Mapping the availability, price, and affordability of antiepileptic drugs in 46 countries

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SUMMARY

Purpose: In low- and middle-income countries (LMICs), a large proportion of people with epilepsy do not receive treatment. An analysis of the availability, price, and affordability of antiepileptic drugs (AEDs) was conducted to evaluate whether these factors contribute to the treatment gap.

Methods: Data for five AEDs (phenytoin, carbamazepine, valproic acid, phenobarbital, and diazepam) were obtained from facility-based surveys conducted in 46 countries using the World Health Organization/Health Action International (WHO/HAI) methodology. Outcome measures were percentage availability, ratios of local prices to international reference prices, and number of days’ wages needed by the lowest-paid unskilled government worker to purchase treatment. Prices were adjusted for inflation/deflation and purchasing power parity.

Key Findings: The average availability of generic AEDs in the public sector was <50% for all medicines except diazepam injection. Private sector availability of generic oral AEDs ranged from 42.2% for phenytoin to 69.6% for phenobarbital. Public sector patient prices for generic carbamazepine and phenytoin were 4.95 and 17.50 times higher than international reference prices, respectively, whereas private sector patient prices were 11.27 and 24.77 times higher, respectively. For both medicines, originator brand prices were about 30 times higher. The highest prices were observed in the lowest income countries. The lowest-paid government worker would need wages from 1–2.6 days to purchase a month’s supply of phenytoin, whereas carbamazepine would cost 2.7–16.2 days’ wages. Despite its widespread use in LMICs, WHO/HAI survey data for phenobarbital was only available from a small number of countries.

Significance: In LMICs, availability and affordability of AEDs are poor and may be acting as a barrier to accessing treatment for epilepsy. Ensuring a consistent supply of AEDs at an affordable price should be a priority.

KEY WORDS: Epilepsy, Antiepileptic drugs, Medicines, Treatment gap, Availability, Price, Affordability, Originator brands, Generics, Pharmaceuticals, Developing countries.

Epilepsy is a common neurologic disorder accounting for 0.5% of the world’s disease burden (WHO, 2008). A recent meta-analysis provided a global estimate of 70 million for cases of life-time epilepsy (Ngugi et al., 2010). More than 80% of people with epilepsy live in resource-poor countries where the incidence of epilepsy is two to three times higher than in high-income countries (de Boer et al., 2008). People with epilepsy in resource-poor countries are about five times more likely to die prematurely than their peers in the general population; the risk is especially high among young people (Mu et al., 2011). When left untreated, epilepsy can result in multiple health problems such as fractures and burns. Epilepsy is also associated with social consequences, including human rights violations and discrimination resulting from the stigma of epilepsy (de Boer et al., 2008).

It is estimated that up to 70–80% of people with epilepsy could lead normal lives if properly diagnosed and treated (Kwan & Brodie, 2008). However, despite the availability...
of cost-effective antiepileptic drugs (AEDs), the majority of affected individuals in resource-poor settings do not receive treatment. A recent systematic review estimated that the epilepsy “treatment gap,” or the proportion of people with active epilepsy who were not receiving treatment, was >75% in low-income countries and >50% in most middle-income countries, compared to <10% in many high-income countries (Meyer et al., 2010). It has been suggested that this treatment gap results from a combination of factors, including lack of prioritization on health agendas; insufficient health care financing; health systems issues, such as inadequate skilled manpower and poor drug supply; long travel times to reach health care facilities; and cultural beliefs, including the stigma associated with epilepsy (Meinardi et al., 2001; Scott et al., 2001; Mbuba et al., 2008).

The availability and affordability of medicines are two key factors that affect patients’ access to treatment. A study of the availability and prices of AEDs carried out in southern Vietnam showed that only 57% of the public and private pharmacies surveyed had AEDs available. Monthly treatment costs ranged from US$ 3.30 for carbamazepine 200 mg to US$ 22.50 for valproic acid 200 mg (Mac et al., 2006). A second study conducted in Zambia found that nearly one-half of the government, private, and nongovernmental organization (NGO) pharmacies surveyed did not carry AEDs. Pediatric syrups were universally not available. Adult out-of-pocket monthly costs ranged from US$ 7.51 for carbamazepine to US$ 29.88 for valproic acid (Chomba et al., 2010).

Although the preceding two studies provide some insight into the magnitude of the availability and cost issues around AEDs, both have been conducted on a subnational level, limiting the generalizability of the results. Further, differences in the methodologies make it difficult to compare results across studies. The purpose of this article is, therefore, to conduct an analysis of the availability, price, and affordability of AEDs across a range of primarily low- and middle-income countries.

Methods

Primary data source

Data on the availability, price, and affordability of AEDs were obtained from facility-based surveys conducted using a standard method (WHO & Health Action International (HAI), 2008; Cameron et al., 2009). In the surveys, the availability and prices of approximately 50 medicines were collected during visits to a sample of medicine outlets in the public sector (primary health care facilities and hospital outpatient services) and private sector (pharmacies and licensed drug stores). Government procurement prices were also collected. The surveys included standard medicines collected in all surveys to enable international comparisons as well as supplementary medicines selected locally for their clinical relevance (WHO & HAI, 2008). For each medicine, a fixed dosage form and strength were used, and data were collected for both the originator brand first authorized worldwide for marketing (normally as a patented product), and the lowest priced generic equivalent found at each facility. In WHO/HAI surveys, generic medicines are defined as pharmaceutical products intended to be interchangeable with the originator brand product, manufactured without a license from the originator manufacturer, and marketed after the expiry of patent or other exclusivity rights (WHO & HAI, 2008). The survey was conducted by trained data collectors, following which data were double-entered into a preprogrammed Excel workbook (Microsoft Corp., Redmond, WA, U.S.A.) that allowed for standardized analysis. Availability was reported as the percentage of outlets in which individual medicines were found on the day of data collection. Prices were expressed as median price ratios (MPRs), calculated as ratios of median local unit prices to Management Sciences for Health (MSH) international reference prices (Management Sciences for Health, 2010). MSH prices represent recent procurement prices offered by suppliers to developing countries. Median prices were also used to estimate treatment affordability, calculated as the number of day’s wages required for the lowest-paid government worker to purchase a course of treatment.

Secondary data analysis

Composite data on medicine availability and price (e.g., median price ratios, percentage availability) were extracted from the HAI global database of survey results for individual medicines summarized across medicine outlets (HAI, 2010). Affordability data were obtained from individual survey workbooks.

Survey inclusion criteria

All surveys that included data on the AEDs at the time of data extraction in February 2011 were included in the analysis. Where surveys were repeated in a country, the most recent dataset was used. In countries where multiple surveys were carried out in subnational regions (India, China, and Sudan), results were averaged.

Selection of antiepileptic drugs

The AEDs included in this study were phenytoin 50- and 100-mg tablets; phenobarbital 15-, 30-, and 100-mg capsules/ tablets and 200 mg/ml injection; carbamazepine 100- and 200-mg capsules/tablets; valproic acid 200-mg capsules/tablets; and diazepam 5 mg/ml injection. The selection of individual AEDs was based on the data available and the inclusion of these medications on the WHO Model List of Essential Medicines (WHO, 2011).

Availability of antiepileptic drugs

The mean availability of both the originator brand product and the lowest-priced generic equivalent were calculated for each AED in both private and public sectors.
Because individual countries surveyed different strengths of each AED based on local usage patterns, results for different strengths were combined to determine average availability of each AED across the countries studied. Average availability stratified by World Bank country income level (World Bank, 2011) was also analyzed for carbamazepine and phenytoin, although given the relatively small number of countries in each income group, results are descriptive only. Other AEDs in the study had insufficient country data to allow for disaggregation by income level.

**Price of AEDs**

Price data were adjusted to increase comparability across countries as recommended by the WHO/HAI methodology WHO & HAI, 2008 methodology and as reported elsewhere (Cameron et al., 2009; van Mourik et al., 2010). Different sources of exchange rates used in the surveys were standardized against International Monetary Fund rates, and the Consumer Price Index (CPI) (International Monetary Fund, 2007) was used to adjust prices for inflation/deflation. Patient prices (i.e., retail prices) were also adjusted for purchasing power parity (PPP) (International Monetary Fund, 2007), to account for differences in purchasing power of individual currencies.

The mean MPRs were calculated for each AED, for both originator brands and lowest-price generic equivalents in each of the public and private sectors. In the price analysis, different strengths were kept separate as price levels would be expected to vary according to medicine strength. MPRs were also analyzed according to World Bank income group for phenytoin and carbamazepine (World Bank, 2011). Surveys that provided price data on both the originator brand and the lowest-price generic equivalent of a given AED were identified so that any price differential between brands and generics (“brand premium”) could be analyzed.

**Affordability of AEDs**

Treatment affordability was estimated as the number of days’ wages that the lowest-paid government worker would need to purchase a month’s supply of AEDs. The daily wage of the lowest-paid government worker was identified in each country survey. Monthly treatment costs for AEDs were estimated based on the defined daily doses (DDDs) published by the WHO Collaborating Centre for Drug Statistics Methodology (WHO, 2009). A DDD is defined as the assumed average maintenance dose per day for a drug used for its main indication in adults.

**RESULTS**

A total of 46 countries were included in the analysis, corresponding to 57 surveys conducted between 2003 and 2010 (Table 1). Of the five study medicines (carbamazepine, phenobarbital, phenytoin, valproic acid, and diazepam), survey data were most frequently available for carbamazepine and phenytoin, particularly 200- and 100-mg strengths, respectively. Results, therefore, focus primarily on these two medicines.

**Availability of AEDs**

The availability of AEDs in the public sector was <50% for all medicines except diazepam injection (Table 2). The average availability of generic carbamazepine and phenytoin was 45.3% and 37.7%, respectively. In the private sector, the availability of oral AEDs (42–70% for generics) was consistently higher than in the public sector, whereas private sector availability of injectables (12–43% for generics) was lower than in the public sector. Generic AEDs were generally more available than their corresponding originator brands in both the public and private sectors; however, in the private sector the availability of originator brand phenytoin (48.7%) was slightly higher than that of generic equivalents (42.2%).

Analysis of medicine availability by World Bank Income Group showed that in low-income countries, generic phenytoin and carbamazepine were each available in about one third of the public sector facilities surveyed (data not shown). In the private sectors of low-income countries, availability was slightly higher but was still <50%. For some products (e.g., generic phenytoin and originator brand carbamazepine in the public sector and originator brand phenytoin in the private sector), availability increased with increasing country income level.

**Price of AEDs**

Public sector procurement prices for generic carbamazepine and phenytoin were on average 1.56 and 2.53 times the

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**Table 1. Countries included in the analysis**

<table>
<thead>
<tr>
<th>Country Group</th>
<th>Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-income countries (12)</td>
<td>Burkina Faso, Chad, Democratic Republic of Congo, Ethiopia, Ghana, Kenya, Kyrgyzstan, Mali, Tajikistan, Tanzania, Uganda</td>
</tr>
<tr>
<td>Lower-middle income countries (22)</td>
<td>Bolivia, Cameroon, China,* Congo, Ecuador, El Salvador, India,* Indonesia, Jordan, Mongolia, Morocco, Nicaragua, Nigeria, Pakistan, Philippines, São Tomé and Principe, Syria, Sudan,* Thailand, Tunisia, Ukraine, Uzbekistan, Yemen</td>
</tr>
<tr>
<td>Upper-middle income countries (9)</td>
<td>Brazil, * Colombia, Fiji, Iran, Kazakhstan, Lebanon, Malaysia, Peru, South Africa*</td>
</tr>
<tr>
<td>High Income countries (3)</td>
<td>Kuwait, Oman, United Arab Emirates</td>
</tr>
</tbody>
</table>

*Average of three provincial surveys conducted in Shaanxi, Shandong, and Shanghai. 
*Average of seven state surveys conducted in Chennai, Tamil Nadu, Haryana, Karnataka, Maharashtra (12 districts), Maharashtra (four regions), Rajasthan and West Bengal. 
*Average of four state surveys conducted in Ghadarif, Khartoum, Kordofan, and North Kordofan. 
*Rio Grande do Sul State. 
*C Gauteng province.
international reference prices, respectively, whereas the prices of originator brands were 6.19 and 5.19 times higher (see Appendix S1). Data also showed that diazepam injection (available for only three countries) was being procured competitively at prices 13% lower than international reference prices.

In countries where patients pay for medicines in the public sector, the PPP-adjusted patient prices of generic carbamazepine and phenytoin were 4.95 and 17.50 times higher than international reference prices, respectively (Table 3). Originator brand products cost even more, although data were limited. Some data were also available on the price of injectable AEDs in the public sector, with phenobarbital and diazepam costing approximately four and five times more than international reference prices, respectively. When the prices of originator brands and their lowest-priced generics were compared in countries reporting prices on both product types, it was found that originator brand carbamazepine and phenytoin cost 2.4 and 2.8 times more, respectively, than their lowest-priced generic equivalents (data not shown).

In the private sector, the PPP-adjusted patient prices of generic carbamazepine and phenytoin were 11.27 and 24.77 times higher than international reference prices, respectively (Table 3). For both medicines, originator brand prices were more than 30 times higher than international reference prices. Originator brand carbamazepine and phenytoin cost 3.1 and 2.1 times more, respectively, than their lowest-priced generic equivalents (data not shown).

Analysis of private sector patient prices by World Bank country income level found that PPP-adjusted patient prices of generic phenytoin were comparable in low- and lower-middle income countries, and were about two times more than in upper-middle income countries (Fig. 1A). No trends could be identified between country income level and price level for originator brands, possibly owing to the small number of countries in each income level. For both originator brand and generic carbamazepine, an inverse relationship was found between MPR and country income level (Fig. 1B). That is, medicine prices decreased with increasing income level, particularly for originator brand products.
Affordability of AEDs

Epilepsy treatment with phenytoin was found to cost the lowest-paid government worker 1–2.5 days’ wages depending on the sector and product purchased (Table 4). Lowest-price generic carbamazepine was found to cost the lowest-paid government worker 2.7 and 5.2 days’ wages in the public and private sectors, respectively, whereas the originator brand required 10.3 and 16.2 days’ wages, respectively. In countries for which data on both carbamazepine and phenytoin were available, carbamazepine was consistently less affordable than phenytoin. In the private sector, treatment with generic carbamazepine was double the cost of the equivalent treatment using generic phenytoin, whereas treatment with originator brand carbamazepine cost 3.8 times more than the equivalent treatment with originator brand phenytoin (data not shown).

**Discussion**

The results of this study show that the availability of AEDs in low- and middle-income countries is poor. The average availability of generic AEDs in the public sector was <50% for all medicines except diazepam injection, the relatively high availability (79%) of which may be due to its use for treatment of acute seizures. The low availability of AEDs in the public sector, where the poor seek care, suggest that access to AEDs may be inequitable in that the poor may be particularly disadvantaged in terms of their access to AEDs. In the private sector the availability of oral AEDs was higher than in the public sector, but was still inadequate. Because epilepsy management requires sustained treatment with AEDs to avoid seizures and other health and social sequelae, the low availability...
found no clinical difference in randomized clinical trials, of studies comparing brand-name AEDs to generic drugs and against generics (Moore et al., 2010). A meta-analysis financial considerations and conflicts of interest both for and generic AEDs has risen in prominence recently; con-

shifting a proportion of the originator brand products pur-
achased to lower-priced, quality-assured generics is another possibility given that epilepsy is a chronic disease requiring life-
longetreatment that is not amenable to short-term financial coping strategies such as borrowing or selling assets. In addition, the affordability metric used in this study does not include other treatment costs such as physician consultation fees, which would render treatment even more unaffordable. Furthermore, for the large segments of developing country populations earning substantially less than the lowest-paid government worker, treatment would be even less affordable than reported here.

Because public sector procurement prices were found to be higher than international supplier prices, it may be possible to improve purchasing efficiency, for example, through price negotiation with manufacturers or national pooled procurement. A previous study has shown that many low- and middle-income countries are able to achieve medicine procurement prices that are equal to or lower than MSH reference prices (Cameron et al., 2009). Shifting a proportion of the originator brand products purchased to lower-priced, quality-assured generics is another strategy for improving availability of AEDs at public facilities. The issue of the interchangeability of brand-name and generic AEDs has risen in prominence recently; concerns about drug quality and patient safety interact with financial considerations and conflicts of interest both for and against generics (Moore et al., 2010). A meta-analysis of studies comparing brand-name AEDs to generic drugs found no clinical difference in randomized clinical trials, although observational studies indicated differences in health services utilization (Kesselheim et al., 2010). In addition to availability and affordability, the quality of AEDs is another important consideration, especially given their narrow therapeutic index and the resulting risk of loss of efficacy and/or toxicity. One cross-sectional study from Mauritania found that of 146 samples of phenobarbital collected from 45 pharmaceutical stores, 14% were of sub-standard quality (Laroche et al., 2005). AEDs require stringent regulatory control including the capacity to ensure quality to allow the most cost-effective medicines to be used while minimizing the risks of adverse events and breakthrough seizures (Sankar & Glauser, 2010). In an effort to ensure that price data are collected for medicines that are of assured quality, the WHO/HAI survey methodology only collects data on registered products circulating in regulated pharmaceutical channels. As such, variation in quality is not likely to be a significant factor in the results presented in this study.

The results of this study are subject to certain limita-
tions, the most significant of which is the small number of countries with data on certain important AEDs such as phenobarbital. Phenobarbital the most widely used AED in the developing world (Kwan & Brodie, 2004), is included on the essential medicine list of nearly all low-income countries (96%) (WHO et al., 2005), and has been previously reported as the least expensive AED (Kwan & Brodie, 2008). As this analysis was based on existing WHO/HAI survey data, it was not possible to obtain additional information on the availability and price of phenobarbital, but given its importance as a first-line treatment option, this should be a priority for future research. Conversely, the large volume of data on carbamazepine and phenytoin compared to other AEDs can be explained by the fact that until 2008 these agents were recommended for inclusion in all WHO/HAI surveys. This study is also limited in that availability results from WHO/HAI surveys reflect the availability of individual products on the day of data collection and not averages over time. Given that the treatment of epilepsy depends upon the continuous supply of AEDs, it would have been useful to have data on the consistency in supply over time, particularly in the public

<table>
<thead>
<tr>
<th>Sector</th>
<th>Product type</th>
<th>Carbamazepine 200-mg cap/tab (n)</th>
<th>Phenytoin 100-mg cap/tab (n)</th>
<th>Phenobarbital 300-mg cap/tab (n)</th>
<th>Phenobarbital 100-mg cap/tab (n)</th>
<th>Valproic acid 200-mg cap/tab (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Public</td>
<td>Originator brand</td>
<td>10.34 (4)</td>
<td>1.05 (2)</td>
<td>ND (0)</td>
<td>ND (0)</td>
<td>ND (0)</td>
</tr>
<tr>
<td></td>
<td>LPG</td>
<td>2.70 (14)</td>
<td>1.58 (10)</td>
<td>ND (0)</td>
<td>ND (0)</td>
<td>ND (0)</td>
</tr>
<tr>
<td>Private</td>
<td>Originator brand</td>
<td>16.17 (35)</td>
<td>2.59 (18)</td>
<td>ND (0)</td>
<td>3.00 (1)</td>
<td>7.76 (1)</td>
</tr>
<tr>
<td></td>
<td>LPG</td>
<td>5.23 (32)</td>
<td>2.43 (24)</td>
<td>0.88 (1)</td>
<td>ND (0)</td>
<td>ND (0)</td>
</tr>
</tbody>
</table>

*cap/tab, capsule/tablet; n, number of countries; LPG, lowest-price generic; ND, no data; DDD, defined daily dosage.*
sector; however, these data were not collected as part of the WHO/HAI surveys used in this analysis. Availability results are also specific to the individual formulation and strength included in the survey; the availability of other common strengths of the same medicine is unknown. However, medicines included in the surveys are selected to reflect medicines commonly used worldwide as well as those selected nationally based on disease and consumption patterns, and should therefore provide a reasonable estimate of availability. An additional limitation was the scarcity of data related to injectable and pediatric formulations. In relation to the affordability metric, it should be noted that results vary as a function of medicine price but also national wage levels. Differences in the interpretation of the “lowest-paid government worker” may have led to some variation in results across countries. In addition, the defined daily doses used to calculate affordability are estimates only, as the doses for individual patients and patient groups (e.g., children) vary.

Despite these limitations, this study raises important concerns about the availability and affordability of AEDs in low- and middle-income countries, including possible over-reliance on higher-cost originator brand products. Reducing the cost of effective medications and improving their supply are part of the top five grand challenges for mental, neurologic, and substance use disorders (including epilepsy), that should serve as a starting point for immediate research and prioritization of policies (Collins et al., 2011). Treatment with AEDs has been shown to be cost-effective, and their scale-up to an 80% coverage rate could reduce the global burden of epilepsy by 36% (Chisholm and WHO-CHOICE, 2005). Efforts to improve the availability and affordability as well as quality of AEDs are therefore warranted. To this end, greater attention should be given to rational selection, regulatory issues, and measures to ensure adequate and sustainable financing of AEDs. Supply and distribution should be assessed to analyze barriers and facilitators and to identify possible gains in efficiency. Implementation of epilepsy guidelines, together with advocacy and education targeted at health care providers and patients, are needed to ensure that the most cost-effective treatments are used. A step-wise approach to treatment should be adopted, with the use of more costly treatments on an as-needed basis.

Epilepsy is one of the noncommunicable diseases (NCDs), which have historically received little attention on health and development agendas (Strong et al., 2005; Yach et al., 2006). For example, a recent study showed that in low- and middle-income countries, medicines used for NCDs were significantly less available than those for acute illness (Cameron et al., 2011). The study also found that the availability of AEDs was lower than medicines used for other NCDs such as hypertension. There is substantial evidence to suggest that epilepsy is associated with high mortality and premature death with significant economic burden. Epilepsy should therefore be recognized as a neglected NCD that requires greater priority in low- and middle-income countries.

**Conclusion**

Previous studies have quantified the epilepsy treatment gap in low- and middle-income countries and have found this to be substantial. This study shows that the availability and affordability of AEDs is suboptimal and may act as a barrier to accessing treatment for epilepsy.

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**Disclosure**

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We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

**Additional Contributors**

AC contributed to study design, data analysis, data interpretation, and preparing the first draft of the manuscript. AB was involved in data analysis, data interpretation, and preparing the first draft of the manuscript. TD contributed to conceptualization, study design, data analysis, data interpretation, and preparing the first draft of the manuscript. SH, SLM, AMT, and SS were involved in study design and data interpretation. All authors contributed to critical revisions of the manuscript and approved the manuscript.

**References**


