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Review

Interventional programs to improve therapeutic management of people with epilepsy in low- and middle-income countries

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ABSTRACT

Objective: To assess the current status of initiatives carried out in developing countries to improve therapeutic management of people with epilepsy.
Methods: A literature review was performed in 2015 to identify and analyze interventional programs carried out in countries with low- and middle-income economies. Electronic databases were reviewed with no time restriction. Each intervention was categorized according to the level of evidence achieved (A: blind randomized controlled trial, B: randomized controlled trial, C1: randomized trial, C2: controlled trial, D: prospective cohort, E: retrospective evaluation).
Results: A total of 46 intervention projects were identified, 13 with no quantitative assessment. The 31 remaining projects were carried out in 18 countries, 52% (16) in Africa, 42% (13) in Asia, and 6% (2) in Latin America. Among those, 13% (4) were level B, 3% (1) C1, 6% (2) C2, 74% (23) D, and 3% (1) were level E. The effectiveness of the intervention, assessed by the efficacy of antiepileptic drugs, was the primary objective in 81% (25). People with epilepsy were on average seizure-free in 44.6% ± 14.4% of cases at one year, ranging from 25.0% to 78.4%. At two years, on average 50.9% ± 29.7% are seizure-free, ranging from 4.6 to 92.7%. The median compliance was 79.3% with a minimum of 21.6% and a maximum of 100.0%.
Discussion: No blind randomized controlled trial has been used to assess the efficacy of a program to improve access to antiepileptic drugs (AEDs) in developing countries, and the level of evidence was globally low. Phenobarbital remains the AED predominantly used in programs. Adherence to treatment management has been pointed out to be a key element in the success of a program, sometimes not sufficiently considered. Monthly supply of AEDs, at specific and community level, reducing the costs and time spent traveling, appeared to be the most effective strategies. Homogenization and standardization of evaluation practices of programs to improve the management of epilepsy in resource-limited settings would lead to comparison and meta-analysis which would ultimately improve strategies of support for not only epilepsy but also other noncommunicable diseases in developing countries.

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1. Introduction

Epilepsy is a chronic noncommunicable neurological disorder affecting approximately 70 million people, of whom nearly 85% live in low- and middle-income countries (LMICs) [1]. This represents 0.5% to 1% of the total global burden of morbidity and mortality [2]. In industrialized countries, the incidence is about 50 per 100,000 cases per year [3], and the prevalence is 7 per 1000 cases per year (2.7 to 17.6) [4]. Epidemiological evidence suggests material differences in developing countries. In sub-Saharan Africa, the average incidence is 80 per 100,000 cases per year and the average prevalence is 13 per 1000 cases per year, as determined by door-to-door monitoring studies [5]. The estimated number of cases is greater among children and young adults and in rural areas [6].

Effective management of epilepsy involves the use of antiepileptic drugs (AEDs), as drug-resistant forms account for 20 to 30% of

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cases [7]. To date, 27 different AEDs with a wide range of dosages and formulations (tablet, capsule, parenteral solution, syrup, immediate or modified/extended forms, etc.) have been introduced, along with formulations for various routes of administration (oral, buccal, parenteral, rectal). This variability allows for optimal individual adaptation of the treatment of epilepsy.

Different AEDs are distinguished not only by their mechanisms of action, but also by their safety profiles. In fact, AEDs as a class have many adverse effects and drug interactions. They have narrow therapeutic ranges, and many require therapeutic drug monitoring (TDM).

In developing countries, the provision of care is extremely poor, and only the following first-line major AEDs are prescribed: phenobarbital, carbamazepine, sodium valproate, phenytoin, and less frequently diazepam, ethosuximide, and clonazepam. These AEDs (with the exception of clonazepam) are on the list of essential drugs published and updated every two years by the World Health Organization (WHO). Additional problems relate to availability, accessibility and low quality drugs. Few different dosages and formulations are available and accessible. One of the major causes of low availability is the cost of treatment, which is very high for this class of drugs, particularly for later generation AEDs.

In 1997, the WHO, the International League Against Epilepsy (ILAE), and the International Bureau against Epilepsy (IBE) promoted a worldwide campaign entitled "Out of the Shadow" with the main objectives of sensitizing people to the disease and improving the care of patients living with epilepsy (PWE). Several projects have been developed to reduce the treatment gap (proportion of PWE who need an AED but do not receive any) [8]. Depending on the socioeconomic context, the treatment gap (TG) in LMICs varies between 25% and 100%. In Africa, nine out of ten people do not have access to treatment, compared to only 10% in industrialized countries [8–12]. A meta-analysis conducted by the WHO in 2010 reported a treatment gap of over 75% for low-income countries, with even larger proportions in rural areas [13].

Questions arise regarding the actual situation and initiatives to improve the management of epilepsy in LMICs. What methods have been implemented to improve the management of PWE and to decrease the TG? Have they been evaluated? Which strategies were the most appropriate, under which conditions? The main objective of the present study was to provide an overview of intervention programs aimed at improving the drug management of PWE in LMICs. The secondary objectives were to describe these programs (study design, research objectives, judgment criteria, etc.), classify them by level of evidence, and analyze their main results.

2. Method

2.1. Databases and keywords

A literature review was carried out with no time restrictions, including only items published in English, French, Spanish, or Portuguese. The following electronic databases were reviewed independently: ScienceDirect (publisher, Elsevier), Medline (via PubMed interface), Pascal, Public Health Database (BDSP, based on CNRS), SciELO (Scientific Electronic Library Online), LILACS database (comprehensive index of scientific and technical literature of Latin America and the Caribbean), LIPECS database (Literatura Peruana en Ciencias de la Salud, Peruvian Literature in Health Sciences), and the internal database of the Institute of Neurological Epidemiology and Tropical Neurology (www.unilim.fr/ient/base-bibliographique-de-l-ient/). Each keyword belonged to MeSH (Medical Subject Headings). The method has been adapted to other databases. Keywords combinations were ("Program Evaluation"[Mesh] OR "Health Surveys"[Mesh]) AND "epilepsy/drug therapy"[Mesh Terms]; ("Program Evaluation"[Mesh] OR "Health Surveys"[Mesh]) AND "epilepsy/drug therapy"[Mesh Terms] AND "Developing countries"[Mesh]; "Developing countries"[Mesh] AND "epilepsy/drug therapy"[Mesh Terms]; ("Program Evaluation"[Mesh] OR "Health Surveys"[Mesh]) AND "epilepsy"[Mesh] AND "developing countries".

For each algorithm of keywords, the term "developing countries" was replaced successively by each country (n = 139) in the categories low income (LIC, n = 34), intermediate income, lower bracket (LMIC, n = 50), and intermediate income, upper bracket (UMIC, n = 55) as classified by the World Bank in 2015.

2.2. Criteria for inclusion of intervention programs

The criteria for study inclusion covered all publications without restriction in type (original article, editorial, conference summary, oral communications, and posters but excluding reviews of the literature on the subject) reporting the efficacy results of an interventional program for PWE (across all forms of epilepsy). To be included the purpose of the program's intervention had to improve the drug management of people with epilepsy by using AEDs. Other aspect of the management of epilepsy such as diagnosis, monitoring, etc., have not been considered in this review. The program could focus on epilepsy alone or be wider, but had to have a component dedicated to the management of PWE. To be included in this review, quantitative data, even partial, regarding the effectiveness of the program were required.

2.3. Endpoint and variables of interest

After the identification of interventional programs, a descriptive analysis and classification by level of evidence was undertaken. It shows five types of studies, classified from A to E, according to decreasing strength (Table 1).

For each program included, the following variables were collected in the following ad hoc form: country, date of publication, journal of publication, antiepileptic drug(s) concerned, size of the study population, study design, research objectives (primary and secondary), primary and secondary endpoints, monitoring duration, number of subjects lost on follow up (people whose fate is unknown and for whom the endpoint is unavailable), main results, and statistical methods. The type of study area (rural or urban) and the level of health facilities that supported the program (primary, secondary, tertiary) were also noted. The WHO definitions of rural and urban areas were used. A rural area (village) is located outside a city or metropolitan district and considered underdeveloped in terms of infrastructure and specialized services. An urban area (city, district) is a developed location planned to be autonomous in terms of health services. Health facility levels were those recommended by the WHO: the primary level (center of primary health care, primary point of contact for patients with a health professional), secondary (district referral hospital, the first level hospital of a district or a defined geographical area containing a defined population), and tertiary (general and specialized hospitals).

Qualitative and quantitative variables were descriptively analyzed using position indexes (mean, median, and frequency) and dispersion (variance, standard deviation, range). Statistical analysis was conducted using STATA v12 software (Stata Corp., College Station, TX).

3. Results

3.1. Studies selected by the literature review

The literature review identified a total of 1073 relevant articles. A flow chart (Fig. 1) illustrates the selection process, which yielded 47 that were eligible for analysis.

For nine cases (20%) no quantitative results about the effectiveness of the programs were provided, these publications were not selected for the final analysis. Six publications providing program results that did not concern effectiveness were also not taken into account. Finally,

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