

# Epilepsy, diagnostics and treatment

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This evidence brief provides a summary of management of epilepsy, including diagnostics, acute stabilization and long-term management with generic antiepileptics, with a particular emphasis on parameters used in *FairChoices: DCP Analytics Tool* (FairChoices). This includes basic psychosocial support, advice, and follow-up, and anti-epileptic medication.

Table 1: Epilepsy interventions in FairChoices

NEUR01-01 Diagnosis	Epilepsy diagnosis
NEUR01-02 Acute stabilization	Psychosocial support, advice, follow-up, Phenobarbital + diazepam
NEUR01-03 Long term management	Psychosocial support, advice, follow-up, Phenobarbital/carbamazepine

## Model assumptions

Table 2: Summary of model parameters and values used in FairChoices – DCP Analytical Tool

Population:	All prevalent cases of <i>ideopathic epilepsy</i> , both genders, all ages (100% assumed to need long term management and 40% need acute treatment of seizure annually)
Intervention	Long term management (Phenobarbital 100 mg o.d.) Acute treatment (Diazepam 10mg - 1 line (65% of cases), phenobarbital 100 mg - 2. line (in 35% of cases))
Comparator	No intervention
Outcome	Disability weight (health related quality of life) and mortality
Effect	Long term management are assumed to reduce Disability / improve HRQoL by 80% (use upper end of effect estimate above) and acute management of seizures to reduce mortality by 100%* Diagnostics has no direct health benefits, but needs to be implemented alongside antiepileptic medications
Unit cost**	Diagnostics: 2,05 US\$ LIC; 5,87 US\$ LMIC Acute stabilization of seizures: 8,26 US\$ LIC; 19,54 US\$ LMIC Long term management: 5,11 US\$ LIC; 10,89 US\$ LMIC

\* Annegers et al. (1979); Goodridge, et al. (1983); Placencia et al. (1994); Cockerell et al. (1995); Strand et al. 2016; Tudur Smith et al. (2009)

\*\* Annual cost per treated patient, 2021 currency, see cost assumptions and calculations below

## Description of condition and intervention

Epilepsy is a neurological disease characterized by seizures due to abnormal electrical brain activity. Epileptic seizures are most often categorized in terms of partial (/focal) onset seizures, and in the vast majority of the cases (70%) as generalized seizures. The seizure types often include motor symptoms such as atonic, tonic, and/or clonic seizures, or non-motor symptoms such as absence, change in sensation or autonomic function (Howlett, 2012, see table 1 in the appendix). Epilepsy can be genetic or acquired. The manifestation usually peaks before the 20<sup>th</sup> year of life or after 60 years of life due to the increased risk of stroke/brain trauma in the latter group. For the majority of cases of epilepsy in Africa, the etiology remains unknown (Howlett, 2012).

### Diagnosis

Epilepsy can be diagnosed if the health care worker witnesses a seizure, however this only occurs quite seldom. Without observing a seizure, epilepsy can be diagnosed through interviews with the patient, or close family or partner. A patient can be examined to assess if there are signs of epilepsy (such as tongue biting) and ideally a neurological assessment is performed to assess overall neurological functioning (Howlett, 2012). In high income countries (HIC) diagnosis is usually made using additional diagnostic methods. One of these methods is an electroencephalogram (EEG) that measures electrical brain activity. Other types of imaging methods, such as CT-scans or X-rays, as well as spinal taps or MRI can rule out other possible abnormalities or infections, such as meningitis. However, in LLMIC these types of diagnostic methods are predominantly not an option (Howlett, 2012).

Studies are limited on how the different types of epilepsy are distributed in (East) Africa. Due to limited access to neurologists and electroencephalographic devices, generalized tonic-clonic seizures are likely to be more recognized than other types of epilepsy and therefore represented more often in research studies than generalized partial seizures, (Ba-Diop et al., 2014). Limited literature can be found for the prevalence of the other subtypes of epilepsy in Africa. Table 2 shows some key epidemiologic parameters for epilepsy.

*Table 2: key epidemiological characteristics of ideopathic epilepsy global/East Sub-Saharan Africa*

What happens?	Active idiopathic epilepsy	Seizure free treated idiopathic epilepsy	Certainty of evidence	Source
<i>Idiopathic epilepsy</i>				
Epilepsy-related morbidity low-middle SDI, age standardized prevalence	326,6 per 100 000	34,5 per 100 000	High	GBD 2016 study
Disability (YLDs) low-middle SDI, age standardized prevalence	108,3 per 100 000	1,6 per 100 000	High	GBD 2016 study

### Socio-economic burden of epilepsy in LLMICs

Patients diagnosed with epilepsy often are misunderstood and experience high levels of stigmatization, as epileptic attacks viewed as possession by evil spirits or as an infectious disease with a possibility of spreading to the community. This results in isolation and discrimination by the community, and deprivation of rights from insurance companies (Ba-Diop et al., 2014). Consequently, patients might refuse to seek care

or treatment, keeping the stigmatization sustained. This broadens the already existing treatment- and quality gap, maintains the high burden of disease, and the economic burden that is inextricably linked to this (Patel et al., 2016).

### *Treatment of epilepsy*

There is a treatment gap for epilepsy in LLMIC. Epilepsy is treated by anti-epileptic drugs (such as phenobarbital, or carbamazepine), but these drugs are not always consistently available (Patel et al., 2016). WHO-Choice estimates show that the accessibility and availability of antiepileptics is less than 50% in LLMICs. Around 73% of LLMICs use primarily out-of-pocket funding for these drugs. Providing a cost-effective alternative for antiepileptics can reduce mortality and disability by 60% (Strand et al., 2016). One health economic evaluation of antiepileptics conclude that incremental cost-effectiveness rates of first line drugs (like phenobarbital or carbamazepine) may be below the willingness to pay threshold in India (Megiddo et al., 2016), and WHO found similar results in 9 low-income regions worldwide (Evans et al., 2005).

Reducing the discrimination and stigmatization, as well as focusing on optimization of policy to improve accessibility to medication can lead to both a disease reduction as well as reduce high economic burden. Antiepileptic drug treatment is effective on a broad spectrum on controlling various types of seizures. WHO recommends phenobarbital as the first line drug targeting seizures in LLMICs and it is included in the list of essential medicines (WHO).

**Table 3. International guidelines for epilepsy**

Organization	Guideline for epilepsy treatment	Applicability in LIC & Lower MIC settings
World Health Organization (2011)	Mental health Gap Action Programme: Scaling up for mental, neurological and substance use disorders	√

## Intervention attributes

### Type of intervention

Chronic management care

### Delivery platform

Health centre is suggested to be the primary delivery, although severe and complicated cases should be managed at higher specialised facilities.

## Equity

In addition to considerations like cost-effectiveness and health systems factors, dimensions of equity can be relevant for priority setting. The opportunity for a long and healthy life varies according to the severity of a health condition that individuals might have, so there are inequities in individuals' opportunities for long and healthy lives based on the health conditions they face. Metrics used to estimate the severity of illness at an individual level can be used to help prioritize those with less opportunity for lifetime health. FairChoices: DCP Analytics Tool uses Health adjusted age of death (HAAD), which is a metric that estimates the number of years lived from birth to death, discounting years lived with disability. A high HAAD thus represents a disease less severe in terms of lifetime health loss, while a low HAAD represents a disease that is severe on average, causing early death or a long period of severe disability. It is also possible to estimate the distribution of HAAD across individuals with a health condition. FairChoices shows for each intervention an average HAAD value of the conditions that are affected by respective interventions that have health effects. Additionally, a plot shows HAAD values for around 290 conditions (Johansson KA et al 2020).

## Time dependence

Moderate level of urgency and treatment outcomes may be affected by some days of delay. A co-mortality risk exists, i.e. trauma, drowning, or choking.

## Population in need of interventions

All prevalent cases of idiopathic epilepsy would receive and benefit from this intervention. The prevalence of epilepsy is relatively in Africa due to the higher incidence of trauma (for example through head injury, or during birth), and infection with parasites that can lead to the development on epilepsy (Howlett, 2012). A meta-analysis of epilepsy in East-Africa shows a prevalence of epilepsy in Ethiopia of 29,5 per 1000, and in Tanzania the prevalence is estimated between 2,9 – 13,2 per 1000 people (see Table 3 in the appendix) (Ba-Diop et al., 2014). As a comparison, the prevalence of epilepsy in West-Africa is 13.14 per 1000, according to Frodjo et al. (2020). In FairChoices, we have country specific prevalence data from GBD.

## Disease stage addressed

Treatment is initiated when the patient has been diagnosed with epilepsy.

## Intervention effectiveness and safety

Phenobarbital is considered the most cost-effective drug for long term treatment of epilepsy (Brody & Kwan, 2012), but we have also added carbamazepine as an alternative since some patients may respond better to this drug and clinicians can then switch between two drugs (or have two drugs combined) if one does not provide sufficient remission. Treatment of epilepsy includes both long term management and treatment of acute seizures:

Long term management: Phenobarbital 60-180 mg in 1-2 divided doses is the drug of choice of all cases with idiopathic epilepsy because of high availability and low costs, but carbamazepine 100-1400mg in 2-3 divided doses may replace/be added to this (remission reduction 0.6 [ref Strand]). Phenytoin and Sodium Valproate may also be considered as additional essential drugs for long term management of epilepsy, but prices are higher for these drugs.

Acute treatment: Diazepam 10mg (reiterated if needed) is the drug of choice for first-line treatment of acute seizures (probability of seizure stop 0.73 [ref Prasad et al. 2014]). However, when diazepam fails to stop seizures, phenobarbital 100 mg (reiterated until seizures stop) is recommended second line treatment (probability of seizure stop 0.8 [ref Sanchez-Fernandez et al., 2019]).

In addition to impact on disability and mortality, we expect non-health benefits from this intervention that we currently are not able to model:

- Reduced burden on health care system due to fewer acute cases
- Reduction of stigma and stress upon close relatives
- Increase in productivity and education for individuals, households and society
- Reduces inequity in health due to high severity and improved access to care

## Need for future research

Long term-controlled design studies with sufficient power and follow-up period needed to estimate the effect of treatment of epilepsy in terms of mortality and morbidity, disability, incidence/prevalence of epilepsy in other LLMIC.

## Intervention Cost

Costing includes Basic psychosocial support, advice, and follow-up, and anti-epileptic medication.

Assumptions and values are based on a health economic evaluation from Malawi, Tanzania and Ethiopia involving national experts and specialists in neurology. The calculated HR-time per patient is calculated as an average case (see costing tables below), based on the following input:

### *Acute seizures at hospital level:*

On average, patients are admitted into the hospital for 3-7 days in Malawi, and 5 days in Tanzania. During this phase, patients may have stabilized, however delays in lab work in order to rule out infectious causes can be the cause of longer hospitalization. Patients requiring a CT scan will even stay longer waiting for the procedure. During these visits, doctors will review these patients at least twice in 7 days. Due to shortage of nurses, patients will only be attended to by a nurse in cases of emergency i.e. when the guardians report that the patient is actively having seizures; the patient will either be given Diazepam IM/IV and be observed briefly. Once stable the nurse will resume her other duties thus this can last less than 10 minutes really. Only if seizures persist will a doctor be called to review and manage the patient. On daily basis /stabilized patients will be attended to by their guardians and nurses will only come to give medications. It is mostly clinical officers or medical assistants observing these patients daily. Other medications available are Carbamazepine and Sodium valproate.

### *Long-term management of epilepsy at hospital level:*

- On average, once stabilized, patients are reviewed 1 month post discharge of hospital admission. Thereafter its 3-monthly visits, resulting in follow-ups 4 times a year unless other medical problems persist. These patients will be attended to by medical assistants or nurses, unless they are referred to a doctor due to worsened seizure control. The time per control is around 10 minutes.

### *Long term management of epilepsy at health centre level:*

- On average, patient will have at least 3-4 follow-ups at the health centre, since they have to collect medications every 3 months simultaneously. On average, per visit, patients get visited by a nurse or medical assistant for 5 minutes. Treatment consists of 100 mg phenobarbital daily.

### *Treated fraction:*

Less than 75 % of patients with epilepsy (acute and long-term management) receive treatment for the following reasons:

1. Traditional healers/medicine and stigma associated with epilepsy result in fewer hospital visits.

2. Unavailability of basic antiepileptic medications in most rural hospitals in Malawi, resulting in no medical treatment
3. Poor infrastructure in Malawi discourages patients from visiting the hospital.

### Costing tables:

Table 4: HR costs – diagnosis - acute stabilization per hospitalization

Human resources	Inpatient visits (days)	Minutes per stay (per day)	Outpatient visits (number)	Minutes per visit	Total minutes
Diagnosis					
Neurologist	0	0	1	30	30
Nurse	0	0	1	10	40
Acute stabilization					
Neurologist	5	7	2	10	55
Nurse	5	15*	2	10	95
Clinical officers	5	10	2	10	70

\*at least 2 visits in 7 days (10 minute per visit) = 3 min per day = 15 min per 5 days

Table 5: Long-term management per year

Human resources	Outpatient visits (number)	Minutes per visit	Total minutes
Health centre			
Neurologist	4	10	40
Nurse	2	10	20
Clinical officers	2	10	20

Table 6: Salaries health care personnel LIC / LMIC settings (2021)

	Cost per minute Ethiopia	Cost per minute Malawi	Cost per minute Tanzania	Cost per minute Zanzibar	Cost per minute LIC (average)	Cost per minute LMIC (Tanzania)
Neurologist	0,060	0,064	0,178	unreliable	0,062	0,178
Pharmacists	0,024	0,028	0,070	unreliable	0,026	0,070
Medical doctor	0,047	0,044	0,131	unreliable	0,045	0,131
Nurse	0,019	0,020	0,054	unreliable	0,020	0,054
Community health worker	0,014	0,005	0,020	unreliable	0,010	0,020
Physical therapist	0,029	0,033	0,097	unreliable	0,031	0,097
Clinical health officer	0,014	0,016	0,038	unreliable	0,015	0,038

Table 7: Drug/supply component for treatment of epilepsy

## EVIDENCE BRIEF

Epilepsy, treatment

(DCP4 ID: NEUR01)

Cluster: Neurological disorders

**FairChoices**

DCP Analytics Tool

Drug/Supply	Number of units	Times per day	Days per case	Units per case	Drug unit costs (in US\$)	Cost per case
Phenobarbital	1	1	365	365	0,0053	1,94
Carbamazepine	1	1	365	365	0,032	11,68
Diazepam	1,5	1	1	1	0,0094	0,014

Table 8: Total unit costs

	Total HR Costs LIC(in US\$)	Total HR Costs LMIC (in US\$)	Total drug costs	Other costs	Total costs LIC	Total costs LMIC
Diagnosis	2,05	5,87	n/a		2,05	5,87
Acute stabilization	6,308	17,59	1,95		8,26	19,54
Management	3,171	8,96	1,94		5,11	10,89



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