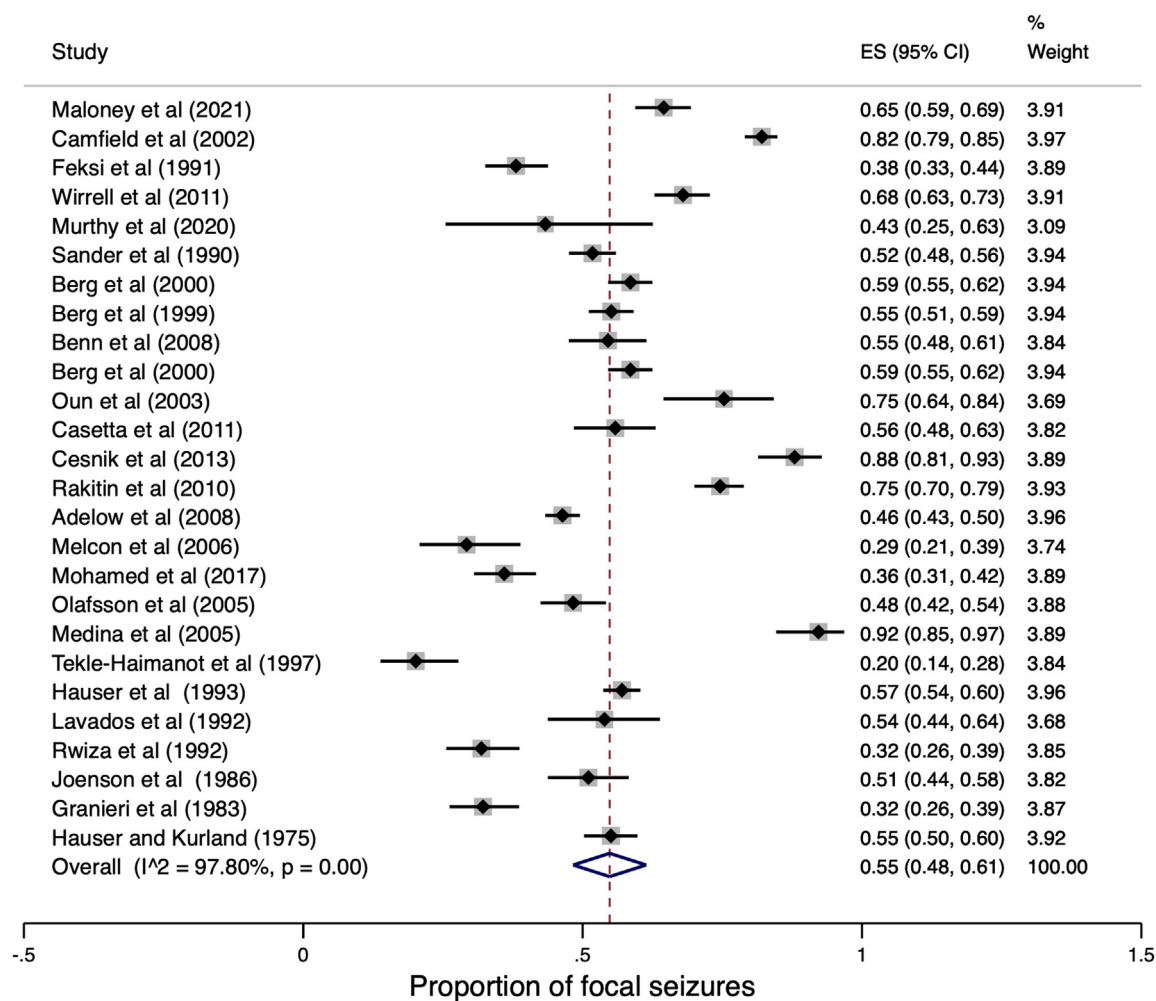


Fig. 3: Forest plot of the proportion of focal seizures among population-based samples of new-onset epilepsies.

Once suitably competent, primary health care providers would be able to educate a range of community stakeholders, including community health workers, school teachers, parents and lay persons on the recognition of focal and non-motor seizures. For instance, it might be really helpful if school teachers know that deteriorating cognitive performance in children could be on account of absence seizures.

3. Integrate innovative technology in primary health care to drive epilepsy management

Primary health care providers in LMICs are usually overstretched in terms of clinical load and different health conditions they have to handle. They often lack the initiative, resources and time to locate and absorb information on such broad-ranging clinical topics. Required for them are actionable knowledge and skill

points, which can be readily integrated into their workflow. In this context, app-based decision-making systems, either web-based, native or hybrid, have been developed and started to impact care. Some of them solely cover epilepsy.^{40,41} Their methodological features have been reported and validated in limited settings.^{42–44} Testing their efficacy and safety in clinical trials and real-world settings may be desirable. Key issues that need addressing include their acceptability among different healthcare provider groups, ability to function with limited connectivity in rural locations or hilly terrains, and safety and privacy of individual data. Specialist teleconsultations may complement the use of Apps, and there is Class I evidence that even telephonic clinical reviews are feasible and acceptable to most users and save time and decrease costs.⁴⁵ Remote electroencephalographic recordings, telemedicine and electronic data capture technologies are other examples of

S. No.	Antiseizure medication	Oral tablets	Syrup	Intravenous injection	Rectal gel or solution	Oromucosal/buccal solution
1.	Phenobarbital	15 mg, 30 mg, 60 mg, 100 mg	15 mg/5 mL	200 mg/mL		
2.	Phenytoin	Solid form: 25 mg; 50 mg; 100 mg (sodium). Chewable form: 50 mg	25 mg/5 mL; 30 mg/mL	50 mg/mL (sodium) in 5 mL vial		
3.	Carbamazepine	Chewable form: 100 mg; 200 mg. Scored tablet: 100 mg; 200 mg	100 mg/5 mL			
4.	Valproic acid	Crushable tablet: 100 mg; Enteric-coated tablet: 200 mg; 500 mg	200 mg/5 mL	Injection: 100 mg/mL in 4 mL ampoule; 100 mg/mL in 10 mL ampoule		
5.	Lamotrigine	Solid form: 25 mg; 50 mg; 100 mg; 200 mg. Chewable, dispersible tablets: 2 mg; 5 mg; 25 mg; 50 mg; 100 mg; 200 mg				
6.	Ethosuximide	Capsule: 250 mg.	250 mg/5 mL			
7.	Diazepam				5 mg/mL in 0.5 mL; 2 mL; 4 mL tubes	
8.	Lorazepam			2 mg/mL in 1 mL ampoule; 4 mg/mL in 1 mL ampoule.		
9.	Midazolam					5 mg/mL; 10 mg/mL (or 1 mg/mL; 10 mg/mL ampoule)

Formulation recommended.
 Formulations not recommended.

Re. <https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2021.02>. Magnesium sulphate is excluded from the list as it is recommended for use in eclampsia and severe pre-eclampsia and not for other convulsant disorders.

Table 1: Antiseizure medications on the WHO model list of essential medicines – 22nd list, 2021.

technology-enabled aids which may be suitable in remote and rural settings, where specialist availability is unlikely to improve in the short term.

Digital technology, when applied to end-users, has its advantages and disadvantages. Electronic decision support systems have the potential to advance evidence-based and affordable healthcare delivery in primary care. They can provide standardised care across multiple health conditions and are suitable for training and monitoring. In addition, they allow task-sharing whilst also providing appropriate specialist support without imposing undue demands on healthcare systems.^{46,47} In resource-limited settings, technology-enabled solutions may be constrained by poor reach, adoptability and understanding.⁴⁸ Technological innovations tend to get

institutionalised slowly and should be tested or adapted to local contexts.

4. The WHO model NLEM antiseizure medications' range should be extended

The WHO model list of essential medicines includes six oral epilepsy medicines, i.e., phenobarbital, phenytoin, carbamazepine, valproate, lamotrigine and ethosuximide, four parenteral preparations, i.e., phenobarbital, phenytoin, valproate-sodium and lorazepam, one rectal preparation, i.e., diazepam and one oro-buccal formulation, i.e., midazolam (Table 1).⁴⁹ Apart from ethosuximide, these medicines are widely available and relatively inexpensive. A cost analysis from 2001 estimated the annual cost of phenobarbital as low as US\$ 11.⁵⁰

Despite long-term use, data on the enduring safety of some ASMs in the WHO model list is limited. In a recent report, the hazards of incident cardiovascular disease were significantly elevated among users of enzyme-inducing ASMs compared to those who did not use them.⁵¹ Cumulative risks were marginally elevated for the first ten years of use but increased considerably beyond that period. Risk also increased with increasing doses. These findings have not fully been replicated in other studies with either different study designs or shorter follow-up periods.^{52,53} One follow-up study on post-stroke epilepsy found lower cardiovascular mortality rates with lamotrigine and levetiracetam compared to carbamazepine.⁵⁴ Many of these data need to be assimilated and absorbed carefully over time but provide a cautionary preamble to use of enzyme-inducing ASMs over the long term.

The impact of enzyme-inducing ASMs on bone health and fracture risk is also relevant to using these medications over long periods. A systematic review concluded that the fracture risk was elevated in users of enzyme-inducing ASMs but could not provide quantitative outcomes.⁵⁵ The systematic review findings were influenced mainly by one large cohort of over 60,000 people with epilepsy.⁵⁶

The adverse cardiovascular and musculoskeletal outcomes associated with some of the ASMs eventually translate to increased total health care costs in people with epilepsy, for instance, on account of vitamin D supplementation, the cost of remedying fractures and treating cardiovascular disease.⁵⁷

The use of some traditional ASMs can be complicated. The British National Formulary lists 153 clinically relevant drug interactions for phenytoin and 136 for carbamazepine, for which there is empirical evidence from human studies and several drug–disease interactions.⁵⁸ Dosage adjustments can be complex due to the narrow therapeutic index of phenytoin and auto-induction in the case of carbamazepine. Several complicated nomograms and formulae have abounded to guide dosage adjustments.⁵⁹ The use of many traditional ASMs has substantially declined in western clinical practice in the past two decades.⁶⁰ In comparison, some of the newer ASMs, although equally efficacious, afford better tolerability and fewer drug–drug interactions.^{61,62} This “ease of use” of some, e.g., levetiracetam and lacosamide, makes them convenient and appealing for use in primary care.^{63,64}

“*Primum non nocere*” could be a fair argument against traditional enzyme-inducing ASMs. The argument may, however, be conveniently rescinded as traditional ASMs might be the only medications available for use in many resource-limited settings.⁶⁵ It is imperative to ensure their rational use, including in efficacious and safe combinations. Many newer ASMs are beset with availability and cost issues, which need careful consideration, although there is emerging evidence that public financing of some of the newer

medications may further reduce the disease burden and avert financial losses.⁶⁶ It is, therefore, timely to introduce newer ASMs to the WHO model list so that once widely available and affordable, these could eventually replace some of the ASMs on current lists. Importantly, this could be integrated within wider efforts to provide universal health coverage as indeed relevant not just to IGAP but also the United Nations Sustainable Development Goals.

In conclusion, approval of the IGAP is a long-awaited and alluring development. The targets might appear daunting but need not be so if countries, states and institutions globally and Southeast Asia begin planning and preparing earnestly. Many approaches, e.g., community engagement and timely referral, are already recommended but re-emphasised here for broader implementation. For instance, a top-down approach with firm commitment on the part of governmental agencies might be the key to motivating primary health care providers to provide quality and efficacious epilepsy care. Such a series of reforms in current approaches might be the key to bridging the gap between the desired and current situations. As well as reducing epilepsy diagnostic and treatment gaps, the proposed measures could go a long way in diminishing the global burden of all neurological disorders on account of shared disease burdens and common diagnostic and therapeutic approaches.

Contributors

G.S. conceived the idea behind the manuscript and wrote the preliminary draft. M.B.S., D.D., P.M. and J.W.S. provided substantial intellectual inputs in the form of adding to the draft and revising the manuscript several times over. The graph was made by G.S.

Editor note

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Declaration of interests

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.lansea.2022.100135>.

References

- 1 World Health Organization. <https://www.who.int/news/item/27-05-2022-seventy-fifth-world-health-assembly-daily-update27-may-2022>; 2022. Accessed July 20, 2022.
- 2 De Boer HM. "Out of the shadows": a global campaign against epilepsy. *Epilepsia*. 2002;43 Suppl 6:7–8. <https://doi.org/10.1046/j.1528-1157.43.s.6.4.x>.
- 3 Dua T, de Boer HM, Prilipko LL, Saxena S. Epilepsy care in the world: results of an ILAE/IBE/WHO Global Campaign Against Epilepsy survey. *Epilepsia*. 2006;47:1225–1231. <https://doi.org/10.1111/j.1528-1167.2006.00595.x>.
- 4 World Health Organization. Epilepsy. A public health imperative. <https://apps.who.int/iris/handle/10665/325293>; 2019. Accessed July 10, 2022.
- 5 World Health Organization. https://apps.who.int/gb/ebwha/pdf_files/WHA68-REC1/A68_R1_REC1-en.pdf; 2015. Accessed July 10, 2022.
- 6 World Health Organization. <https://www.who.int/news-room/feature-stories/detail/pilot-studies-help-close-the-epilepsy-treatment-gap>; 2019. Accessed July 10, 2022.
- 7 World Health Organization. https://apps.who.int/gb/ebwha/pdf_files/WHA73/A73_R10-en.pdf; 2020. Accessed July 10, 2022.
- 8 GBD 2016 Epilepsy Collaborators. Global, regional, and national burden of epilepsy, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. 2019;18:357–375. [https://doi.org/10.1016/S1474-4422\(18\)30454-X](https://doi.org/10.1016/S1474-4422(18)30454-X).
- 9 Thurman DJ, Logroscino G, Beghi E, et al. The burden of premature mortality of epilepsy in high-income countries: a systematic review from the Mortality Task Force of the International League Against Epilepsy. *Epilepsia*. 2017;58:17–26. <https://doi.org/10.1111/epi.13604>.
- 10 Levira F, Thurman DJ, Sander JW, et al. Premature mortality of epilepsy in low- and middle-income countries: a systematic review from the Mortality Task Force of the International League Against Epilepsy. *Epilepsia*. 2017;58:6–16. <https://doi.org/10.1111/epi.13603>.
- 11 Beghi E. Social functions and socioeconomic vulnerability in epilepsy. *Epilepsy Behav*. 2019;100:106363. <https://doi.org/10.1016/j.yebeh.2019.05.051>.
- 12 Singh B, Mahajan N, Singh G, Sander JW. Temporal trends in the epilepsy treatment gap in low- and low-middle-income countries: a meta-analysis. *J Neurol Sci*. 2022;434:120174. <https://doi.org/10.1016/j.jns.2022.120174>.
- 13 Singh G, Sander JW. The global burden of epilepsy report: implications for low- and middle-income countries. *Epilepsy Behav*. 2020;105:106949. <https://doi.org/10.1016/j.yebeh.2020.106949>.
- 14 Szaflarski M. Social determinants of health in epilepsy. *Epilepsy Behav*. 2014;41:283–289.
- 15 International League Against Epilepsy. <https://www.ilae.org/files/dmfile/ICNA-ILAE-WFN-letter-to-WHO-12-August-2021.pdf>; 2021. Accessed July 10, 2022.
- 16 World Health Organization. <https://www.who.int/publications/i/item/9789241596206>; 2008. Accessed July 10, 2022.
- 17 Singh G, Sharma M, Krishnan A, et al. Models of community-based primary care for epilepsy in low- and middle-income countries. *Neurology*. 2020;94(4):165–175. <https://doi.org/10.1212/WNL.0000000000008839>.
- 18 Fisher RS, van Emde Boas W, Blume W, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia*. 2005;46:470–472. <https://doi.org/10.1111/j.0013-9580.2005.66104.x>.
- 19 Nizamie SH, Akthar S, Banerjee I, Goyal N. 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. <https://doi.org/10.1016/j.eplepsyres.2009.01.008>.
- 20 Kaddumukasa M, Bongomin F, Kaddumukasa MN, Blixen C, Sajatovic M, Katabira E. Feasibility, acceptability, and efficacy of an adopted novel self-management intervention among people with epilepsy in Uganda. *Epilepsy Behav*. 2021;122:108200. <https://doi.org/10.1016/j.yebeh.2021.108200>.
- 21 World Health Organization. Community engagement. <https://www.who.int/publications/i/item/9789240010529>; 2020. Accessed July 31, 2022.
- 22 Mbuba CK, Ngugi AK, Fegan G, et al. Risk factors associated with the epilepsy treatment gap in Kilifi, Kenya: a cross-sectional study. *Lancet Neurol*. 2012;11:688–696. [https://doi.org/10.1016/S1474-4422\(12\)70155-2](https://doi.org/10.1016/S1474-4422(12)70155-2).
- 23 Anonymous. Guidelines for epidemiologic studies on epilepsy. Commission on Epidemiology and Prognosis, International League Against Epilepsy. *Epilepsia*. 1993;34:592–596. <https://doi.org/10.1111/j.1528-1157.1993.tb00433.x>.
- 24 World Health Organization. *mhGAP: mental health gap action programme: scaling up care for mental, neurological and substance use disorders*. Geneva: World Health Organization; 2008.
- 25 Dos Santos PF, Cumbe V, Gouveia ML, de Fouchier C, Teuwen D, Dua T. Implementation of mhGAP in Mozambique: integrating epilepsy care into the primary health care system. *Int J Ment Health Syst*. 2019;13:36. <https://doi.org/10.1186/s13033-019-0296-5>.
- 26 Berg AT, Loddenkemper T, Baca CB. Diagnostic delays in children with early onset epilepsy: impact, reasons, and opportunities to improve care. *Epilepsia*. 2014;55:123–132. <https://doi.org/10.1111/epi.12479>.
- 27 Firkin AL, Marco DJ, Saya S, et al. Mind the gap: multiple events and lengthy delays before presentation with a "first seizure". *Epilepsia*. 2015;56:1534–1541. <https://doi.org/10.1111/epi.13127>.
- 28 Pellinen J, Tafuro E, Yang A, et al. Focal nonmotor versus motor seizures: the impact on diagnostic delay in focal epilepsy. *Epilepsia*. 2020;61:2643–2652. <https://doi.org/10.1111/epi.16707>.
- 29 Alessi N, Perucca P, McIntosh AM. Missed, mistaken, stalled: identifying components of delay to diagnosis in epilepsy. *Epilepsia*. 2021;62(7):1494–1504. <https://doi.org/10.1111/epi.16929>.
- 30 Parviainen L, Kälviäinen R, Jutila L. Impact of diagnostic delay on seizure outcome in newly diagnosed focal epilepsy. *Epilepsia Open*. 2020;5(4):605–610. <https://doi.org/10.1002/epi4.12443>.
- 31 Beghi E. Does diagnostic delay impact on the outcome of epilepsy? *Epilepsia Open*. 2021;6:470–471.
- 32 Njamnshi AK, Angwafor SA, Baumann F, Angwafo 3rd FF, Jallon P, Muna WF. Knowledge, attitudes, and practice of Cameroonian medical students and graduating physicians with respect to epilepsy. *Epilepsia*. 2009;50:1296–1299. <https://doi.org/10.1111/j.1528-1167.2009.02155.x>.
- 33 Buddhiraja R, Sharma S, Sharma S, et al. Epilepsy knowledge, attitudes, and practices among primary healthcare providers in an Indian district. *Epilepsy Behav*. 2020;104:106899. <https://doi.org/10.1016/j.yebeh.2019.106899>.
- 34 Chomba EN, Haworth A, Atadzhanov M, Mbewe E, Birbeck GL. Zambian health care workers' knowledge, attitudes, beliefs, and practices regarding epilepsy. *Epilepsy Behav*. 2007;10:111–119. <https://doi.org/10.1016/j.yebeh.2006.08.012>.
- 35 Dedeken P, Muhumuza SN, Sebera F, et al. Long-term impact of single epilepsy training on knowledge, attitude and practices: comparison of trained and untrained Rwandan Community health workers. *Int J Public Health*. 2021;66:645598. <https://doi.org/10.3389/ijph.2021.645598>.
- 36 Knowledge translation unit. Adult primary care 2020. <https://kuonline.school.datafree.co/courses/APC-full-course>. Accessed February 15, 2022.
- 37 Patel AA, Wibecan L, Tembo O, Kalyeje P, Mathews M, Ciccone O. Improving paediatric epilepsy management at the first level of care: a pilot education intervention for clinical officers in Zambia. *BMJ Open*. 2019;9:e029322.
- 38 Carrizosa J, Braga P, Albuquerque M, et al. Epilepsy for primary health care: a cost-effective Latin American E-learning initiative. *Epileptic Disord*. 2018;20:386–395.
- 39 Singh G, Braga P, Carrizosa J, et al. An epilepsy curriculum for primary health care providers: a report from the Education Council of the International League Against Epilepsy. *Epileptic Disord*. 2022;24(6):983–993.
- 40 Patterson V, Pant P, Gautam N, Bhandari A. A Bayesian tool for epilepsy diagnosis in the resource-poor world: development and early validation. *Seizure*. 2014;23:567–569. <https://doi.org/10.1016/j.seizure.2014.03.010>.
- 41 Asadi-Pooya AA, Beniczky S, Rubboli G, Sperling MR, Rampp S, Perucca E. A pragmatic algorithm to select appropriate antiseizure medications in patients with epilepsy. *Epilepsia*. 2020;61:1668–1677. <https://doi.org/10.1111/epi.16610>.
- 42 Beniczky S, Rampp S, Asadi-Pooya AA, Rubboli G, Perucca E, Sperling MR. Optimal choice of antiseizure medication: agreement among experts and validation of a web-based decision support application. *Epilepsia*. 2021;62:220–227. <https://doi.org/10.1111/epi.16763>.

- 43 Asadi-Pooya AA, Beniczky S, Rubboli G, Sperling MR, Rampp S, Perucca E. The EpiPick algorithm to select appropriate antiseizure medications in patients with epilepsy: validation studies and updates. *Epilepsia*. 2022;63:254–255. <https://doi.org/10.1111/epi.17129>.
- 44 Patterson V, Singh M, Rajbhandari H, Vishnubhatla S. Validation of a phone app for epilepsy diagnosis in India and Nepal. *Seizure*. 2015;30:46–49. <https://doi.org/10.1016/j.seizure.2015.05.011>.
- 45 Bahrani K, Singh MB, Bhatia R, et al. Telephonic review for out-patients with epilepsy — a prospective randomised, parallel group study. *Seizure*. 2017;53:55–61. <https://doi.org/10.1016/j.seizure.2017.11.003>.
- 46 Garg AX, Adhikari NK, McDonald H, et al. Effects of computerized clinical decision support systems on practitioner performance and patient outcomes: a systematic review. *JAMA*. 2005;293:1223–1238.
- 47 Maulik PK, Devarapalli S, Kallakuri S, Bhattacharya A, Peiris D, Patel A. The systematic medical appraisal referral and treatment mental health project: quasi-experimental study to evaluate a technology-enabled mental health services delivery model implemented in rural India. *J Med Internet Res*. 2020;22:e15553. <https://doi.org/10.2196/15553>.
- 48 Bashingwa JJH, Shah N, Mohan D, et al. Examining the reach and exposure of a mobile phone-based training programme for front-line health workers (ASHAs) in 13 states across India. *BMJ Glob Health*. 2021;6:e005299. <https://doi.org/10.1136/bmjgh-2021-005299>.
- 49 World Health Organization. <https://www.who.int/publications/item/WHO-MHP-HPS-EML-2021.02>; 2021. Accessed July 16, 2022.
- 50 Krishnan A, Sahariah SU, Kapoor SK. Cost of epilepsy in patients attending a secondary-level hospital in India. *Epilepsia*. 2004;45:289–291. <https://doi.org/10.1111/j.0013-9580.2004.63102.x>.
- 51 Josephson CB, Wiebe S, Delgado-Garcia G, et al. Association of enzyme-inducing antiseizure drug use with long-term cardiovascular disease. *JAMA Neurol*. 2021;78:1367–1374. <https://doi.org/10.1001/jamaneurol.2021.3424>.
- 52 Lee-Lane E, Torabi F, Lacey A, et al. Epilepsy, antiepileptic drugs, and the risk of major cardiovascular events. *Epilepsia*. 2021;62:1604–1616. <https://doi.org/10.1111/epi.16930>.
- 53 Gao J, Seki T, Usami K, Fan D, Ikeda A, Kawakami K. Complications associated with the use of enzyme-inducing and non-enzyme-inducing antiseizure medications in the Japanese population: a retrospective cohort study. *Epilepsy Behav*. 2022;129:108610. <https://doi.org/10.1016/j.yebeh.2022.108610>.
- 54 Larsson D, Baftiu A, Johannessen Landmark C, et al. Association between antiseizure drug monotherapy and mortality for patients with poststroke epilepsy. *JAMA Neurol*. 2022;79:169–175. <https://doi.org/10.1001/jamaneurol.2021.4584>.
- 55 Fraser LA, Burneo JG, Fraser JA. Enzyme-inducing antiepileptic drugs and fractures in people with epilepsy: a systematic review. *Epilepsy Res*. 2015;116:59–66. <https://doi.org/10.1016/j.eplepsyres.2015.07.003>.
- 56 Nicholas JM, Ridsdale L, Richardson MP, Grieve AP, Gulliford MC. Fracture risk with use of liver enzyme inducing antiepileptic drugs in people with active epilepsy: cohort study using the general practice research database. *Seizure*. 2013;22:37–42. <https://doi.org/10.1016/j.seizure.2012.10.002>.
- 57 Borghs S, Thieffry S, Noack-Rink M, et al. Health care cost associated with the use of enzyme-inducing and non-enzyme-active antiepileptic drugs in the UK: a long-term retrospective matched cohort study. *BMC Neurol*. 2017;17:59. <https://doi.org/10.1186/s12883-017-0837-y>.
- 58 British National Formulary. https://www.medicinescomplete.com.libproxy.ucl.ac.uk/#/content/bnf/_998594489_interactions; 2022. Accessed July 16, 2022.
- 59 Rambeck B, Boenigk HE, Dunlop A, Mullen PW, Wadsworth J, Richens A. Predicting phenytoin dose - a revised nomogram. *Ther Drug Monit*. 1979;1(3):325–333. <https://doi.org/10.1097/00007691-197901030-00007>.
- 60 Chen Z, Brodie MJ, Liew D, Kwan P. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs: a 30-year longitudinal cohort study. *JAMA Neurol*. 2018;75:279–286. <https://doi.org/10.1001/jamaneurol.2017.3949>.
- 61 Perucca E, Brodie MJ, Kwan P, Tomson T. 30 years of second-generation antiseizure medications: impact and future perspectives. *Lancet Neurol*. 2020;19:544–556. [https://doi.org/10.1016/S1474-4422\(20\)30035-1](https://doi.org/10.1016/S1474-4422(20)30035-1).
- 62 Cross JH, Tomson T. Newer versus older antiseizure medications: further forward? *Lancet*. 2021;397(10282):1327–1329. [https://doi.org/10.1016/S0140-6736\(21\)00435-9](https://doi.org/10.1016/S0140-6736(21)00435-9).
- 63 Shih JJ, Whitlock JB, Chimato N, Vargas E, Karceski SC, Frank RD. Epilepsy treatment in adults and adolescents: expert opinion, 2016. *Epilepsy Behav*. 2017;69:186–222. <https://doi.org/10.1016/j.yebeh.2016.11.018>.
- 64 Terman SW, Youngerman BE, Choi H, Burke JF. Antiseizure medication treatment pathways for US Medicare beneficiaries with newly treated epilepsy. *Epilepsia*. 2022;63:1571–1579. <https://doi.org/10.1111/epi.17226>.
- 65 Singh MB, Bhatia R, Patterson V. Premature mortality in epilepsy—a reminder for the untreated millions. *JAMA Neurol*. 2020;77:525. <https://doi.org/10.1001/jamaneurol.2019.5091>.
- 66 Megiddo I, Colson A, Chisholm D, et al. Health and economic benefits of public financing of epilepsy treatment in India: an agent-based simulation model. *Epilepsia*. 2016;57:464–474. <https://doi.org/10.1111/epi.13294>.