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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