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The Current Availability of Antiepileptic Drugs in Zambia: Implications for the ILAE/WHO "Out of the Shadows" Campaign

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Abstract. Recent concerns regarding antiepileptic drug (AED) availability in Zambia led us to conduct a study in the Lusaka and Southern Provinces to quantify the availability and cost of AEDs and assess determinants. Among 111 pharmacies, almost one-half did not carry AEDs ($N = 54$; 49.1%). Available AEDs were phenobarbitone (21; 18.9%), carbamazepine (27; 24.3%), valproic acid (4; 3.6%), and phenytoin (3; 2.7%). Adult out-of-pocket monthly costs ranged from US $7 to $30. Pediatric syrups were universally unavailable. Interviews revealed several barriers to AED provision, including that handling phenobarbitone (historically the most affordable AED) has become increasingly difficult because of newly enforced regulatory requirements. Personal communications with epilepsy-care providers in other low income countries suggest that this problem may be widespread. Improved enforcement of existing drug regulations may be contributing to the AED shortage. Social programs aimed at encouraging people with epilepsy to come "out of the shadows" must be preceded by improved AED access.

INTRODUCTION

Epilepsy is considered by the World Health Organization (WHO) to be one of the most cost-effective chronic conditions to treat.[1] Despite the cost-effective nature of epilepsy treatment, the epilepsy treatment gap remains > 75% in most of the developing world, where ~80% of people with epilepsy (PWE) reside, meaning that less than 25% of people with active epilepsy in the developing world are receiving treatment.[2] Even when treatment is initiated, many PWE fail to continue medications on a long-term basis. In a prospective observational study of 1,450 patients followed-up in an urban clinic in northeast India, 620 (43%) discontinued treatment within 1 year, and 80% of these individuals had more than two seizures after antiepileptic drug (AED) discontinuation. The principal reason for discontinuation of AEDs was inability to afford treatment and lack of information about consequences of non-adherence.[3]

In addition to the medical morbidity of untreated seizures, the impact of non-availability of AEDs has serious implications on the social and cognitive development of children with epilepsy. In one report from India, ~one-third of children attending urban clinics had been expelled or withdrawn from school because of their seizures, and in rural areas, 85% of children with epilepsy did not attend school.[4,5]

Many efforts are underway to bring epilepsy "out of the shadows" through community-based programs to encourage PWE to seek medical services.[6–8] One essential issue to consider before initiating such social marketing and public-education programs is whether AED treatment is actually available if/when efforts to improve care-seeking behaviors among PWE succeed. As a precursor to scaling up community-based epilepsy education programs in Zambia, we conducted a survey to assess the general availability and cost of AEDs in Zambia's Lusaka and Southern Provinces.

Anecdotally, as epilepsy care providers in Zambia, we had recently (past ~2 years) noted a persistent shortage of AEDs in our own districts, especially phenobarbitone, but were uncertain as to the underlying cause. This perception made us reluctant to expand our existing community-based activities and further motivated this study.

METHODS

Study populations. To identify as comprehensive a list of pharmacies as possible, healthcare providers with prescribing privileges [physicians and clinical officers (paramedical professionals who receive at least 3 years of healthcare training after secondary school and often practice without the direct supervision of a physician)] from the largest rural and urban healthcare facilities in two provinces (Southern and Lusaka) in Zambia were contacted through e-mail and/or by verbal interviews to name all the pharmacies that they could identify where patients could get prescription medications. Pharmacy identification was continued until saturation was evident, with no new pharmacies being identified. This comprehensive list was further cross-checked against the Zambian Pharmacy Regulatory Agency (PRA) listing of registered pharmacies. Pharmacies were categorized by ownership status (government, private, or non-governmental), urbanicity (urban or rural), and registration status with PRA (registered or not registered).

As part of drug purchasing for epilepsy clinic use, research staff members were provided with a valid prescription for a 1-month supply of each of the four most commonly used AEDs (phenobarbitone, carbamazepine, valproic acid, and phenytoin). From March to June 2009, staff members with these prescriptions attempted to obtain AEDs at each of the identified pharmacies. When the AED was not available, the person trying to obtain the medication specifically asked pharmacy staff if that AED would be available in the future. Where available, the cost per tablet and available tablet size were noted, and the monthly average cost of the medication for an adult was calculated. The consumer price for purchasing AEDs relative to the range of median wholesale buyer prices per the 2007 International Price Guide adjusted for dollar:kwacha exchange rates for March 2009 was assessed.[9]

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Six urban and six rural pharmacies stratified by ownership, urbanicity, and drug availability were selected to have their pharmacist participate in a semi-structured interview aimed at further elucidating barriers to AED stocking and provision. A senior team researcher contacted the pharmacy staff in person to request to speak with the head pharmacist. To maintain anonymity, only verbal consent was obtained, and coded identifiers were used for the pharmacies. Participating pharmacy staff were given a desktop calculator as a token of appreciation for their participation in the interviews and were assured that a final report of this work will be made available to them. Note that answers to each question potentially opened up discussions related to the initial answer. These questions were used as a starting point for an in-depth discussion with the interviewee.

Analysis. Descriptive statistics were compiled regarding characteristics of the identified pharmacies, overall and individual AED availability, and cost; χ^2 and *t* tests were conducted to assess the association between ownership or urbanicity and AED availability or cost. Before conducting the analysis, the registration-status variable and other unique identifiers were removed to protect the identities of interviewees from unregistered pharmacies (they comprised < 10% of the sample) who might be vulnerable to legal action. Thus, no analyses using the registration-status variable were conducted.

Detailed written notes from pharmacy-staff interviews were compiled and reviewed by the team. Common issues and themes relevant to AED availability and cost were identified and are presented here.

Human subjects protection. This study was approved by the University of Zambia's Biomedical Research Ethics Committee and Michigan State University's Biomedical Institutional Review Board.

RESULTS

Forty-five prescribing healthcare workers at eight institutions assisted in identifying 111 pharmacies. No additional pharmacies were identified through the PRA listing of registered pharmacies. Characteristics of the 111 pharmacies are provided in Table 1.

Almost one-half of the pharmacies carried no AED (*N* = 54; 49.1%), and 34 (30.6%) of these had no plans to stock AEDs in the future. Specific AED availability was as follows: phenobarbitone, 21 (18.9%); carbamazepine, 27 (24.3%); valproic acid, 4 (3.6%); and phenytoin, 3 (2.7%). Consumer prices were substantially higher than wholesale purchase prices (details in Table 2). Common tablet sizes were 30 mg for phenobarbitone, 200 mg for carbamazepine, 200 mg for valproic acid, and 100 mg for phenytoin. Pediatric syrups were universally unavailable. The estimated out-of-pocket monthly cost for an adult based on posted international exchange rates as of March 1, 2009 was $8.89 for phenobarbitone, $7.51 for carbamazepine, $29.88 for valproic acid, and $17.15 for phenytoin.

Table 1
Characteristics of pharmacies (*N* = 111)

Macro-level variables	*n* (%)
Urbanicity	
Urban	56 (50.0%)
Rural	55 (49.5%)
Ownership	
Government	61 (55.0%)
Non-governmental organizations	7 (6.3%)
Private	43 (38.7%)

AEDs were provided free at government facilities, but 45.9% of government pharmacies had no AED in stock. The difference in overall or individual AED availability based on ownership or urbanicity was not significant (all *P* values > 0.05) (Table 3). The cost of specific AEDs, outside of government facilities where they were provided free of charge when available, did not differ between urban and rural pharmacies where these were in stock (all *P* values > 0.05).

In conducting interviews, the lack of trained pharmacists became evident. Many pharmacies lacked any staff with formal expertise or training. Pharmacists or the managing personnel reported that stocking phenobarbitone was especially problematic because of onerous documentation and record-keeping requirements based on long-standing legislation that is being newly enforced. These regulations require a completed form to be presented to the PRA for approval delineating exactly which scheduled medication is being requested for purchase, from whom, and at what cost. All forms must be typed, and no corrections can be made to the form or it will not be accepted. After PRA authorization is obtained, the approved form must then be taken to the purchasing source at a separate, often quite distant, location. After the scheduled medication is obtained, records of the precise distribution of the medication must be kept, including number of tablets, to whom, and when. Any discrepancies in tablet receipt versus distribution or failure to keep complete records leave one open to prosecution. Concerns regarding potential punitive actions related to mishandling phenobarbitone were significant enough to inhibit and sometimes prohibit the stocking of phenobarbitone altogether, even at government facilities where the low wholesale price of this AED was otherwise appreciated. Where phenobarbitone was stocked, pharmacist interviewees noted that some additional mark-up in the wholesale price was made to try and offset the increased handling costs. Recent programs held by the WHO Expert Committee on Drug Dependence were cited as potential reasons for the recent enforcement of long-standing regulations.[10]

Private pharmacists noted that the sale of AEDs was unpredictable, because patients only come to purchase them when government facilities do not have them in stock. Hence, AEDs often expire before they can be sold. AED provision was also viewed as generally unprofitable because of little demand from patient populations with the ability to pay. Unregistered pharmacies had no avenues for purchasing scheduled medications, including phenobarbitone. Smaller government clinics and pharmacies reported that they are not given AEDs as part of their drug supplies, because nearby larger government facilities stock them; however, the named larger facilities were frequently among those that did not have AEDs in stock in our survey.

DISCUSSION

This survey of Zambian pharmacies identified limited and unpredictable AED access in two large Zambian provinces and supports clinician concerns and patient complaints that AED access has recently worsened. Similar problems have been reported for other essential medications, indicating a stark gap between policy and practice in developing regions.[11]

Table 2
AED availability and cost ($N = 111$)

	In stock day of survey	Ever stocked	Mean consumer cost for 1 month's supply for adults*	Range of wholesale cost for 1 month's supply for adults	Mean wholesale cost for pediatric syrup†
Phenobarbitone	21 (18.9%)	34 (30.6%)	$8.89	$0.29–$5.34	$0.12–$1.37
Carbamazepine	27 (24.3%)	45 (40.5%)	$7.51	$1.55–$17.79	$0.78–$8.90
Valproic acid	4 (3.6%)	10 (9.0%)	$29.88	$12.22–$14.87	$10.29–$13.24
Phenytoin	3 (2.7%)	8 (7.2%)	$17.15	$0.25–$1.29	$12.62–$17.98

*Among private pharmacies only.
†Using pediatric syrups in a 10-kg child.

Historically, phenobarbitone has been the AED most commonly used and available in Zambia because of its low cost.[12] Phenobarbitone is, however, a scheduled drug based on the United Nations Convention on Psychotropic Substances (1971).[13] Recent efforts through the WHO Expert Committee on Drug Dependence have emphasized to authorities in low- and middle-income countries the need for proper management of scheduled medications.[10,14] These well-intended efforts may play a role in the recent enforcement activities of the Zambian PRA that have had the unintended consequence of decreasing AED access. The selection of medications for inclusion in the 1971 schedule IV drug list was based on the chemical structure of the agent without consideration of the actual abuse potential in human populations. Personal communications with epilepsy-care providers in other low- and middle-income countries suggest that Zambia is probably not alone in being affected by new regulatory activities that are causing a shortage of affordable AEDs, with phenobarbitone being especially unavailable (J.W.A.S. Sander, personal communication; C.A. Schwartzmann, personal communication).

Obviously, the need to balance drug availability with proper regulatory oversight is a difficult one. The lack of trained pharmacists in our survey suggests that the human resources for appropriate management of prescription drugs are limited. Recent health-services publications have suggested that low- and middle-income countries may be able to use pharmacy services to enhance public health,[15] but where no expertise are available, this will not be possible. When AEDs are only available through private pharmacies, the cost is likely prohibitive for many PWE, because the average monthly income in Zambia is $125,[16] with median household incomes being < $2/day, and PWE as a group have a particularly low socioeconomic status.[17] In resource-poor countries like Zambia, work undertaken by physicians in developed countries is often taken over by other healthcare personnel, such as clinical officers. One might consider the need to develop formal training for pharmacy dispensers in a setting where adequate numbers of fully trained pharmacists are not readily available.

Theoretically, epilepsy care can be cost-effective in low- and middle-income countries. Chisholm,[18] among others, has concluded that the large treatment gap in resource-poor countries can be reduced considerably by scaling up the routine availability of low-cost AEDs. However, this otherwise reasonable assertion does not include the potential additional costs imposed by regulatory actions on phenobarbitone as a scheduled medication.

Table 3
Macro-level determinants of AED availability ($N = 111$)

Macro-level determinant	Availability (%)	*P* value
Ownership		
Government ($N = 61$)	33 (54.1%)	0.74
Private ($N = 43$)	20 (46.5%)	0.74
Non-governmental organization ($N = 7$)	3 (42.9%)	0.74
Urbanicity		
Urban ($N = 56$)	31 (55.4%)	0.49
Rural ($N = 52$)	25 (48.1%)	0.49

Many additional drug-access and quality issues need to be addressed urgently. The lack of safe and effective outpatient AED therapy for neonates and infants given the absence of pediatric syrups is especially concerning. In 2007, the Expert Committee on Essential Medicines added a number of pediatric dosage forms of AEDs to the list,[19,20] and there have been recent calls for better AED access for children.[21] Nevertheless, pediatric AED formulations are not presently available in Zambia, and the probability of inconsistent dosing of AEDs and potential toxicity looms large for clinicians and parents trying to divide adult-size tablets for pediatric populations, especially with AEDs that have a narrow therapeutic margin. Of course, encouraging preparation of these syrups by untrained pharmacy staff could be disastrous. Even when apparent dosing is correct, problems may remain. Recent data from Rwanda indicated that routine storage facilities for antihypertensive medications in low-income tropical settings may result in 20% of these medications having substandard content by the time of distribution.[22] We have been unable to find any data on the shelf life of common AEDs when they are stored outside of the tight specifications recommended by the drug manufacturers.

This study did not identify any macro-level determinants of AED availability or cost based on urbanicity or ownership. A *post hoc* power calculation for the availability analysis indicates that this analysis had 90% power to detect a 2.5-fold difference in availability. Because government pharmacies provide AEDs for free, the cost analysis was limited to private pharmacies ($N = 42$), and hence, the power was substantially lower for this analysis. Despite these findings, the indirect costs of accessing medications, in terms of transport costs and time, are almost certainly higher for rural PWE.

This work has several strengths and limitations. We were able to complement the quantitative survey data with qualitative interviews, but only a subset of pharmacies was included in the interview sample. To protect the identity of study participants from unregistered pharmacies, the PRA registration status variable was dropped from the dataset, and data were deidentified; therefore, we could not formally assess whether AED availability or cost was related to this characteristic, but unregistered pharmacies comprised < 10% of pharmacies identified.

It might be sufficient for only a core group of pharmacies to carry AEDs, if such pharmacies were geographically distributed and they could provide AEDs consistently. However, based on our findings, AED availability, even within a given pharmacy, is inconsistent (note the number of pharmacies

that did not have a given AED on the date of the survey but report carrying the medications at times). A repeated survey design with data on spacial distribution would be needed to clarify whether there could be a core of pharmacies identified that could reliably provide AEDs for the population. We report findings from only one African country, and within that country, we studied two provinces. However, the provinces selected were two of the three most populated, and we have some anecdotal information through personal communications with epilepsy-care providers working in other low-income regions that indicate that the problem of increasing drug regulation causing declining AED availability may be widespread.

In catchment areas with dedicated epilepsy clinics, it may be possible for local staff to assure availability of AEDs to their immediate clinic population through dedicated purchase and persistent requests to government pharmacy staff to assure timely stocking. However, large-scale, community-based efforts to encourage PWE to come "out of the shadows" must only be undertaken when adequate access to AEDs can be assured for those PWE convinced to seek care. Collaborative and intra-programmatic discussions are urgently needed within local and international governmental bodies to examine the complex realities of AED drug supplies in low-income countries and to develop processes for more affordable and accessible AED options. Otherwise, epilepsy will, indeed, remain in the shadows.

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