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Medication prescribing and patient-reported outcome measures in people with epilepsy in Bhutan

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ABSTRACT

Objective: The aim of this study was to assess medication prescribing and patient-reported outcomes among people with epilepsy (PWE) in Bhutan and introduce criteria for evaluating unmet epilepsy care needs, particularly in resource-limited settings.
Methods: People with epilepsy in Bhutan (National Referral Hospital, 2014–2015) completed a questionnaire, the Quality of Life in Epilepsy Inventory (QOLIE-31), and an electroencephalogram (EEG). Management gap was the proportion of participants meeting any of six prespecified criteria based on best practices and the National Institute for Health and Care Excellence (NICE) guidelines.
Results: Among 253 participants (53% female, median: 24 years), 93% (n = 235) were treated with antiepileptic drugs (AEDs). Seventy-two percent (n = 183) had active epilepsy (≥1 seizure in the prior year). At least one criterion was met by 55% (n = 138) of participants, whereas the treatment gap encompassed only 5% (n = 13). The criteria were the following: 1. Among 18 participants taking no AED, 72% (n = 13) had active epilepsy. 2. Among 26 adults on subtherapeutic monotherapy, 46% (n = 12) had active epilepsy. 3. Among 48 participants reporting staring spells, 56% (n = 27) were treated with carbamazepine or phenytoin. 4. Among 101 female participants aged 14–40 years, 23% (n = 23) were treated with sodium valproate. 5. Among 67 participants reporting seizure-related injuries, 87% (n = 58) had active epilepsy. 6. Among 111 participants with a QOLIE-31 score below 50/100, 77% (n = 86) had active epilepsy. Years since first AED treatment (odds ratio: 1.07, 95% CI: 1.03, 1.12) and epileptiform discharges on EEG (odds ratio: 1.95, 95% CI: 1.15, 3.29) were significantly associated with more criteria met.
Conclusions: By defining the management gap, subpopulations at greatest need for targeted interventions may be prioritized, including those already taking AEDs.

1. Introduction

Epilepsy affects at least 50 million people worldwide, more than 80% of whom live in developing countries [1,2]. Efforts to reduce the global burden of epilepsy have focused on the epilepsy treatment gap, the proportion of people with epilepsy (PWE) who require treatment but do not receive it. The treatment gap for active epilepsy exceeds 75% in most low-income countries and 50% in most lower-middle-income countries [3]. The treatment gap concept focuses on providing antiepileptic drugs (AEDs) as an initial measure of adequate epilepsy care.

However, many PWE take AEDs but continue to suffer from seizures and the sequelae of uncontrolled epilepsy because of suboptimal management. Here, we newly define a proposed epilepsy management gap and analyze its magnitude in a cohort of PWE in the lower-middle-income country of Bhutan. Data from PWE in Bhutan are used as an illustrative example of epilepsy care in settings with available AEDs but limited training in epilepsy care, a scenario likely common in many countries worldwide.

2. Methods

2.1. Ethics

The research ethics boards of Bhutan, Massachusetts General Hospital (USA), and the University of Ottawa (Canada) approved the study.

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All participants provided individual consent or, when appropriate, assent with proxy consent.

2.2. Study site

The Kingdom of Bhutan (population: 742,000) is served by a health workforce including 197 physicians, 827 nurses, and 491 community healthcare workers (HCWs) [4]. There are no allopathic medical schools in Bhutan [5]. Postgraduate medical education programs were first introduced in 2014. There are no training programs available in neurology, neurosurgery, or psychiatry, and there are no neurologists practicing in Bhutan. Traditional doctors and basic community HCWs (6–18 months of training) practice in regions across the country, while most physicians, including specialists, are concentrated in urban centers. Most referrals of PWE are handled by the country's psychiatrist, based at the Jigme Dorji Wangchuck National Referral Hospital (JDWNRH), the tertiary referral center located in the capital city [6]. The JDWNRH is a 350-bed hospital, providing care to approximately 13,000 patients per year [4]. Bhutan has a universal healthcare system, with physician consultation and medications, including AEDs, available at no cost to the patient. Medication orders are nationally centralized and are contingent upon the prior year's prescribing frequency, limiting the opportunity to increase the number and/or expand to newer AEDs. "Stockouts" of AEDs have occurred, and when an AED is no longer available locally, patients' medication regimens may be switched more often than is clinically indicated.

2.3. Participant enrollment

People with epilepsy or those with suspected seizures at any age were enrolled at the JDWNRH (July 2014–April 2015). Participants were recruited through physician referral from the JDWNRH Departments of Psychiatry and Pediatrics and the Institute of Traditional Medicine Services or an existing registry of PWE at the Department of Psychiatry. Patients could be self-referred or referred by HCWs working in other districts. Participants also asked to be enrolled through "word of mouth". Participants were reimbursed the equivalent of nine United States dollars for travel.

2.4. Data collection

The study questionnaire and interviews were conducted in Dzongkha, the official language of Bhutan, or English. Each participant completed a structured interview including the Quality of Life in Epilepsy Inventory (QOLIE-31) [7] and a clinical questionnaire which included seizure characteristics, AED treatment, and seizure-related injuries. Carbamazepine, lamotrigine, levetiracetam, phenobarbital, phenytoin, and sodium valproate use were asked by medication name. Participants were also invited to list other medications they were taking.

Participants completed outpatient electroencephalograms (EEGs). Recordings lasted for a minimum of 20 minutes and captured wakefulness and, when possible, sleep. Recordings were carried out in accordance with the standards of the American Clinical Neurophysiology Society. Interpretation of EEG recordings was completed by one or more board-certified pediatric (ECWL, RT) or adult (AJC, ASPL, AL, RZ, SSC) neurologists with specialized expertise in epilepsy. Classification as epileptiform by one or more neurologists was sufficient for an EEG to be considered epileptiform in this analysis.

Participants were excluded from this analysis if they did not meet diagnostic criteria for epilepsy (e.g., history of one seizure or febrile seizures only) based on their responses to the clinical questionnaire ($n = 15$).

2.5. Management gap criteria

We designed the epilepsy management gap criteria (Box 1) to identify participants experiencing suboptimal epilepsy management, including those failing to receive indicated AED treatment, per the treatment gap definition (criterion 1), and extending to those on contraindicated or suboptimal AED regimens (criteria 2–4) and those experiencing sequelae of poorly controlled epilepsy (criteria 5 and 6). Active epilepsy was defined as ≥1 seizure in the past year, as per the International League Against Epilepsy (ILAE) definition [8].

Box 1
Epilepsy management gap criteria.

Any of the following:

(1) Participants not taking an AED who had active epilepsy
(2) Participants on a subtherapeutic dose of a single AED who had active epilepsy
(3) Participants with staring spells on carbamazepine or phenytoin
(4) Women and girls of childbearing potential (14–40 years) on sodium valproate
(5) Participants who had unintentional seizure-related injuries and active epilepsy
(6) Participants with a QOLIE-31 score <50/100 and active epilepsy

AED: Antiepileptic drug
QOLIE-31: Quality of Life in Epilepsy Inventory

Criterion 1: Participants were considered treated with an AED if they reported intake of the following: carbamazepine, lamotrigine, levetiracetam, phenobarbital, phenytoin, sodium valproate, topiramate, or benzodiazepines.

Criterion 2: Recommended AED dose ranges, in milligrams per day, were taken from guidelines published in the United Kingdom [9]. A dose less than or equal to the minimum recommended dose, in the context of active epilepsy, was considered subtherapeutic in adult participants on a single AED. The minimum total daily recommended doses are 400 mg carbamazepine, 100 mg lamotrigine, 1000 mg levetiracetam, 50 mg phenobarbital, 200 mg phenytoin, or 500 mg sodium valproate [9]. Dose information for topiramate or benzodiazepines was not collected on the clinical questionnaire.

Criterion 3: Carbamazepine and phenytoin may exacerbate absence seizures. The use of these AEDs in patients with absence seizures is advised against by the 2012 UK National Institute for Health and Care Excellence (NICE) evidence-based guidelines (NICE 1.9.4.5, 1.9.6.5) [10]. Absence seizures were classified based on the seizure description of "staring spells" on the clinical questionnaire.

Criterion 4: The use of sodium valproate is discouraged in girls and women of childbearing potential because of a high risk of serious developmental disorders and/or congenital malformations in children exposed to valproate *in utero* (NICE 1.9.1.10) [11].

Criterion 5: Unintentional seizure-related injuries, in the context of active epilepsy, may represent morbidity and mortality that are preventable with optimal neurological management [12,13]. Seizure-related injuries were self-reported via the clinical questionnaire and further classified as burns, fractures, car accidents, head injuries, or other injuries.

Criterion 6: The QOLIE-31 was used to assess epilepsy-related quality of life in participants ≥12 years old. This tool contains seven multi-item subscales: seizure worry, overall quality of life, emotional well-being, energy/fatigue, cognition, medication effects, and social function, and the total score is a

weighted sum of the subscale scores out of 100 [7]. An item about driving was eliminated because of the low rate of driving in the study population, and points were redistributed across the social function subscale. A score below 50/100, in the context of active epilepsy, was chosen as the cutoff score for establishing the management gap.

2.6. Data analysis

Each participant was categorized as meeting or not meeting each management gap criterion. Where relevant data were missing, participants were dropped from the defined risk group. When data were incomplete, follow-up calls to participants were made to ensure clarity and completion of data. Participants who reported staring spells had their interictal EEGs further characterized on whether epileptiform abnormalities were focal or generalized in post hoc analyses. This was meant to determine whether clinical description of staring spells was actually due to absence seizures in this group.

Potential clinical and demographic risk factors for participants with active epilepsy were determined *a priori* and included age, sex, years since first AED treatment, epileptiform abnormalities on EEG, and residence in the capital city versus not. Logistic regression models were used to determine the association of each potential predictor with the outcome of active epilepsy. An ordered logistic regression model was constructed to determine the association of these potential predictors with the number of management gap criteria met per participant. A p-value of <0.05 was considered statistically significant. All analyses were performed using Stata (version 11.1, College Station, TX, USA).

3. Results

Among the 253 participants (53%, n = 133 female, median age: 24 years, interquartile range = 15), 93% (n = 235) were treated with AEDs. Seventy-two percent (n = 183) of the participants had active epilepsy (Table 1), and 36% (n = 92) had epileptiform abnormalities on EEG.

Table 1
Participant demographics and clinical characteristics (n = 253).

Age	
Median (interquartile range)	24 (15)
<18 years, n (%)	73 (29)
Sex, n (%)	
Female	133 (53)
Diagnosis, n (%)	
Previously diagnosed with epilepsy	229 (91)
Most recent seizure, n (%)	
Last week	68 (27)
Last month	75 (30)
Last year	40 (16)
More than a year ago	69 (27)
Seizure characterization, n (%)	
Loss of consciousness	182 (72)
Staring spells	44 (17)
Electroencephalogram findings, n (%)	
Epileptiform abnormalities	92 (36)
Treatment, n (%)	
Take medications regularly	224 (89)
0 AED	18 (7)
1 AED	144 (57)
2 AEDs	60 (24)
≥3 AEDs	26 (10)
Carbamazepine	88 (35)
Lamotrigine	8 (3)
Levetiracetam	29 (11)
Phenobarbital	49 (19)
Phenytoin	90 (36)
Sodium valproate	59 (23)
Benzodiazepines	23 (9)
Topiramate	3 (1)
Seizure-related injuries, n (%)	
Any seizure-related injury	67 (26)
Burns	24 (9)
Bone breaks, fractures, dislocations	10 (4)
Head injuries	42 (17)
Car accidents	2 (1)
Other injuries	4 (1)
QOLIE overall score (0–100)	
Median (interquartile range)	48.4 (24)
<50 points, n (%)	111 (44)

AED: Antiepileptic drug. QOLIE-31: Quality of Life in Epilepsy Inventory.

3.1. Treatment versus management gap

At least one management gap criterion was met by 55% (n = 138) of participants (Table 2). The treatment gap (criterion 1) encompassed only 5% (n = 13) of the study participants.

Of the 18 participants taking no AED, 72% (n = 13) had active epilepsy (Fig. 1). Of the 26 adult participants on subtherapeutic monotherapy, 46% (n = 12) had active epilepsy. Forty-eight participants reported staring spells, 56% (n = 27) of whom were treated with carbamazepine or phenytoin. Among the 101 female participants aged 14–40 years, 23% (n = 23) were treated with sodium valproate. Unintentional seizure-related injuries were reported by 67 participants, 87% (n = 58) of whom had active epilepsy. Among the 204 participants who completed the QOLIE questionnaire, 54% (n = 111) fell below the 50/100-point score, 77% (n = 86) of whom had active epilepsy. Some participants met multiple management gap criteria: 31% (n = 79) of participants met a single criterion, 16% (n = 40) met two criteria, 6% (n = 16) met three criteria, and 1% (n = 3) met four criteria.

In post hoc analyses, we reviewed the EEG findings of people with staring spells to confirm whether absence seizures were the most likely final epilepsy diagnosis. Of 48 participants, 14 had epileptiform EEGs. Of these, 8 people had focal epileptiform discharges, and 6 had generalized epileptiform discharges. Among those with generalized discharges, 3 were treated with carbamazepine, 1 was treated with phenytoin, and 2 were untreated with AEDs.

3.2. Risk factors for active epilepsy and management gap

The potential risk factors for active epilepsy and meeting higher numbers of management criteria are presented in Table 3. Younger age and epileptiform discharges on EEG were predictors of active epilepsy. A higher number of years since epilepsy diagnosis and epileptiform discharges were each associated with a higher number of management criteria met.

4. Discussion

Epilepsy outcomes may be measured through both objective criteria, including medication-prescribing patterns, and subjective criteria, including quality of life reporting by PWE. We propose here that the management of care for PWE may be optimized even in setting where AEDs are readily available. Those patients who fall within the cracks of epilepsy care are considered to be part of an epilepsy management gap. In Bhutan, our study site, the management gap criteria were met by 55% of participants, while just 5% of participants met the treatment gap definition. Although this cohort was not population-based and likely represents a referral bias of cases requiring more sophisticated care, a high number of participants would be expected to achieve seizure freedom if care was optimized.

The management gap criteria, proposed in this study for future use in other resource-limited locations, therefore go beyond a “pills-to-mouths” measure of epilepsy care. The chosen criteria emphasize

Table 2
Quantification of the management gap in the cohort of Bhutanese people with epilepsy.

#	Criterion and risk group	Affected/risk group (%)	% of total study cohort affected (n = 253)
1	Criterion: active epilepsy Risk group: no AED treatment	13/18 (72)	5
2	Criterion: active epilepsy Risk group: >18 years on a subtherapeutic dose of a single AED	12/26 (46)	5
3	Criterion: treatment with carbamazepine or phenytoin Risk group: staring spells concerning absence seizures	27/48 (56)	11
4	Criterion: treatment with sodium valproate Risk group: women and girls of childbearing potential (14–40 years)	23/101 (23)	9
5	Criterion: active epilepsy Risk group: experienced seizure-related injuries	58/67 (87)	23
6	Criterion: active epilepsy Risk group: patients with QOLIE-31 score <50	86/111 (77)	34
Total	Patients meeting any of 1–6	138/253 (55)	55

AED: Antiepileptic drug. QOLIE-31: Quality of Life in Epilepsy Inventory.

common, recognized problems in epilepsy management and were selected because they are both clearly identifiable and remediable by HCWs even where resources are limited. From a policy-setting perspective, the management gap emphasizes that the provision of AEDs is not the endpoint of epilepsy management. The ILAE defines the treatment gap as "the difference between the number of people with active epilepsy and the number whose seizures are being appropriately treated in a given population at a given point of time" [8]. In population-based studies, the treatment gap is reported as the percentage of PWE who are not receiving AEDs [3,14]. The management gap therefore reflects the more realistic situation of many countries achieving an epidemiological transition and providing improved access to AEDs in their populations.

The challenges in epilepsy management identified in Bhutan likely exist in other countries, particularly in the many low- and lower-middle-income countries. In 2004, the World Health Organization (WHO) reported a median of 0.03 neurologists per 100,000 people in low-income countries and 0.74 neurologists per 100,000 in lower-middle-income countries, compared to the 2.96 neurologists per 100,000 in high-income countries [15]. Where neurological expertise is unavailable, epilepsy care falls to HCWs who have little or no formal training in epilepsy. Acknowledgment of specific criteria for epilepsy management is an opportunity for addressing presently unmet needs at the provider and health system level. Rarely, management gap criteria were influenced by demographic or clinical factors of the patients themselves.

Management priorities for children are of additional importance although they did not become specific criteria here. These include weight-based AED dosing, assessment for neurodevelopmental disorders, and evaluation of the impact of epilepsy on academic and overall functioning. Subtherapeutic monotherapy in children was not measured here since participants were not weighed. Quality of life was also not assessed in participants less than 12 years old.

Polytherapy at subtherapeutic AED doses, as reported in other countries, is a related management issue. At a tertiary care center in Southern India, 58% of patients were receiving AED polytherapy at the time of referral, 95% of whom were considered to be receiving inadequate doses [16]. This trend has been attributed to the availability of a broad range of AEDs and insufficient knowledge of current recommendations for prescribing correct doses [17]. In our cohort, 23% were taking two AEDs, and 10% were taking three or more AEDs; however, we lacked sufficient information to classify inappropriately subtherapeutic polytherapy versus medication resistance.

There are limitations of our study. Here, patient-reported outcome measures are by definition self-reported. There may be recall bias. The QOLIE-31 has not been validated in Bhutanese PWE. Antiepileptic drug levels were not available, making adherence to AEDs known only by self-report. Use of neuroimaging in routine clinical practice was not assessed because of our study design but is an important recommendation of NICE, relevant to LMICs. Incorporation of CT or MRI of the brain, particularly in PWE with seizures in spite of AED treatment and focal

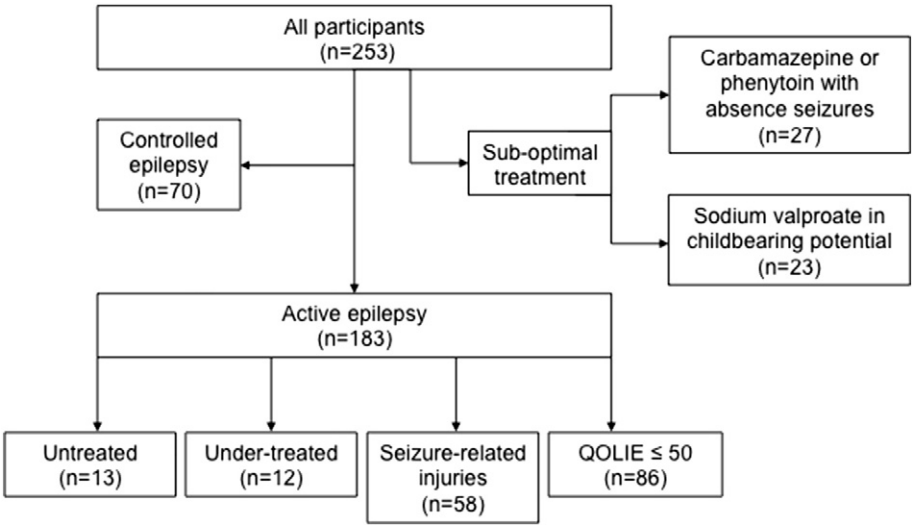

Fig. 1. Participants meeting each management gap criterion (participants could fit into multiple management gap criteria, e.g., a participant with active epilepsy could be untreated and have experienced seizure-related injuries).

Table 3
Regression models: predictors of active epilepsy and of the total number of management gap criteria met.

	Active epilepsy[a,b] (n = 236)			Total number of management gap criteria met[c] (n = 235)		
	Odds ratio	95% CI	p-Value	Odds ratio	95% CI	p-Value
Age	0.96	0.93, 0.98	0.001	1.00	0.98, 1.02	0.771
Sex	0.90	0.49, 1.66	0.741	1.46	0.88, 2.42	0.144
Years since first AED	1.03	0.99, 1.09	0.125	1.07	1.03, 1.12	0.001
Epileptiform EEG	2.77	1.35, 5.69	0.005	1.95	1.16, 3.29	0.012
City residence versus not	1.60	0.54, 4.73	0.397	0.80	0.32, 2.01	0.642

EEG: electroencephalogram.
[a] Participants missing variables of interest were removed from the regression analyses.
[b] Logistic regression.
[c] Ordered logistic regression.

epileptiform patterns on EEG, would be an important criterion to include in future studies of this nature.

The treatment and management gaps are also almost certainly underestimated in this study because of ascertainment bias. Many un- and undertreated individuals likely did not seek care or study participation for a variety of reasons. Epidemiologically, participants accessing medical care may differ from those who do not by geographic location, socioeconomic status, and/or epilepsy severity. Participants from the capital city, with superior access to medical care, as well as clinically challenging cases, who are referred to specialists, may be overrepresented. This study was referral-based and unlikely to capture the treatment gap of the entire country. Nonetheless, our study includes participants from each of the 20 districts of Bhutan, showing geographic dispersion of residence of the study participants.

Our post hoc analyses to determine whether staring spells equated to absence seizures, by review of interictal discharges on EEG, found that more participants had focal discharges than the generalized epileptiform discharges compatible with absence epilepsy. This suggests that several people with staring spells did not have absence seizures and had other forms of epilepsy. In these cases, carbamazepine and phenytoin were not contraindicated if they had just one spell type that represented focal epilepsy. However, using interictal EEGs to confirm absence seizures without photic stimulation or routine hyperventilation should be interpreted cautiously. It is possible that additional participants could have clarified the type of their staring spells if their EEGs were done with these provocative measures. It is also possible and in fact likely that several participants had multiple seizure and spell types.

In 2007, Duncan estimated the treatment gap in Bhutan to approach 80% [6]. This has likely improved since then because of development and increased communications technology in Bhutan in general. A population-based study of epilepsy in Bhutan is still needed but pragmatically difficult given the small population residing over a very mountainous terrain, including nomadic groups. In spite of this limitation, we present a scenario likely typical of many lower-income countries where the treatment gap population is “transitioning” to management and how management itself may represent the next frontier of optimal epilepsy care in low- and middle-income countries.

The implications of the management gap are practically important to each individual with epilepsy. For instance, from a meta-analysis of pregnancy registries and cohorts primarily in Europe and North America, gestational exposure to sodium valproate was associated with a 10.7% risk of a major congenital malformation [18]. This is a higher rate than what occurs with other available AEDs including those freely available in resource-limited settings. Given the higher fertility rate in most lower-income countries, the risk to women of childbearing potential who take an AED is considerable. Similarly, unintentional injuries could be substantially reduced with better seizure control. In our study, unintentional injuries related to seizures had serious consequences such as burns, amputations, disfigurement, and related physical disabilities.

Countries worldwide experience different challenges to epilepsy care. Other salient issues include limited AED options, drug stockouts, poor quality generic formulations [19,20], undue restrictions on the use of phenobarbital [21], in-country disparities in access to specialists, concentration of HCWs in the private sector [22], and high prevalence of stigmatizing traditional beliefs preventing access to care [23]. The Bhutanese health system has several strengths including universal health coverage for care and prescription drugs. Other countries are presently aiming for such care. As access to medications and healthcare workforces are improved in other lower-income countries, similar challenges surrounding management and prescribing practices may emerge and can be mitigated. In the present study, gaps in management due to unavailability of epilepsy surgery were not estimated but represent future pragmatic implications of the management gap. Notably, in 2005, epilepsy surgery was available in only 13% of low-income and 42% of lower-middle-income countries [1].

Closing the epilepsy management gap will require resources to support PWE and HCWs (Box 2). Providing current HCWs, including traditional healers, with educational materials outlining achievable standards of care aligned with accepted guideline recommendations may be an efficient way to reduce the management gap. The Interventions Guide published by the WHO's Mental Health Gap Action Programme provides one example of a practical education resource for HCWs [24]. Task sharing and shifting with nonphysician HCWs, as seen in other disciplines, may also be used in epilepsy care. Meanwhile, campaigns to increase medication uptake may exacerbate issues of inappropriate prescribing of AEDs. Unlike the treatment gap, which should ideally approach zero, the ideal management gap may be above zero, for example, because of the judicious use of sodium valproate in some women of childbearing potential in the appropriate clinical circumstances. Research and policy efforts informed only by

Box 2
Strategies to close the epilepsy management gap.

(1) Educational programs targeting current care providers, including basic HCWs and traditional healers, about the diagnosis and management of epilepsy
(2) Developing and strengthening training opportunities in the care of PWE and other brain disorders in developing countries
(3) Physician extension and telemedicine to deliver expertise to rural and remote areas
(4) Task sharing with nonphysician HCWs
(5) Improving awareness of unintentional injury among HCWs, PWE, and the public
(6) Validating outcome scales for epilepsy in local contexts

HCW: Healthcare worker
PWE: People with epilepsy

the treatment gap focus on increasing the fraction of PWE receiving AEDs; however, as our results demonstrate, medication itself does not equal management.

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Conflict of interest statement

All authors have nothing to disclose in relation to this study.

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