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Medication Side Effects among People with Epilepsy Taking Phenobarbital in Zambia

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Abstract

Phenobarbital remains one of the most widely used antiepileptic drugs worldwide, yet there are limited data regarding side effects associated with its use in routine clinical care settings in low-income countries. Available data suggests that phenobarbital is as effective as other first-line drugs for treating tonic-clonic seizures, but side effect reports differ widely between high and low-income settings. A better understanding of phenobarbital side effect profile and severity in low-income settings is warranted given its role in efforts to decrease the epilepsy treatment gap. We used the Liverpool Adverse Events Profile (LEAP) to assess side effects in consecutive patients with epilepsy on phenobarbital seeking care in rural Zambia. Data regarding age, gender, medication dose, and medication adherence were also collected. T-tests and Spearman's correlation coefficient were used to assess predictors of LEAP score and medication adherence. Thirty-five patients receiving a mean dose of 2.1 mg/kg/day (SD: 2.78 mg/kg/day) of phenobarbital were assessed. All participants reported at least one side effect in the previous four weeks with a median of 6 symptoms (IQR: 4–8) and a mean side effects score of 28/76 (SD: 5.38). Over half reported sleepiness and dizziness. Memory problems and depression were also common (both 46%). Total LAEP score was not associated with age ($p=0.88$), gender ($p=0.17$), or phenobarbital dose ($p=0.13$). Medication adherence was not associated with side effects total score ($p=0.56$). Rural Zambian adults taking phenobarbital at doses recommended by the WHO report a significant number of side effects. The most common side effects reported were similar to those

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reported in high-income countries. The significant burden of phenobarbital-associated side effects in this African cohort is in contrast to data from non-randomized clinical trials in China that reported phenobarbital to be well-tolerated with few side effects. Additional investigations regarding phenobarbital side effects in routine care in low income settings is warranted.

Keywords

antiepileptic drugs; adherence; low-income setting; sub-Saharan Africa; treatment outcome; treatment gap; phenobarbital; LEAP; adverse effects

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1. Introduction

One hundred years after its introduction, phenobarbital continues to be one of the most widely used antiepileptic drugs (AEDs) worldwide. In high-income countries, phenobarbital has been replaced by newer AEDs with fewer reported adverse events [1]. Due to its cost, convenient dosing, and broad spectrum of activity, the World Health Organization (WHO) recommends phenobarbital as first-line monotherapy in resource-limited settings [2]. The cost advantages of phenobarbital are substantial. In Zambia, where most people live on less than two US dollars (USD) per day, the monthly out-of-pocket cost for phenobarbital in the private sector is about nine USD, half the cost of phenytoin and one third the cost of valproic acid. In the public sector, wholesale costs for adult dosing of phenobarbital are less than a dollar a month [3].

Research from low and high-income settings has shown that phenobarbital is as effective as other first-line AEDs for tonic-clonic seizure control [4]. However, meta-analyses suggest that phenobarbital is more likely to be withdrawn due to side effects than carbamazepine, phenytoin, or valproic acid [4, 5]. People taking phenobarbital in high-income settings experience more frequent/severe side effects than people taking carbamazepine [6], phenytoin [7], or valproic acid [6, 7] yet, observational studies in low-income settings suggest that phenobarbital is well tolerated [8, 9]. As presented in the supplementary table, randomized trials worldwide have shown mixed results.

Conflicting findings regarding phenobarbital tolerability are largely attributed to heterogeneity between studies [5]. Side effect assessment is often a secondary outcome and, as a result, little detail is provided regarding the instruments used. Also overlooked is the potential for disparate presentation of complaints based on culture [10] and acceptance of and minimization of side effects due to limited alternative therapies [8, 11]. As most AED side effects data in low-income settings are associated with efforts to reduce the epilepsy treatment gap and hence are occurring among patients with limited access to epilepsy treatment, inadvertent overestimation of phenobarbital tolerability may occur [5].

Research in upper-middle and high-income settings suggests that people obtaining AED therapy continue to report AED-related side effects even after seizures are controlled [12]. Unfortunately, there are limited data from individuals provided phenobarbital in routine clinical care in low-income settings. We assessed drug side effects experienced by people with epilepsy obtaining phenobarbital during routine clinical care in rural Zambia using a

standard instrument. We also examined predictors of phenobarbital-related side effects and medication adherence.

2. Methods

Consecutive patients presenting to Chikankata Hospital Epilepsy Care Team (ECT) who met the inclusion criteria and consented to participate were interviewed during January 2006. Chikankata Hospital is a mission hospital that provides the only source of health care for a catchment area of approximately 55,000 people in an isolated rural region of Zambia's Southern Province. The ECT consists of a neurologist in residence, on average, six months a year; a clinical officer; a ward auxiliary; and a research assistant/administrator. At the time of survey, phenobarbital was the most widely available AED and was provided at no cost to the patient. Carbamazepine and phenytoin were available as second line treatments at low cost, but both agents were infrequently used due to their limited local supply.

Individuals were eligible for study inclusion if they were at least 18 years old, on a stable dose of an AED for at least two months, and could answer questions in Tonga (the local language) or English. Written, informed consent was obtained from participants in the language of his/her choice. Side effects were ascertained using the Liverpool Adverse Events Profile (LEAP) [13]. This 19-item instrument queries the severity of common AED side effects during the four weeks prior to interview using Likert-type scales (from 1–4) with four representing a symptom that occurs “often”. A total side effect score is calculated by summing participant responses (range 19–76). The LEAP was translated into Tonga and then back-translated to ensure content validity.

Data was also collected regarding gender, age, and weight. To assess adherence, AED name, dose, number of pills collected, and last pharmacy collection date were abstracted from the patient file. Self-report of last dose taken was obtained. Patients were deemed adherent if they had taken their medication either the day prior to or the day of their appointment and if pharmacy data reflected that they were not overdue on medication collection. This approach has been used to assess adherence in this setting as serum concentrations are not available [14]. Previous research suggests that patients are comfortable confiding in the ECT research assistants as they are respected community members but do not hold positions of tribal or local governmental authority [15].

Summary statistics were performed for all interviewed patients. Two-tailed comparisons were made between total side effects score and gender, age, and phenobarbital dose (mg/kg) using t-tests and Spearman's correlation coefficient, as appropriate. T-tests were also used to examine the relationship between total side effect score and medication adherence. SAS (version 9.4, SAS Institute Inc., Cary) was used for all data analysis. A p-value of <0.05 was considered statistically significant.

Michigan State University's Biomedical Institutional Review Board (MSU BIRB) and the University of Zambia's Biomedical Research Ethics Committee (UNZA BREC) provided ethical approval of this study. The funding source played no role in study design, conduct, data, analysis, or publication.

3. Results

Thirty-nine PWE (18 female, 46%) were interviewed. Ninety percent (39/43) of individuals approached agreed to participate. Reasons for refusal were not systematically obtained. The mean age of participants was 26.4 years (SD 10.4 years). At the time of interview, all participants were on AED monotherapy. Thirty-five participants were taking phenobarbital, three were taking carbamazepine, and one was taking phenytoin. AED adherence was generally high. Twenty-nine participants (85%) had not missed a dose of their AED; only two had not taken their AED in more than one week (6%). The mean daily dose of phenobarbital was 2.1 mg/kg/day.

All participants interviewed reported at least one side effect in the four weeks prior to interview. As both carbamazepine and phenytoin were used by only four interviewed participants, further side effects analysis was limited to the 35 participants taking phenobarbital. Participants taking phenobarbital endorsed, on average, six symptoms (range 1–12). As shown in Table 1, the most commonly endorsed side effects among individuals taking phenobarbital were sleepiness (74%), dizziness (60%), memory problems (46%) and depression (46%). No participants experienced alopecia. Eleven participants (31%) reported at least one symptom “often” in the previous four weeks. Total side effects scores for participants taking phenobarbital ranged from 20–40 with a mean score of 28 (SD 5.39).

A higher side effects score for participants taking phenobarbital was not related to age ($p=0.72$), gender ($p=0.17$), dose ($p=0.53$), or medication adherence (25.8 vs 26.0, $p=0.54$). A *post hoc* power analysis indicated that with 35 participants, we had 80% power to detect a change in adherence with a difference in mean the side effects total score of 5.34 ($\sigma=5.39$).

4. Discussion

Although the data presented here is from a small consecutive sample of adults with epilepsy, it suggests that adults in rural Zambia taking phenobarbital as part of routine care at doses within the WHO recommended range (1–3 mg/kg/day) [2] experience a significant burden of phenobarbital-related side effects. All participants reported at least one side effect in the previous four weeks. The side effect profile among participants in this study (sleepiness, dizziness, memory problems, depression) are similar to those reported by people taking phenobarbital in high-income settings [6].

The number of people with epilepsy reporting side effects in this study is substantially higher than previously reported from China among participants in the China Demonstration Project who received comparable doses of phenobarbital (Zambia: 107mg, China: 120mg) [9]. As direct inquiry has been associated with increased side effects reporting [16], our population may have endorsed more side effects than participants in the Chinese study because by using the LEAP we formally inquired about more side effects. Since the Kwan et al. study aimed to assess phenobarbital efficacy, side effect reporting was limited to individuals who were adherent to treatment for three consecutive visits [17]. This may have led to underestimation of the incidence of phenobarbital-related adverse events as drug-related side effects can negatively impact adherence [18]. Lastly, Zambian participants

would have no reason to feel uncomfortable reporting side effects to our ECT interviewers as they do not hold positions of authority, official or symbolic, and did not provide participants with their phenobarbital.

Interestingly, the mean total side effects score in this Zambian population taking phenobarbital was lower than that for people with epilepsy taking newer, generally better tolerated AEDs in United States and United Kingdom (37.3 vs. 28, $p < 0.001$) [19]. This may reflect greater acceptance and potential underreporting of adverse effects in our patients who are acutely aware of the limited alternative therapies for their condition.

The findings in this study are limited by our sample size and the cross sectional study design. Although we did not systematically collect reasons why potential participants declined involvement, ongoing work with this patient population suggests that time limitations are the most commonly provided reason for refusal. We do not believe that this substantially impacted our results. We were also unable to examine side effects reported by participants taking either carbamazepine or phenytoin due their infrequent use among interviewed participants. Yet, the high burden of phenobarbital side effects identified indicate a need to further investigate AED side effects among people receiving epilepsy care in low-income settings.

There is a general consensus that decreasing the epilepsy treatment gap is necessary in low-income settings [20]. To succeed, AEDs must be accessible and patients must adhere to treatment. Medication side effects and fear of side effects are common causes of decreased adherence [21]. Accurate assessments of AED side effects among individuals initiating treatment and those on maintenance therapy are essential to understanding a key driver of poor adherence, direct AED selection, and optimize efforts to decrease the epilepsy treatment gap in low income settings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- Phenobarbital side effects among people in Zambia is high—similar to US populations.
- All participants reported 1 side effect using the Liverpool Adverse Events Profile.
- Further investigation into side effects in low-income settings is warranted.

Table 1

Side Effects Reported by People Taking Phenobarbital Using the Liverpool Adverse Events Profile (n=35)

Side Effect, number (%)	Never	Rarely	Sometimes	Often
Ataxia	28 (80)	4 (11)	2 (6)	1 (3)
Tiredness	25 (72)	6 (17)	4 (11)	0 (0)
Restless	26 (74)	8 (23)	1 (3)	0 (0)
Feelings of aggression	21 (60)	7 (20)	5 (14)	2 (6)
Nervousness	24 (69)	6 (17)	5 (14)	0 (0)
Headache	25 (71)	3 (9)	7 (20)	0 (0)
Hair loss	35 (100)	0 (0)	0 (0)	0 (0)
Problems with skin	33 (94)	1 (3)	1 (3)	0 (0)
Double/blurred vision	29 (83)	4 (11)	2 (6)	0 (0)
Upset stomach	23 (66)	6 (17)	4 (11)	2 (6)
Difficulty concentrating	21 (60)	7 (20)	5 (14)	2 (6)
Trouble with mouth or gums	33 (94)	0 (0)	2 (6)	0 (0)
Tremor	28 (80)	5 (14)	2 (6)	0 (0)
Weight gain ^a	33 (94)	1 (3)	0 (0)	0 (0)
Dizziness	14 (40)	9 (26)	8 (23)	4 (11)
Sleepiness	9 (26)	6 (17)	13 (37)	7 (20)
Depression	19 (54)	9 (26)	5 (14)	2 (6)
Memory Problems	19 (54)	5 (14)	8 (23)	3 (9)
Disturbed sleep	24 (69)	6 (17)	3 (9)	2 (6)

^aMissing response for 1 participant (3%)